
1 This supplement file contains the following items: the Precise statistical analysis
2 plan, the original PRECISE protocol, (version 1), and 4 amended protocols (versions
3 2-5). A summary of the amendments precedes each version of the protocol.
4 Note Amendment 1 relates to Protocol version 2, etc.
5 Note the original statistical analysis plan was not amended and was the plan used for
6 the final analysis.

7

8 Pages are as follows:

9

10 2 Statistical Analysis Plan
11 10 Original Protocol (version 1)
12 101 Summary of amendment 1
13 102 Version 2 of Protocol
14 194 Summary of amendment 2
15 195 Version 3 of protocol
16 285 Summary of amendment 3
17 286 Version 4 of protocol
18 382 Summary of amendment 4
19 384 Version 5 of protocol

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21 Laurence Klotz

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29 **Study:** A phase III Multi-Centre Open-Label Randomized Controlled Trial of Multi-
30 Parametric Magnetic Resonance Imaging (MRI)-Targeted Biopsy Compared to
31 Systematic Trans-Rectal Ultrasound (TRUS) Guided Biopsy for the Diagnosis of
32 Prostate Cancer in Men without Prior Biopsy (**PRECISE**)

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Statistical Analysis Plan (SAP)

36

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Version: Draft #1

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Date: 26 February 2016

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Author: Gregory R. Pond

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51 **OBJECTIVES**

52 **Overall aim**

53 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
54 standard of care systematic TRUS guided biopsy in the detection of clinically
55 significant and clinically insignificant prostate cancer in men without prior biopsy.

56

57 **Hypotheses**

58 The proportion of men with clinically significant cancer detected by MRI-targeted
59 biopsy will be no less than that detected by systematic TRUS guided biopsy.

60

61 **Primary Objective**

62 To determine whether the proportion of men with clinically significant cancer
63 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
64 guided biopsy.

65

66 **Secondary Objectives**

- 67 1. To determine whether the proportion of men with clinically significant cancer
68 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
69 guided biopsy.
- 70 2. Proportion of men in each arm with clinically insignificant cancer detected.
- 71 3. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 72 4. Proportion of men in MRI arm who avoid biopsy.
- 73 5. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
74 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
75 detected.
- 76 6. Proportion of men in each arm who go on to definitive local treatment (e.g. radical
77 prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone
78 therapy, chemotherapy).
- 79 7. Maximal cancer core length of the most involved biopsy core (maximum cancer
80 core length, MCCL) in each arm.
- 81 8. Total contiguous cancer core length of the most involved biopsy core (maximum
82 cancer core length, CMCL) excluding intervening normal regions.
- 83 9. Proportion of men with a negative MRI who develop a positive MRI and/ or

-
- 84 Gleason ≥ 7 cancer by 2 years.
- 85 10. Proportion of men with post-biopsy adverse events
- 86 11. Health-related quality of life scores.
- 87 12. Proportion with Gleason grade upgrading in men undergoing radical
- 88 prostatectomy.
- 89 13. To determine the cost per diagnosis of cancer.
- 90

91 **Explanation for non-inferiority hypothesis**

92 Due to the putative advantages of MRI-TB in reducing the number of men who

93 require a biopsy, reducing the number of cores required in each man who is

94 biopsied, more accurate representation of disease burden, less insignificant disease

95 detected and reducing the number of men at risk of complications of biopsy, the

96 primary outcome of detection of clinically significant cancer in each arm will be

97 compared using a non-inferiority hypothesis. Even if a similar amount of clinically

98 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these

99 advantages would support the use of MRI-TB instead of systematic TRUS guided

100 biopsy in clinical practice.

101

102 **STUDY POPULATIONS**

103 The per protocol population will consist of all subjects who satisfy all eligibility

104 criteria and are randomized to the study, who undergo MPMRI-TB or systematic

105 TRUS guided biopsy and have their primary outcome measured.

106

107 The intent-to-treat (ITT) population will consist of all subjects randomized to the

108 study, regardless of any protocol violations or if they do not complete the study as

109 defined in the protocol.

110

111 **DEFINITIONS**

112 **Primary Outcome**

113 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will

114 be calculated based on histology results from biopsy procedures. The proportion

115 within each arm will be calculated as the number of patients with clinically

116 significant cancer divided by the number of evaluable patients.

117

118 **Secondary Outcomes**

119 Standard summary statistics will be presented for secondary outcomes. For
120 continuous variables, summary statistics will include n, mean, standard deviation,
121 median, interquartile range, minimum and maximum. For categorical variables,
122 proportions and frequencies will be presented. Time to cancer diagnosis or death,
123 and time to first intervention will be collected and estimated using the Kaplan-Meier
124 method.

125

126 **STATISTICAL METHODS**

127 **Primary Analysis**

128 Absolute differences in the proportion of clinically significant cancer detected
129 between arms will be calculated and compared using the Clopper-Pearson method.
130 If the lower boundary of an one-sided, 97.5% confidence interval for the difference
131 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less
132 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower
133 bound is greater than zero, superiority can be claimed.

134

135 A supportive analysis will be performed by using a logistic regression model,
136 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification
137 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of
138 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower
139 bound was calculated to approximate an absolute 5% difference of interest (NOTE:
140 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

141

142 **Secondary Analyses**

143 For each secondary outcome, where appropriate, a difference in proportions with
144 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.
145 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for
146 time-to-event outcomes.

147

148 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
149 differences between allocation arms in secondary outcomes. Logistic regression and

150 Cox proportional hazards regression will be used to examine the effect of allocation
151 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
152 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
153 adjustments will be made due to multiple testing, however, results for secondary
154 outcomes will be interpreted cautiously, acknowledging that tests were performed
155 on secondary outcomes and numerous secondary tests were performed. Figures and
156 tables will be used to illustrate results of interest.

157

158 **Treatment Allocation and Stratification**

159 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
160 use of a dynamic allocation scheme. Specifically, the first 20 patients will be
161 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 patients, a
162 biased coin method will be used, whereby the number of patients within each
163 stratum will be calculated, and the next eligible patient will be allocated (with
164 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
165 allocation to each arm will occur with probability $p=0.5$.

166

167 Stratification

168 For treatment allocation, the subjects' individualized risk of high-grade prostate
169 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
170 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
171 subjects will be stratified by:

172 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);

173 (2) clinical centre.

174

175 **Sample Size**

176 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
177 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
178 50% from another study [36].

179

180 Rates of clinically significant cancer detection from one the largest studies of
181 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
182 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will

183 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
184 systematic TRUS guided biopsy.

185

186 For this study, it will be conservatively hypothesized that systematic TRUS guided
187 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
188 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
189 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
190 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
191 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
192 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
193 choice of 5% as the margin of non-inferiority represents a difference that would be
194 considered clinically important.

195

196 Thus total men required in study = **422**.

197

198 To account potential withdrawal / loss to follow up and the effect of stratification,
199 the sample size will be inflated by 5%, and a target of **450 men** will be recruited.

200

201 Note that the rate of clinically significant cancers is very dependent on the
202 population registered for this study. It is possible that fewer (or more) subjects will
203 have clinically significant cancers than what is initially hypothesized. However, if the
204 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
205 biopsy detection rate is <30%) and other statistical assumptions remain as stated
206 previously, the statistical power will increase. The minimum statistical power would
207 be obtained if the clinically significant cancer detection rate was 45% for systematic
208 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
209 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
210 rate of clinically significant cancer in the population is miss-specified, assuming an
211 absolute difference of 10% between targeted and systematic TRUS guided biopsy
212 detection rates, and a 5% margin of non-inferiority.

213

214 **Statistical Conventions**

215 For categorical data, tables will be presented showing the n and percentage
216 (n/N*100%) of patients. Analyses will be presented by study allocation arm
217 separately.

218

219 Duration of time will be described in either years, months or weeks, and calculated
220 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months,
221 or X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date
222 – date of birth + 1)/365.25.

223

224 Transformations of the data in order to meet statistical assumptions may be
225 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
226 assess any of the model fittings. All the statistical analysis will be carried out using
227 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-
228 project.org) or higher.

229

230 **Missing Data**

231 Missing values for the primary endpoint will be examined closely. Sources and
232 reasons for the absence of data incurred as a result of subjects lost-to-follow up,
233 dropouts, and intermittent missing values will be described and explored by various
234 summary statistics as well as graphical displays between the two allocation arms.
235 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
236 those subjects will be described by allocation arm and tested using Fisher's exact
237 tests or Wilcoxon rank sum tests.

238

239 Missing data for secondary endpoints will be described. The methods for evaluating
240 missing data of the primary endpoint may be employed for endpoints of interest. For
241 summarization of baseline data, the following conventions will be used for partial
242 missing date information occurring prior to randomization (e.g. for medical history
243 or prior treatment). If year is missing, the date will be set at missing. If year is
244 available, but month and date is missing, the month and date will be set to July 1st of
245 the respective year. If date is missing, but year and month available, the day will be
246 set to the 15th of the respective month.

247

248 **Interim Analyses**

249 A formal futility analysis will be performed after approximately 200 subjects are
250 enrolled and have their primary outcome ascertained. Simulation will be used to
251 estimate the conditional probability of futility assuming the study was to continue to
252 completion, and assuming the clinically significant cancer detection rate is 30% in
253 both arms. If the conditional probability is 0.95 or higher that continuation of the
254 study will result in a negative result, the DSMC will recommend a suspension of
255 recruitment to the trial, and initiation of a quality assurance review. A decision to
256 permanently close the study or continue with accrual will be determined by the
257 Steering Committee, based on the results of the quality assurance review, and the
258 recommendation of the DSMC.

259

260 **Timing of Final Analysis**

261 A single, final, analysis will occur after all patients have undergone their initial biopsy
262 and all data related to the initial biopsy is documented and validated. Follow-up
263 analyses will be conducted after all patients have completed two years of follow-up.

264

265

266 1. Title Page
267 Full title:
268 **A phase III multi-centre open-label randomized controlled trial of**
269 **multi-parametric magnetic resonance imaging (MRI)-targeted biopsy**
270 **compared to systematic trans-rectal ultrasound (TRUS) guided biopsy**
271 **for the diagnosis of prostate cancer in men without prior biopsy.**
272
273 **Short title: PRostate Evaluation for Clinically Iimportant disease: MRI vs**
274 **Standard Evaluation procedures. (PRECISE)**
275
276 **Date: 27 September 2016**
277 **Version 1.0**
278
279 **Sponsor:**
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281
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2. Signature of Investigators

A phase III multi-centre open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.

Date: 27 September 2016

Version 1.0

The signatory agrees to the content of the final clinical study protocol as presented.

Signature: _____

Name: _____

Title: _____

Date: _____

Site name: _____

Site #: _____

3. Synopsis

Title	A phase III multi-centre, open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.
Short Title	<u>P</u> rostate <u>E</u> valuation for <u>C</u> linically <u>I</u> mportant disease: MRI vs <u>S</u> tandard <u>E</u> valuation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	<p>Primary Objective</p> <p>To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.</p> <p>Secondary Objectives</p> <ol style="list-style-type: none"> 1. To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy. 2. Proportion of men in each arm with clinically insignificant cancer detected. 3. Proportion of men in each arm with Gleason $\geq 4+3$ detected. 4. Proportion of men in MRI arm who avoid biopsy. 5. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected. 6. Proportion of men in each arm who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy). 7. Maximal cancer core length of the most involved biopsy core (maximum cancer core length, MCCL) in each arm. 8. Total contiguous cancer core length of the most involved biopsy core (contiguous maximum cancer core length, CMCCCL) excluding intervening normal regions. 9. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer by 2 years. 10. Proportion of men with post-biopsy adverse events 11. Health-related quality of life scores. 12. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy. 13. To determine the cost per diagnosis of cancer.
Test procedures	Subjects will be randomized to either ARM A: multi-parametric magnetic resonance imaging (MRI)

	<p>which, depending on outcome, may be followed by (MRI)-targeted biopsy.</p> <p>ARM B: systematic trans-rectal ultrasound (TRUS) guided biopsy.</p> <p>Subjects in both arms will complete a number of different questionnaires and will have PSA measurements taken. If subjects consent to participate in correlative studies, they will also need to provide blood, urine, and semen samples at pre-specified time points.</p>
Indication	Clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy.
Diagnosis and main criteria for inclusion	<p>In order to be eligible, <u>all</u> inclusion criteria must be met.</p> <ol style="list-style-type: none"> 1. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy; 2. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk assessment of prostate cancer calculator, PCPTRC 2.0, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp; 3. Serum PSA ≤ 20ng/ml; 4. Fit to undergo all procedures listed in protocol; 5. Able to provide written informed consent.
Exclusion Criteria	<p>Men who meet the following criteria at the time of screening will be excluded:</p> <ol style="list-style-type: none"> 1. Prior prostate biopsy; 2. Prior treatment for prostate cancer; 3. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min); 4. Contraindication to prostate biopsy; 5. Men in whom artifact would reduce the quality of the MRI; i.e, previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work; 6. Unfit to undergo any procedures listed in protocol.
Study Design	This is a multi-centre open-label, randomized two arm study. Men are either randomized to receive MRI or a systematic trans-rectal ultrasound (TRUS) guided biopsy.
Methodology	<p>Eligible subjects will be randomized in a 1:1 ratio to receive either (ARM A) multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy, or (ARM B) systematic trans-rectal ultrasound (TRUS) guided biopsy. The time frame for data collection is shown in Appendix 1.</p> <p><u>All subjects</u> will have a PSA test prior to, or at Visit 1, and will complete a baseline EQ-5D-5L questionnaire. In addition, they will contribute optional blood, urine and semen samples if they consent to correlative studies.</p> <p><u>All subjects in ARM A</u> will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire</p>

	<p>following the MRI.</p> <p><u>Subjects in ARM A who do not receive a subsequent biopsy</u> will complete an EQ-5D-5L questionnaire and a 30-day post MRI/TRUS Fusion Biopsy questionnaire when they find out the results of the MRI 3 weeks (\pm 1 week) after the procedure. They will have another MRI and PSA test 2 years after the initial MRI. When they complete the study after 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>Subjects in ARM A who do receive a MRI-targeted biopsy</u> will complete an EQ-5D-5L questionnaire and an immediate post-biopsy questionnaire at the time of the biopsy, another an EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test each year for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>All subjects in ARM B</u> will complete an EQ-5D-5L questionnaire and an immediate post-biopsy questionnaire following the standardized TRUS-guided biopsy. They will complete another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test each year for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p>
Type of control	This is an open-label randomized study.
Number of subjects	This study requires 422 subjects (211 in each arm). To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size will be inflated by 5%, and a target of 450 men will be recruited.
Primary endpoint	The proportion of men in each arm with clinically significant cancer (Gleason \geq 7) will be calculated based on histology results from biopsy procedures. Analysis will be on the per protocol study population.
Secondary endpoints	See section 7.4
Plan for statistical analysis	See section 14.0.
Funding	The total budget for this trial is \$3,000,000. (see attached). Ontario Institute for Cancer Research (OICR) has committed to \$1,500,000 in support of this study (letter appended). We hope to obtain the additional \$1,500,000 from the Movember Accelerated Translational Research Grant Competition

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487		

488 4. Abbreviations and definitions

489 Abbreviations:

490		
491	ADC	Apparent diffusion coefficient
492	CI	Confidence interval
493	CRF	Case report form
494	DSMC	Data Safety and Monitoring Committee
495	DRE	Digital rectal examination
496	DWI	Diffusion weighted imaging
497	DCE	Dynamic contrast enhancement
498	ITT	Intention to treat
499	MCCL	Maximum cancer core length
500	MPMRI	Multi-parametric MRI, used interchangeably with MRI
501		in this protocol.
502	MPMRI-TB	Multi-parametric magnetic resonance image-targeted
503		biopsy of the prostate
504	MRI	Magnetic resonance imaging, used interchangeably
505		with MPMRI in this protocol
506	MRS	Magnetic resonance spectroscopy
507	PI	Principal Investigator
508	PI-RADS	Prostate Imaging Reporting and Data System
509	PTC	Permission to Contact
510	PSA	Prostate specific antigen
511	REB	Research Ethics Board
512	STARD	Standards for the reporting of diagnostic studies
513	TRUS	Trans-rectal ultrasound
514	TSC	Trial Steering Committee
515	T2W	T2-weighted imaging

516

517

518 Definitions:

519

520	MP MRI-targeted biopsy	A biopsy technique where an MP MRI scan is
521		used to determine the location of a suspicious
522		target prior to biopsy.

523

524	Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure
525		is not influenced by findings on MRI imaging.
526		Currently this is the standard of care for
527		prostate cancer in the province of Ontario.

528

529

530

531 **5. Trial summary**

532

533 **5.1 Aim and Rationale**

534

535 The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided
536 (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is
537 performed primarily for anatomic guidance as the ultrasound poorly discriminates
538 between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are
539 concentrated in areas of the peripheral zone, thought to harbor the majority of
540 cancer.

541

542 An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to
543 perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer.
544 This information is used to direct a subsequent biopsy, known as an MRI-targeted
545 biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a
546 similar or greater amount of clinically significant cancer than systematic TRUS guided
547 biopsy and has several other potential advantages including: the ability to
548 differentiate between clinically significant and insignificant cancer, reducing
549 unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related
550 side-effects.

551

552

553 A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an
554 individual's life expectancy and therefore does not warrant treatment. However
555 when diagnosed with low grade cancer that is likely to be insignificant, a large
556 proportion of subjects request treatment in case a more significant cancer is present
557 [1]. A challenge in this area is that subjects are typically not aware that their cancer
558 is clinically insignificant, and often view the early diagnosis and aggressive treatment
559 they have been subjected to as life-saving.

560 A prostate cancer detection procedure that differentiates clinically significant cancer
561 from clinically insignificant cancer is therefore a major unmet need.

562

563 The potential implications of this trial include:

564

565

566

567

568

569

570

571

- A redefinition of the prostate cancer diagnostic pathway;
- A reduction in the number of subjects undergoing prostate biopsy;
- A reduction in the number of biopsy cores taken per subject;
- A reduction in biopsy-related adverse events including sepsis and pain;
- A reduction in the over-diagnosis of clinically insignificant prostate cancer;
- A reduction in the economic burden of diagnosing and treating prostate cancer.

572 **5.2 Methods**

573

574 Men referred with clinical suspicion of prostate cancer who have had no prior biopsy
575 are randomized to either systematic TRUS guided biopsy (standard of care) or to a
576 multi-parametric MRI (MPMRI) arm (the investigational arm). In the MRI arm, areas
577 of the prostate are scored on a 5-point scale of suspicion for clinically significant
578 cancer based on the Prostate Imaging Reporting and Data System
579 (PI-RADS) v2[2]:

580 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
581 present)

582 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

583 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
584 equivocal)

585 PI-RADS 4 – High (clinically significant cancer is likely to be present)

586 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
587 present)

588

589 Each suspicious area will be given a separate score as described by consensus
590 meeting recommendations [2, 3]. Lesions scoring 3, 4 or 5 will undergo targeted
591 biopsy; up to three suspicious areas will be targeted.

592

593 In the control arm, subjects will undergo a standard 12 core systematic TRUS guided
594 biopsy as per standard recommendations [4]. Suspicious sonographic lesions will be
595 targeted (12 cores *in toto*).

596

597 Pathologic findings from all biopsies will be recorded and will undergo statistical
598 analysis (see statistics section, 14.0).

599

600 In both arms, self-reported questionnaires to capture biopsy-specific side effects will
601 be administered immediately post-procedure, and at the post-procedure
602 appointment which will take place 3 weeks (\pm 1 week) after the procedure. EuroQOL
603 group 5 domain EQ-5D-5L questionnaires or a comparable QOL instrument will also
604 be completed at baseline (prior to MRI or TRUS biopsy), 24 hours post MRI and 24
605 hours post-biopsy. Men will be followed up for 30-days post intervention and until a
606 treatment decision is made and recorded. Pathology results from men requiring a
607 radical prostatectomy will be recorded.

608

609 Men will complete the trial after they complete treatment for prostate cancer
610 (radical prostatectomy) or the required follow-up procedures for each arm are met
611 (see study timelines, section 9.3). Once men complete the trial, they revert to
612 standard of care.

613

614 Annual questionnaires will be administered for all men with negative biopsy in both
615 arms during a two-year follow-up period to determine cancer and treatment status.

616

617 No diagnostic test is perfect, and even with the best test some cancers may be
618 missed. To minimize the risk of false negatives, men with negative biopsy results will
619 be followed with serial PSA testing; PSA levels will increase if cancer is present. In
620 addition to serial PSA testing, in this study men who had a negative MRI (defined as

621 no cancer detected) and do not have a biopsy will have a follow up MRI at 24
622 months.

623

624 As recruitment is expected to take up to 24 months (see section 7.6) and each
625 subject will be followed up for two years, the estimated maximal duration of this
626 study is four years in total. The primary end point will be reached at approximately 2
627 years after study initiation.

628 **5.3 Participating Sites**

629 This is a multi-centre study. Institutions participating in the study must be able to
630 perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able
631 to randomize men to one of these two diagnostic tests.

632

633 We expect to recruit 3-6 subjects per month per site, based on recruitment rates
634 from previous diagnostic trials performed by the centers involved. A typical centre
635 sees 15-30 eligible men per month. We expect 5 recruitment sites, with 100 men to
636 be recruited at each site over an 18-24 month period (see section 7.6).

637 **5.4 Study outcomes**

638 **5.4.1 Primary outcome**

639 To determine whether the proportion of men with clinically significant cancer
640 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
641 guided biopsy.

642 **5.4.2 Secondary outcomes**

- 643 1. To determine whether the proportion of men with clinically significant cancer
644 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
645 guided biopsy.
- 646 2. Proportion of men in each arm with clinically insignificant cancer detected.
- 647 3. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 648 4. Proportion of men in MRI arm who avoid biopsy.
- 649 5. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
650 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
651 detected.
- 652 6. Proportion of men in each arm who go on to definitive local treatment (e.g.
653 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
654 hormone therapy, chemotherapy).
- 655 7. Maximal cancer core length of the most involved biopsy core (maximum cancer
656 core length, MCCL) in each arm.
- 657 8. Total contiguous cancer core length of the most involved biopsy core (contiguous
658 maximum cancer core length, CMCL) excluding intervening normal regions.
- 659 9. Proportion of men with a negative MRI who develop a positive MRI and/ or
660 Gleason ≥ 7 cancer by 2 years.
- 661 10. Proportion of men with post-biopsy adverse events
- 662 11. Health-related quality of life scores.
- 663 12. Proportion with Gleason grade upgrading in men undergoing radical

664 prostatectomy.
665 13. To determine the cost per diagnosis of cancer.
666

667 **6. Background**

668 **6.1 Prostate cancer diagnosis**

669 Prostate cancer is the most common male cancer in the Western world with an
670 incidence of 24,000 new cases in Canada and 233,000 in the USA [5, 6]. It is the
671 second most common cause of cancer death in European and North American men,
672 with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe [5, 6].
673 The incidence of the disease has increased by 22% over the last decade due to the
674 widespread use of the prostate specific antigen (PSA) blood test; by 2030 the
675 Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.
676 As prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal
677 digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one
678 million prostate biopsies are performed in North America and Europe every year [7].
679

680 **6.2 Clinically significant versus clinically insignificant prostate cancer**

681
682 Clinically significant prostate cancer is cancer that is likely to progress and affect a
683 man's life expectancy if left untreated. Though there is no universally agreed upon
684 definition on what histological parameters define clinically significant cancer, most
685 agree that larger volume cancers with a higher Gleason grade are more likely to be
686 clinically significant; an historically accepted threshold is a tumour volume above 0.5
687 milliliters or any Gleason pattern 4 or 5 cancer [8-11].
688

689 This definition is likely overly stringent. An increasing consensus views all Gleason
690 pattern 3 (Gleason score 6) cancers and many Gleason 3 plus small amounts of
691 pattern 4 cancers as likely insignificant [12]. About half of newly diagnosed prostate
692 cancers fall into this category, and are unlikely to progress and affect a man's life
693 expectancy if left untreated. The widespread use of PSA testing has led to more men
694 being diagnosed with insignificant cancer that does not warrant any treatment [13];
695 however they are typically monitored closely with active surveillance. This is
696 associated with anxiety about harbouring untreated cancer, and the negative
697 psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate
698 cancer are also subjected to serial biopsies and other tests, requiring long term
699 follow up. Further, many men with low risk disease receive radical treatment, either
700 because their physicians are not advocates of surveillance or because of anxiety
701 [15]. These treatments may expose them to morbidity including urinary incontinence
702 and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate
703 clinically significant cancer from clinically insignificant cancer will help reduce patient
704 anxiety, alleviate further testing, and avoid radical treatment and associated
705 morbidities.
706

707 **6.3 Current standard of care: systematic TRUS guided biopsy**

708 The European association of Urology and NICE guidelines recommend systematic
709 TRUS guided biopsy as the current standard of care for the diagnosis of prostate
710 cancer [4, 17]. This procedure has several advantages: it can be delivered quickly in
711 an outpatient clinic under local anesthetic, it can be offered at most Urology centres,
712 and the expertise is widely distributed.

713
714 Limitations of systematic TRUS guided biopsy are as follows: the procedure requires
715 the operator to take 10-12 samples in the peripheral zone, where it is thought that
716 the majority of prostate cancer can be found (See Appendix 2) [18]. The ultrasound
717 guidance used during the procedure is useful for visualizing the prostate and
718 assessing the location of the needle within the prostate but has a poor ability to
719 discriminate tumour from normal tissue [19], which means that the systematic TRUS
720 guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has
721 been shown to have a high false negative rate of 30-45% [20, 21]. As a systematic
722 TRUS guided biopsy is not specifically targeted to the location of a suspected
723 significant cancer, there is also a greater chance that a significant cancer may be
724 missed.

725 **6.4 The emerging role of MRI in prostate cancer diagnosis and** 726 **treatment**

727 **6.4.1 The role of imaging in prostate cancer diagnosis**

728 Although used to diagnose many other solid organ cancers such as breast, renal and
729 colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic
730 pathway. Imaging in prostate cancer, is typically limited to stage the disease
731 following histological diagnosis. Magnetic resonance imaging (MRI) is used in many
732 centres to assess for extra-capsular extension during prostate cancer staging. In the
733 past five years however, the possibility of using multi-parametric MRI (MPMRI) for
734 diagnosing prostate cancer prior to biopsy, has generated tremendous interest [22].

735 **6.4.2 Limitations of early MRI studies in prostate cancer**

736 Early literature reported conflicting results on the ability of MRI to detect prostate
737 cancer. A recent systematic review of the literature showed that the quality of
738 studies evaluating MRI was disappointing [22]. Limitations of reported studies
739 include:

- 740 • **Poor reporting standards.** Many early studies failed to closely follow
741 published guidelines for the standards of reporting of diagnostic studies
742 (STARD) [23].
- 743 • **Biopsy artifact.** The majority of early studies evaluated MRI after biopsy.
744 Evidence has shown that post-biopsy hemorrhage can remain for several
745 months and affect interpretation of the image [24].
- 746 • **Poor reference standards.** Many early studies use systematic TRUS guided
747 biopsy as a reference standard, which due to its limitations, can influence the
748 validity of the index test of MRI. Using radical prostatectomy specimens as
749 reference standards can lead to a selection bias, as MRI is only validated in
750 men with disease characteristics that require radical prostatectomy. Further,

751 correlation of radical prostatectomy specimen with an MRI image is not
752 without difficulty given the shrinkage (10-20%), distortion, absent perfusion,
753 orientation and tissue loss as a result of specimen trimming.

- 754 • **Incomplete analysis of the prostate.** Many early studies only evaluate the
755 validity of MRI in the peripheral zone, even though studies have shown that
756 around 25% of prostate cancers may be located in the transition zone [18].
- 757 • **Segmentation.** Many early studies artificially divide the prostate into a
758 number of segments in order to increase the amount of data obtained and
759 the power of the analysis. Segments should not be treated as independent
760 regions of interest, and this should be factored into the analysis.
761

762 **6.4.3 Emerging role of MRI in the diagnosis of prostate cancer**

763 Since the publication of these early reports, improvements in diagnostic technology
764 have changed the field and more evidence supporting the role of pre-biopsy MRI has
765 been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla
766 and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image
767 acquisition and the addition of functional sequences including magnetic resonance
768 spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast
769 enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for
770 biopsy artifacts.

771
772 The combination of anatomical sequences (T2-weighted imaging) and functional
773 sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI.
774 Combining the sequences improves the validity of the test [25, 26].
775

776 A systematic review determined that 60% of men with a clinical suspicion of prostate
777 cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI
778 with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity,
779 positive predictive value and negative predictive value of 90%, 88%, 77% and 95%
780 respectively for the identification of prostate tumours greater than 0.5ml [28].
781 Systematic reviews and meta-analysis of recent studies have demonstrated
782 sensitivity and specificity consistently between 70-90% for the detection of clinically
783 significant prostate cancer [26, 29-31].
784

785 As a result of this accumulating evidence, MRI is increasingly used in clinical practice
786 in the diagnostic pathway for prostate cancer. The results of MRI can influence the
787 decision to perform a prostate biopsy, as well as the technique and targeting used
788 during the biopsy.
789

790 MRI has tremendous potential to enhance the outcome of men on active
791 surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA <
792 10) harbor higher-grade disease. This occult high-grade disease "*the wolf in sheep's
793 clothing*", is responsible for the 3-5% of prostate cancer deaths that have been
794 reported in long term surveillance series that did not incorporate MRI [32, 33]. The
795 early use of MRI in men on surveillance has the potential both to reduce the need
796 for confirmatory biopsies, and to identify the *wolf in sheep's clothing* earlier, prior to
797 the development of metastasis.

798

799 This was the rationale for the very successful ASIST study, which recently successfully
800 completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in*
801 *toto* by the Ontario Institute of Cancer Research. The project was managed by the
802 Canadian Urology Research Consortium (CURC). It randomized 273 men recently
803 diagnosed with low risk prostate cancer, on surveillance, between systematic
804 confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end
805 point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or
806 higher prostate cancer. The study had numerous secondary end points and
807 correlative science components. We expect to report the initial results by 3Q 2016.
808 We believe that the success and potential impact of the ASIST trial has created
809 strong momentum to proceed with the PRECISE trial, which has even greater
810 potential to substantially influence prostate cancer screening and diagnosis.

811 **6.4.3.1 MRI can influence the decision to perform a prostate biopsy**

812 With reported negative predictive values of 95% [28, 34, 35], MRI can help
813 determine whether a prostate biopsy is necessary; if the MRI does not identify a
814 suspicious area the biopsy can be avoided. Using MRI, 40-50% of men referred with
815 clinical suspicion of prostate cancer might avoid a biopsy [27]. The recent National
816 Institute for Health Research (NIHR) Health Technology Assessment (HTA) report
817 [11] acknowledged the value of MRI in this context. The NIHR HTA report suggests
818 that using MRI to reduce the number of men who undergo biopsy, can be cost
819 effective despite the costs associated with MRI [11]. Cost savings for the publically
820 funded health care system accrue as a result of reduced number of biopsies and
821 costs of attendant complications, and reduced treatment of clinically insignificant
822 cancer.

823 **6.4.3.2 MRI can influence the biopsy technique**

824 For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI
825 information is used to influence the prostate biopsy technique. This is known as MRI-
826 targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of
827 ways.

828

829 The biopsy operator can use the MRI images or report to direct biopsies into the
830 area of the prostate where the tumour is located. The location of the tumour on the
831 MRI (carried out in advance) is registered to the real-time ultrasound images with
832 the use of software (software assisted registration or image-fusion) or without the
833 use of software (visual registration or cognitive registration), while the prostate is
834 visualized in real-time using transrectal ultrasound. MRI-TB can also be conducted
835 directly “in-bore”, where the biopsy is conducted within an MRI scanner where the
836 target identified on MRI during a prior diagnostic scan is biopsied using guidance
837 from serial MRI scans during the biopsy procedure, performed in an open magnet.

838

839 For the PRECISE study, the biopsy will be performed using an image fusion-targeting
840 device. Two devices have been FDA approved: the Artemis, made by Eigen, and the
841 Urostation, made by Koelis. These devices import the MR target into the TRUS
842 image, and direct the biopsy needle into the target.

843 **6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are** 844 **similar to other methods**

845 A systematic review determined that 60% of men with a clinical suspicion of prostate
846 cancer will have a suspicious area identified on MRI [27]. One study found that a
847 prostate biopsy strategy using only MPMRI-targeted cores resulted in the same
848 detection rate of clinically significant cancer as 20-sector transperineal biopsies [36].
849 Other studies also show that a targeted-alone approach would detect a similar
850 amount of clinically significant cancer when compared to a 10-12 core systematic
851 TRUS guided biopsy [37]. A targeted-alone approach detects 17% less clinically
852 insignificant cancer compared to systematic TRUS guided biopsy [38].

853
854 The detection rates achieved with a targeted-alone biopsy strategy require fewer
855 biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis,
856 targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer
857 detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores
858 compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of
859 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material
860 for histopathological analysis as the maximum cancer core length obtained from
861 targeted biopsies can be greater than that obtained from systematic biopsies[37].

862
863 Robust comparative evidence from randomized controlled trials is needed to
864 determine if MRI scans can improve our ability over systematic TRUS guided biopsy
865 to diagnose clinically significant cancer and our ability to avoid detecting clinically
866 insignificant cancer.

867

868 **6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy**

869 Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine
870 clinical practice for prostate cancer diagnosis. Most existing studies have cohort
871 study designs which make interpretation difficult as they do not conform well to
872 STARD [23] recommendations [27]. Limitations of these studies include:

- 873 • **Broad definition of the study population.** The cancer detection rates depend on
874 the prevalence of the condition in the population being investigated. This varies
875 amongst men with no prior biopsy, prior negative biopsy and prior positive
876 biopsy. In many studies the detection rates are not attributable to a clearly
877 defined population.
- 878 • **MRI conduct and reporting.** The detail in which MRI is conducted and
879 interpreted varies greatly amongst published studies.
- 880 • **Reporting of cancer detection.** The cancer detection by systematic and targeted
881 cores is not always presented separately and cancer detection is not always
882 specified by clinical significance. These are both essential in order to evaluate the
883 technique.

884 There is a strong need for a randomized controlled trial comparing MRI-targeted
885 biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical
886 practice can be established.

887 **6.5 Novelty of PRECISE**

888 PRECISE is the first randomized study in biopsy-naïve men in which men are
889 randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal
890 areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic
891 TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-
892 targeted biopsy approach in the detection of clinically significant cancer. In order to
893 evaluate a biopsy technique that could replace standard of care, the standard of care
894 test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to
895 allow a direct comparison.

896

897 Other constituencies with an interest in MRI in prostate cancer (University College,
898 London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New
899 York) have considered similar studies, however in these centres MRI has largely
900 replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to
901 date. As a result, these centres have acknowledged that randomization to a standard
902 biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as
903 equipoise has been lost.

904

905 In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not
906 recommended for the indication of an elevated PSA in men who have not had a
907 biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed
908 to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a
909 biopsy will make entry into this trial very appealing to potential candidates. Further,
910 the barriers, both financial and physical, to obtaining a quality MRI outside of the
911 health care system are substantial. Thus we believe men who are randomized to the
912 systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant
913 contamination (i.e. men randomized to the systematic biopsy arm seeking out an
914 MRI instead).

915

916 **7. Trial objectives**

917 **7.1 Overall aim**

918 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
919 standard of care systematic TRUS guided biopsy in the detection of clinically
920 significant and clinically insignificant prostate cancer in men without prior biopsy.
921 The implication of this trial is that MRI-targeted biopsy could replace systematic
922 TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

923 **7.2 Hypotheses**

924 The proportion of men with clinically significant cancer detected by MRI-targeted
925 biopsy will be no less than that detected by systematic TRUS guided biopsy.

926 **7.3 Primary Objective**

927 To determine whether the proportion of men with clinically significant cancer
928 (Gleason \geq 7) detected by MRI-targeted biopsy is no less than systematic TRUS
929 guided biopsy.

930 **7.4 Secondary Objectives**

- 931 14. To determine whether the proportion of men with clinically significant cancer
932 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
933 guided biopsy.
- 934 15. Proportion of men in each arm with clinically insignificant cancer detected.
- 935 16. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 936 17. Proportion of men in MRI arm who avoid biopsy.
- 937 18. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
938 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
939 detected.
- 940 19. Proportion of men in each arm who go on to definitive local treatment (e.g.
941 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
942 hormone therapy, chemotherapy).
- 943 20. Maximal cancer core length of the most involved biopsy core (maximum cancer
944 core length, MCCL) in each arm.
- 945 21. Total contiguous cancer core length of the most involved biopsy core (contiguous
946 maximum cancer core length, CMCCCL) excluding intervening normal regions.
- 947 22. Proportion of men with a negative MRI who develop a positive MRI and/ or
948 Gleason ≥ 7 cancer by 2 years.
- 949 23. Proportion of men with post-biopsy adverse events
- 950 24. Health-related quality of life scores.
- 951 25. Proportion with Gleason grade upgrading in men undergoing radical
952 prostatectomy.
- 953 26. To determine the cost per diagnosis of cancer.
954

955 **7.5 Explanation for non-inferiority hypothesis**

956 Due to the putative advantages of MRI-TB in reducing the number of men who
957 require a biopsy, reducing the number of cores required in each man who is
958 biopsied, more accurate representation of disease burden, less insignificant disease
959 detected and reducing the number of men at risk of complications of biopsy, the
960 primary outcome of detection of clinically significant cancer in each arm will be
961 compared using a non-inferiority hypothesis. Even if a similar amount of clinically
962 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these
963 advantages would support the use of MRI-TB instead of systematic TRUS guided
964 biopsy in clinical practice.
965

966 **7.6 Anticipated timeline of study progression**

967 The study will commence once sponsorship, ethical approval and local approvals
968 have been obtained at a participating site and once site initiation training has
969 occurred and a letter of site activation has been issued from the coordinating centre.
970 Additional sites may join after the study has commenced. At this time, five sites will
971 participate. Assuming a minimum recruitment rate of 3-6 men per site per month,
972 recruitment will be complete by 24 months, if not sooner. If accrual is slower than
973 expected, an additional 1-2 sites will be recruited for year 2.
974

Month	Number of Sites	Total recruitment
0	2	0
3	4	18-36
6	5	54-108
9	5	99-198
12	5	144-288
15	5	189-378
18	5	234-468
21	5	279-558
24	5	324-648

975

976 **8. Study Population**

977 **8.1 Number of Subjects**

978 Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or
979 results of digital rectal exam, with no prior biopsy will be eligible for participation.

980 Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be
981 enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

982 **8.2 Subject inclusion criteria**

983 In order to be eligible, all inclusion criteria must be met:

- 984 1. Men at least 18 years of age referred with clinical suspicion of prostate cancer
985 who have been advised to have a prostate biopsy;
- 986 2. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk
987 assessment of prostate cancer calculator, PCPTRC 2.0, found at
988 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>;
- 989 3. Serum PSA ≤ 20 ng/ml within 3 months of randomization
- 990 4. Fit to undergo all procedures listed in protocol;
- 991 5. Able to provide written informed consent.

992 **8.3 Subject exclusion criteria**

993 Men who meet the following criteria at the time of screening will be excluded:

- 994 1. Prior prostate biopsy
 - 995 2. Prior treatment for prostate cancer
 - 996 3. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR \leq
997 50mls/min)
 - 998 4. Contraindication to prostate biopsy
 - 999 5. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip
1000 replacement surgery, metallic hip replacement or extensive pelvic orthopaedic
1001 metal work
 - 1002 6. Unfit to undergo any procedures listed in protocol.
- 1003

1004 **9. Study design**

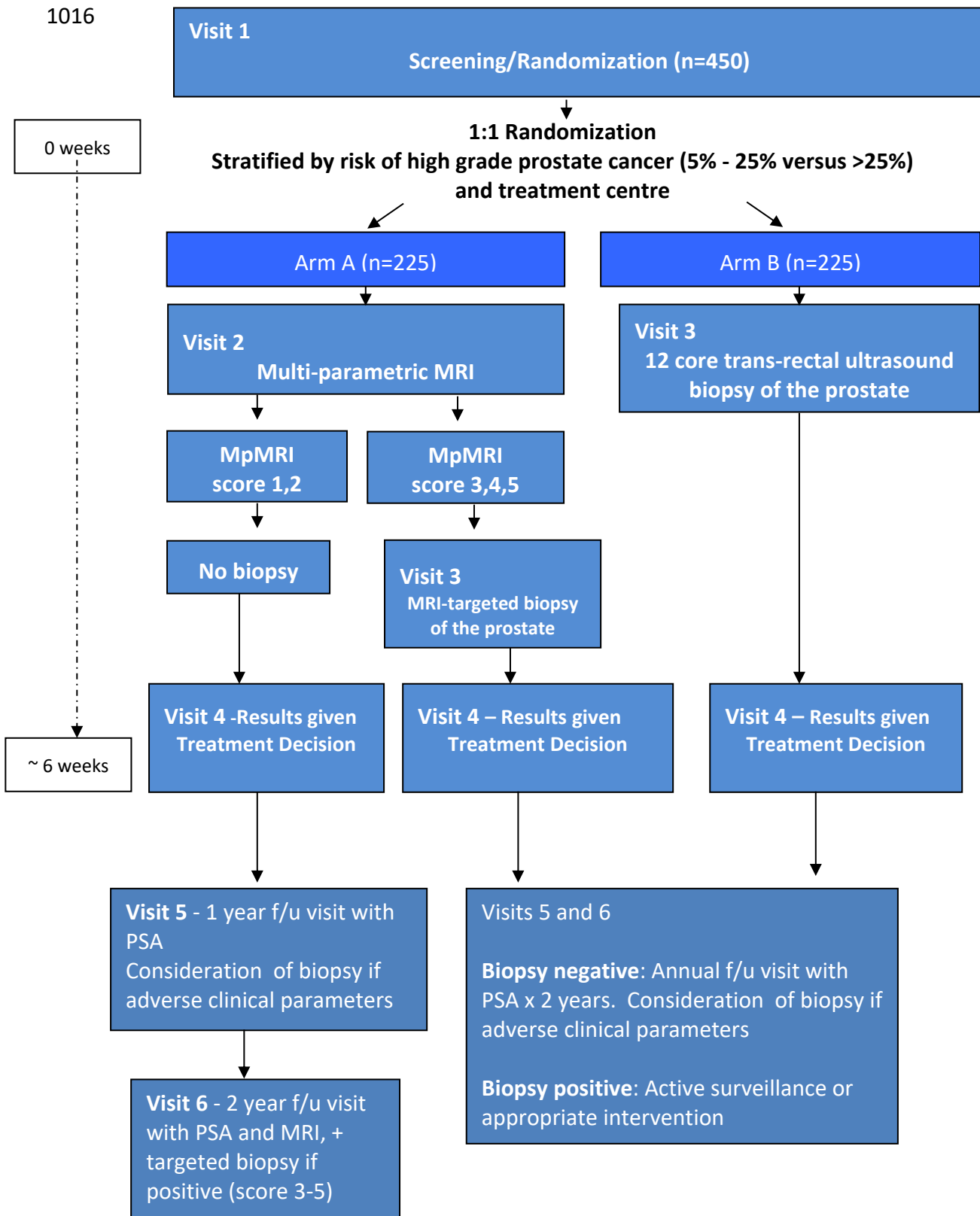
1005 **9.1 Study design**

1006 The study is a multi-centre, open-label randomized controlled trial, with men
1007 randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in
1008 Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or
1009 will be followed for two years if there is no suspicious areas identified by MRI. The
1010 unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-
1011 core systematic TRUS guided biopsy. All men in the study will be followed for two
1012 years or until they have had radical treatment (whichever comes first).

1013

1014
1015
1016

9.2 Study Trial Schema



1017 **9.3 Timeline of subject contact**

1018 Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial.
 1019 The individual pathway that each subject experiences is dependent on both the arm
 1020 he is randomized to and results of the tests.

1021

1022 **Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not**
 1023 **require a biopsy**

	Contact with Subject * all study assessments should be conducted +/- 30 days of scheduled visits				Visit 3	Visit 4 Post-Test	Visit 5 1 year follow up	Visit 6 2 year follow up
	Visit 0 Telephone consult	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3				
Weeks:	-1	0	1	2	5	52	104	
Tele-consult	X			Not required				
Consent		X						
Screening (eligibility review)		X						
Randomization		X						
EQ-5D-5L		X	X			X		X
Optional blood, urine, and semen sample ¹		X					X	X
PSA ²		X					X	X
Systematic TRUS guided biopsy								
MRI			X				X	X
MRI-Targeted Biopsy								X if target
Immediate post MRI/TRUS Fusion Biopsy Questionnaire			X					
Immediate post-biopsy questionnaire								
Follow up for results of tests						X		
Treatment decision ³						X		
30-day post-biopsy questionnaire								
30-day post MRI/TRUS Fusion Biopsy Questionnaire					X			
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							

1024 ¹ Collected at baseline, and annually.
1025 ²PSA will have been done prior to visit 1(within 3 months of randomization, but can be
1026 repeated at visit 1 if necessary.
1027 ³After treatment decision men revert to standard of care.
1028

1029
1030

Table 2: ARM A: men randomized to MRI arm who have a lesion on MRI and require a biopsy

	Contact with Subject * all study assessments should be conducted +/- 30 days of scheduled visits						Visit 5 1 year follow up	Visit 6 2 year follow up
	Visit 0 Telephone consult	Visit 1 Screening/Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post-test	Visit 5 1 year follow up		
Weeks:	-1	0	1	2	6	52	104	
Tele-consult	X							
Consent		X						
Screening (eligibility review)		X						
Randomization		X						
EQ-5D-5L		X	X	X	X		X	
Optional blood, urine and semen sample ¹		X				X	X	
PSA ²		X				X	X	
Systematic TRUS guided biopsy								
MRI			X					
MRI-Targeted Biopsy				X				
Immediate post MRI/TRUS Fusion Biopsy Questionnaire			X					
Immediate post-biopsy questionnaire				X				
Follow up for results of tests					X			
Treatment decision ³					X			
30-day post-biopsy questionnaire					X			
30-day post MRI/TRUS Fusion Biopsy Questionnaire								
AE/SAE		Complete as required at any time following registration						
Withdrawal Form		Complete as required at any time following registration						

1031 ¹ Collected at baseline and annually.

1032 ²PSA will have been done prior to visit 1, but can be repeated at visit 1 if necessary.

1033 ³After treatment decision men revert to standard of care and will be followed at year 1 and
1034 year 2.

1035
1036

Table 3: ARM B: men randomized to systematic TRUS guided biopsy arm

	Contact with Subject * all study assessments should be conducted +/- 30 days of scheduled visits							
	Visit 0 Telephone consult	Visit 1 Screening/Randomization	Visit 2	Visit 3 Biopsy	Visit 4 Post-test visit	Visit 5 1 year follow up	Visit 6 2 year follow up	
Weeks:	-1	0	1	2	6	52	104	
Tele-consult	X		Not Required					
Consent		X						
Screening(eligibility review)		X						
Randomization		X						
EQ-5D-5L		X			X	X		X
Optional blood, urine and semen sample ¹		X					X	X
PSA ²		X					X	X
Systematic TRUS guided biopsy ³					X			
MRI								
MRI-Targeted Biopsy								
Immediate post MRI/TRUS Fusion Biopsy Questionnaire								
Immediate post-biopsy questionnaire					X			
Follow up for results of tests						X		
Treatment decision ⁴						X		
30-day post-biopsy questionnaire						X		
30-day post MRI/TRUS Fusion Biopsy Questionnaire								
AE/SAE		Complete as required at any time following registration						
Withdrawal Form		Complete as required at any time following registration						

1037
1038
1039

¹ Collected at baseline and annually.
² PSA will have been done prior to visit 1 (within 3 months of randomization, but can be repeated at visit 1 if necessary).

1040 ³The biopsy must be done within one month of randomization.

1041 ⁴After treatment decision men revert to standard of care and will be followed up at year 1
1042 and year 2.

1043

1044 **10. Trial Interventions and procedures**

1045

1046 The following procedures will be applied as necessary to subjects enrolled in both
1047 arm of the trial.

1048 **10.1 EQ-5D-5L Questionnaires**

1049

1050 **For all subjects enrolled in trial**

1051 Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L
1052 questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to
1053 evaluate health related quality of life. It takes approximately 2 minutes to complete.

- 1054 • All subjects should complete the baseline questionnaire at the screening visit
1055 before leaving the department.
- 1056 • Subjects randomized into the MRI arm will be given an EQ-5D-5L questionnaire
1057 to fill out 24-48 hours following the MRI.
- 1058 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
1059 be given an EQ-5D-5L questionnaire to fill out 24-48 hours following the biopsy.
1060 Subjects will be given the questionnaire before they leave the department and
1061 the patient should take this home. Subjects can return the completed
1062 questionnaire to the investigator by post in a pre-addressed envelope provided
1063 by the investigator. It cannot be filled out immediately after the procedure in the
1064 department as it assesses domains such as washing, dressing and carrying out
1065 usual activities, which cannot be established immediately after the biopsy.
1066 Subjects will be reminded by the biopsy operator to complete the questionnaire
1067 at home and may be given a phone call by the research team to remind them to
1068 complete the questionnaire.
- 1069 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
1070 be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. If the
1071 patient was in the MRI arm and did not have a biopsy they will have been given a
1072 30-day post MRI EQ-5D-5L, which should be filled out at 30-days post MRI. The
1073 date that the patient should fill out the questionnaires should be written on top
1074 of the questionnaire. (This can also be done at Visit 4).
- 1075 • All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up
1076 visit.

1077 **10.2 Multiparametric MRI imaging procedure**

1078 **For subjects in Arm A only**

1079

1080 **10.2.1 MRI Protocol**

1081 A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic
1082 phased array coil and an automated injector system with the subject in the supine
1083 position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast

1084 enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS
1085 v2.

1086

1087 Within the specified PiRads-2 framework a common protocol will be formulated by a
1088 consensus of the radiologists involved in the trial at each site at a startup meeting.

1089 The highest agreed upon b-value image for DWI (at least 1400s/mm²) will be
1090 selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast
1091 media, injection rates and dynamic scanning temporal resolution will be matched for
1092 all sites. An optional multi b value DWI acquisition will be undertaken as well to
1093 allow for ancillary studies into non log linear apparent diffusion coefficient (ADC)
1094 models for tumor characterization.

1095 **10.2.2 MRI reporting**

1096 The MRI will be reported by an experienced radiologist using the MRI Reporting
1097 Proforma (See Appendix 2) to be filed in the study folder. The subject's clinical
1098 details such as PSA and DRE results will be available to the radiologist. The MPMRI
1099 will be scored based on the PI-RADS v2 scoring system [2].

1100

1101 Lesions in the prostate will be scored on the following scale:

1102 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
1103 present)

1104 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

1105 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
1106 equivocal)

1107 PI-RADS 4 – High (clinically significant cancer is likely to be present)

1108 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
1109 present)

1110 An additional category will be added called PI-RADS 3M. This is a bilateral diffuse
1111 multifocal pattern of restricted diffusion and low or intermediate T2 signal in the
1112 peripheral zone without a clearly definable lesion with a concomitant PSA density of
1113 >0.15 based on an MRI volume calculation.

1114

1115 The location of the suspicious areas in the prostate should be marked on a diagram
1116 of the prostate (see Appendix 2) and the sector numbers containing each suspicious
1117 area should be recorded in the case report form.

1118

1119 Imaging interpretation will be carried out at each site, however ensuring consistency
1120 and quality of imaging interpretation is crucial. A central imaging site will be
1121 designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site
1122 will perform the interpretation of all images for that site. The designated radiologist
1123 must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2. A
1124 startup meeting involving all radiologists will be held prior to start of accrual where
1125 each site will bring 5 MRI cases performed at their site for consensus review, scoring
1126 and discussion. This will provide a commonality of approach to interpretation among
1127 the radiologists before the study begins. After this startup meeting each site will
1128 send one set of MRI images and its interpretation for central review for site
1129 qualification.

1130

1131 A copy of all images will be sent on CD to the central site for archiving.

1132 **10.3 Immediate post MRI/TRUS Fusion Biopsy questionnaire**

1133 **For subjects in Arm A only**

1134 A modified version of a self-reported questionnaire validated previously [39] will be
1135 completed immediately post-MRI (Appendix 5). The subject should complete the
1136 immediate post-MRI questionnaire before they leave the department.

1137 **10.4 No target identified on MPMRI (PiRads 1 or 2)**

1138 **For subjects in Arm A only, who do not require a biopsy**

1139 Men who have MRIs that do not identify any suspicious lesion will not receive a
1140 biopsy. These subjects will benefit from being part of the trial as a result of not
1141 having to undergo an invasive biopsy procedure, avoiding the discomfort associated
1142 with the procedure, the risk of being diagnosed with clinically insignificant cancer
1143 and the risk of sepsis associated with the biopsy procedure. Studies suggest that if
1144 the MRI does not identify areas suspicious for cancer there is an 85-95% chance that
1145 clinically significant cancer is not present [28, 34, 35].

1146
1147 As soon as the results of the MRI are discussed with the subject, their treatment
1148 decision will be recorded and they will return to standard of care management. As
1149 part of standard of care these subjects can undergo further PSA surveillance and / or
1150 prostate biopsies if indicated.

1151 **10.5 30 Day Post-MRI/TRUS Fusion Biopsy questionnaire (PiRads 1 or 2)**

1152 1153 **For subjects in Arm A only, who do not require a biopsy**

1154 If an MRI does not identify any suspicious areas and a decision for no biopsy has
1155 been made, a 30-day post MRI questionnaire should be given to the subject
1156 (Appendix 6). This is a modified version of a self-reported questionnaire validated
1157 previously [39]. Though the side effects typically seen after prostate biopsy are not
1158 expected after an MRI alone, it is important to ensure that this data is captured to
1159 allow both arms to be compared.

1160
1161 This questionnaire should be completed at 30-days post-MRI.

1162
1163 **If the subject is to undergo a biopsy as part of the trial protocol, they do not need**
1164 **to complete the post-MRI 30-day questionnaire as a specific 30-day post-biopsy**
1165 **questionnaire should be completed instead.**

1166 **10.6 MRI-Targeted biopsy**

1167 **For subjects in Arm A who do require a biopsy**

1168 **10.6.1 MRI choice of targets for targeted biopsy**

1169 Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will
1170 subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in
1171 MRI-targeted biopsy. Operator experience (number of targeted biopsies performed

1172 to date) will be recorded before each procedure. The number of biopsy operators
1173 should be kept to the minimum number possible.

1174

1175 Targets will be stratified by PI-RADS score and if the same score then by size and
1176 labeled T1, T2, T3...etc. If there are more than 3 lesions with a score of 3 or more
1177 only T1-T3 will be targeted. The radiologist should record the sectors involved with
1178 tumor in order of most to least involved using the PI-RADS v2 sector scheme.

1179 The number of biopsy operators should be kept to the minimum number possible.
1180

1181 Patients in the MRI cohort will not have systematic biopsies, with one exception.
1182 Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small
1183 volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core
1184 biopsy will be conducted.

1185 **10.6.2 MRI Biopsy**

1186 The procedure will be performed in the outpatient departments of sites possessing
1187 the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An
1188 operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI
1189 fusion system at their institution before they are qualified to participate as an
1190 operator in the study.

1191

1192 Coumarin anticoagulant, clopidogrel treatment and other relevant
1193 anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and
1194 advice sought as to appropriate substitutes if indicated. Aspirin will be continued at
1195 the discretion of the physician doing the biopsy.

1196

1197 Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will
1198 be performed via the trans-rectal route or via the trans-perineal route depending
1199 upon local practice.

1200

1201 Targeted biopsies should be performed by software-assisted fusion devices (i.e.
1202 (Artemis, made by Eigen, or Urostation, by Koelis) [34, 36, 37, 40, 41]. This software
1203 is safe and poses no risks to the subject since the same CE-marked ultrasound
1204 probes that are designed to perform the biopsy when performed as standard of care
1205 biopsy are used during targeted biopsy. Should the operator wish to not use the
1206 information provided by the software registration system and use cognitive (visual)
1207 registration alone they can do so, but should indicate this on the subject's case
1208 report form.

1209

1210 The samples per target will be 4 cores spread across the target region for a
1211 maximum total of 12 cores as a maximum of 3 targets can be identified. Biopsies
1212 should be conducted in order meaning T1 then T2 then T3.

1213

1214 Biopsy cores from different suspicious areas will be aliquoted separately. The vials
1215 will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there
1216 are) which should match the assignment of suspicious areas by the radiologist on the
1217 MRI report. The order of lettering a-d should match the order in which the biopsies
1218 were performed in each region. The first biopsy should be at the center of the target

1219 and the remaining fanning out from the center. Each core from the same suspicious
1220 area must be submitted separately. Alternative methods of storing cores that allow
1221 identification of the order of score samples from each target are acceptable.

1222 **10.7 Systematic TRUS guided biopsy**

1223 **For all subjects in Arm B**

1224 Systematic TRUS guided biopsy is the current standard of care for the diagnosis of
1225 prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local
1226 site of recruitment.

1227

1228 A clinician competent in systematic TRUS guided biopsy will perform the procedure.
1229 The experience of the operator (number of systematic TRUS guided biopsies
1230 performed to date) will be recorded prior to each procedure. Software that guides
1231 clinicians in placing biopsy cores should not be used.

1232

1233 Coumarin anticoagulant, clopidogrel treatment and other relevant
1234 anticoagulant/antiplatelet medication will be discontinued 5 to 10 days before
1235 biopsy and advice sought as to appropriate substitutes if indicated. Aspirin will be
1236 continued at the discretion of the physician doing the biopsy.

1237

1238 The patient will be positioned in left lateral position. 10-12 core biopsies will be
1239 taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed
1240 to the peripheral zone (See Appendix 3 for standardized method for conducting 12-
1241 core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be
1242 given as per local guidelines.

1243 **10.8 Pathology**

1244 The 2005 International Society of Urological Pathology guidelines for Gleason
1245 Grading of Prostatic Carcinoma will be followed [43].

1246

1247 For men undergoing MRI-targeted biopsy it is required that pathology reported per
1248 suspicious area targeted and per targeted core. For systematic TRUS guided biopsy,
1249 each core will be reported and graded. As there are variations across sites in
1250 methods for determination of maximum cancer core length (MCCL) of a single core,
1251 MCCL will be reported by both of commonly used methods, measurement with and
1252 without the benign intervening stroma.

1253 **10.9 Post-procedural care**

1254 **For all subjects in ARMS A and B receiving a biopsy**

1255 After a biopsy procedure the patient can be discharged. The subject will be given
1256 advice and a leaflet on what to expect post-procedurally and when to contact a
1257 healthcare professional if concerned. Subjects will be given a follow-up appointment
1258 within 2-3 weeks for results of the histopathology and treatment options to be
1259 discussed.

1260 **10.10 Immediate post-biopsy questionnaire**

1261 **For all subjects in ARMS A and B receiving a biopsy**

1262 A modified version of a self-reported questionnaire validated previously [39] in the
1263 assessment of post-biopsy complications will be completed immediately post-biopsy
1264 after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject
1265 should complete the immediate post-biopsy questionnaire before they leave the
1266 department. It aims to assess intensity of discomfort and pain associated with the
1267 procedure.

1268 **10.11 30-day post-biopsy questionnaire**

1269 **For all subjects in ARMS A and B receiving a biopsy**

1270 A modified version of a self-reported questionnaire validated previously [39] in the
1271 assessment of post-biopsy complications at 30 days post-biopsy should be given to
1272 all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home
1273 (Appendix 8). The patient should fill this out on day 30 following the procedure. It
1274 should take 5 minutes to fill out. The date that the participant should complete the
1275 questionnaire should be written on top of the questionnaire. Data on specific biopsy-
1276 related complications including pain, fever, hematuria, hematochezia,
1277 hematospermia, urinary retention and urinary incontinence will be recorded. Any
1278 other adverse events will not be recorded. Contact with healthcare and resource
1279 used data following the biopsy will also be ascertained. The completed questionnaire
1280 can be returned to the investigator in a pre-addressed envelope.

1281
1282 Subjects will be called at 30 days to remind them to complete this questionnaire.

1283 **10.12 30-day post Intervention EQ-5D-5L Questionnaire**

1284 Subjects undergoing systematic TRUS guided biopsy or MRI-TB will be given an EQ-
1285 5D-5L questionnaire to fill out at 30-days post biopsy. If the subject was in the MRI
1286 arm and did not have a biopsy they will have been given a 30-day post MRI EQ-5D-
1287 5L, which should be filled out at 30-days post MRI, or can be done at Visit 4. The date
1288 that the patient should fill out the questionnaires should be written on top of the
1289 questionnaire.

1290
1291 Subjects will be called at 30 days to remind them to complete this questionnaire. The
1292 completed questionnaire can be returned to the investigator in a pre-addressed
1293 envelope.

1294 **10.13 Results and treatment decision (Visit 4)**

1295 The results of the biopsies and/or MRI will be explained to the patient by the clinical
1296 care team during this visit, which is approximately 2-3 weeks after the biopsy.

1297 The research team should record the treatment decision in the patient file.

1298 Possibilities for treatment decision include but are not limited to:

- 1299 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 1300 • Active Surveillance
- 1301 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 1302 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 1303 • Hormone therapy

1304 **10.14 Follow up period**

1305 All study participants will be followed up for up to two years or until they have
1306 radical treatment. Each year, subjects will be surveyed to obtain the following
1307 information:

- 1308 • time to cancer diagnosis
- 1309 • Gleason score progression
- 1310 • time to intervention on active surveillance
- 1311 • time on active surveillance
- 1312 • PSA
- 1313

1314 **10.14.1 Indications for biopsies off protocol**

1315 For patients who are not biopsied due to a negative MRI, have negative or non-
1316 significant systematic biopsies, or who have a positive MRI but no or non-significant
1317 cancer on targeted biopsy, the following are guidelines for patients management
1318 during the 2 year follow up period.

1319 It is an accepted standard of care in Ontario for patients on active surveillance or
1320 with a prior negative biopsy who have a worsening risk profile to undergo mpMRI
1321 followed by targeted biopsy. We propose the following guidelines for risk profile
1322 assessment and consideration of repeat biopsy

1323 Patients should continue to be followed with semi-annual PSA and DRE. A biopsy
1324 should be considered under one or more of the following circumstances:

- 1325 1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.
- 1326 2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase
1327 in PSA in 1 year.
- 1328 3. Biopsy if a doubling of the risk of high grade cancer according to the NCI
1329 nomogram.
- 1330 4. Biopsy if development of a suspicious nodule on DRE.
1331
- 1332 5. For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy
1333 which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or
1334 more increase in PSA over 1 year or a PSA density > 0.15.
1335
- 1336 6. For men on the systematic biopsy arm which was negative or showed only
1337 Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or
1338 a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these
1339 patients.

1340
1341
1342
1343

These are guidelines and should be interpreted with clinical judgment.

1344 Follow-up will cease once treatment beyond active surveillance is undertaken
1345 (prostatectomy, radiation therapy, focal therapy, etc.)
1346 PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI
1347 identifies a target.

1348 **10.15 Additional tests for biomarker discovery - Optional**

1349 Though not related to the primary outcome of this study, this cohort represents a
1350 unique opportunity to obtain human samples for future biomarker discovery studies.
1351 Participants will be consented to provide a blood, urine and semen sample after the
1352 consent and screen visit for storage and use in future biomarker studies. In addition,
1353 men will be consented for use of the prostate biopsy tissue in the biomarker
1354 discovery studies.

1355
1356 We propose two initial biomarker analyses for men recruited to the PRECISE study.
1357 First we propose testing the utility of existing validated tests, these potentially
1358 include the Genomic Prostate Score (Oncotype Dx) [44] and a recently developed
1359 multiple Kallikrein biomarker test [45]. We will test the hypothesis that alongside
1360 conventional PSA measurements, the multiple Kallikrein test or other serum
1361 biomarker test, may identify subjects whose MRI was initially negative for prostate
1362 cancer, but who are at high risk of harboring clinically significant disease as detected
1363 by the secondary MRI at 2 years. We will also test the association between serum
1364 biomarkers and clinically significant or clinically insignificant prostate cancer
1365 detected during the PRECISE study. We will also explore the potential for the
1366 Genomic Prostate Score to provide additional information over and above Gleason
1367 grade. These studies will be separately funded from PRECISE.

1368
1369 Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will
1370 be planned to assess markers which might identify men at higher risk of developing
1371 prostate cancer.

1372 **10.15.1 Samples to be collected for future biomarker discovery work** 1373 **(Optional)**

1374 Participants will be consented to provide a blood, urine and semen sample after the
1375 consent and screen visit for storage and use in future biomarker studies. Samples
1376 include:

- 1377 • Blood –10mls serum, 10mls plasma, 5mls whole blood, 5mls buffy coat
- 1378 • Urine – 50mls urine
- 1379 • Semen-1-5 cc (single ejaculate)

1380 This will involve a separate patient information form and consent form.

1381 **10.16 Long-term data linkage – Permission to Contact**

1382 The cohort of men who consent to participate in this study represent a uniquely
1383 characterized group. Their long-term outcomes will contribute to our understanding
1384 of the epidemiology of prostate cancer beyond the questions being addressed in this
1385 study.

1386

1387 Permission to Contact (PTC) is a feasible mechanism to engage subjects in research
1388 programs. This will allow researchers to contact study participants in the future to
1389 assess their willingness to respond to questionnaires. This potentially enables
1390 research that would complement the planned long-term follow up in terms of health
1391 status, for obtaining information about future biopsies not included in the study, and
1392 allow assessment of quality of life.

1393 **10.17 End of Study**

1394 The end of study assessment comprises an essential safety evaluation that should be
1395 completed prior to discharging any subject from the study.

- 1396 • Adverse events;
- 1397 • PSA measurement;
- 1398 • EQ-5D-5L questionnaire;
- 1399 • An MRI in those who did NOT have a biopsy;
- 1400 • Complete CRF.

1401 **10.18 Risks and Benefits to Participants**

1402 An important consideration of this study is that men are being randomized to one of
1403 two biopsy techniques when it is not known which will be more effective. Both
1404 diagnostic tests are currently used in clinical practice at the institutions involved in
1405 the trial. Though systematic TRUS guided biopsy could be considered standard of
1406 care, there is enough evidence to support the concept that MRI-targeted biopsy may
1407 be at least as effective as systematic TRUS guided biopsy[27].

1408 **10.18.1 Risks to subjects**

1409 The intervention proposed in this trial (MRI-biopsy) do not offer participants any
1410 more risk than if they underwent standard of care (systematic TRUS guided biopsy)
1411 for the diagnosis of prostate cancer.

1412 **10.18.1.1 Risk of Systematic TRUS guided biopsy**

1413 Systematic TRUS guided biopsy can be associated with discomfort, haematuria,
1414 haematospermia and dysuria in a large proportion of subjects, which is self-resolving
1415 (See Table 4). There is a 4% risk of systemic urosepsis [46]. To minimize this risk,
1416 urine dipstick and/or microscopy, culture and sensitivity will be checked to ensure
1417 that men are infection-free prior to undergoing biopsy.

1418 **10.18.1.2 Risks of MPMRI**

1419 MRI is associated with few risks. It is a safe procedure used in everyday clinical
1420 practice (See Table 4). Small risks of allergic reactions are associated with the
1421 intravenous administration of gadolinium, the contrast agent used in MRI scans. The
1422 study uses a low molecular weight Gd chelate as a contrast agent (Gadovist, Bayer,
1423 gadobutrol – generic). This contrast agent is used routinely for contrast enhanced
1424 MRI and is approved by Health Canada. Patients will be screened for any
1425 contraindications to Gd injection or to MRI as per current clinical Dept of Medical
1426 Imaging protocols at each institution. The commonest reported sides effects are of
1427 limited duration and mild to moderate in intensity and include headache,
1428 vasodilation, injection site pain, nausea, dizziness, rash, and dyspnea. The incidence

1429 of these are < 1%. Severe life threatening reactions such as severe anaphylaxis occur
 1430 very rarely, about 1:10,000-1: 100,000. These are treatable with epinephrine and
 1431 steroids. The risk of death is <1:100,000. There is a known risk of nephrogenic
 1432 systemic fibrosis, a potentially fatal condition in patients with impaired renal
 1433 function, with an eGFR <30ml/min/1.73m². These patients are ineligible for this
 1434 study.

1435 **10.18.1.3 Risks of MRI-targeted biopsy**

1436 MRI-targeted biopsy is associated with similar risks to the standard of care
 1437 systematic TRUS guided biopsy. As fewer biopsy cores are being taken with MRI-
 1438 targeted biopsy, the theoretical risk of adverse events associated may be less than
 1439 that of systematic TRUS guided biopsy. In addition, as a proportion of men may not
 1440 require a biopsy (approximately 30%) on a group level there will be reduced number
 1441 of men experiencing these complications, which is one of the major advantages of an
 1442 MRI-based approach.

1443

1444 **Table 4: Adverse events associated with procedures**

1445

Procedure Side Effect	Systematic TRUS guided biopsy (Standard of care)	MRI	MRI-targeted biopsy
Pain / discomfort	Some have discomfort Some have pain	Intravenous cannulation (to allow contrast administration) can cause minimal discomfort	Similar / reduced compared to systematic TRUS guided biopsy
Dysuria	Majority have dysuria (self-resolving in 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematuria	Majority (self-resolving, 2- 3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematospermia	Majority (self-resolving, 1- 2 weeks)	No	Similar / reduced compared to systematic TRUS guided biopsy
Erectile dysfunction	30% (self resolving after 1- 2 months)	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary Tract infection	1-8 %	No	Similar / reduced compared to systematic TRUS guided biopsy
Systemic urosepsis	2-4%	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary retention	1%	No	Similar / reduced compared to systematic TRUS guided biopsy
Contrast allergy	N/A	Rare < 1 in 10000 – severe allergic reaction (breathing problems) < 1 in 2000 – moderate allergic reaction (nausea	N/A

		and vomiting) < 1 in 250 – mild allergic reaction (rash, itching)	
Adverse effects of antibiotics	Rare <1%	N/A	Rare <1%

1446

1447 **10.18.2 Benefits to subjects**

1448 Subjects enrolled in this trial will benefit from the following:

- 1449 • Subjects in both arms may benefit from receiving a diagnostic test for suspected
1450 prostate cancer and will receive further treatment if required. The research team
1451 will also ensure streamlined diagnostic investigations to promptly conduct the
1452 diagnostic test and communicate the test outcome for the patient.
- 1453 • Subjects enrolled in the trial will benefit from the dedicated research team
1454 involved in their care in addition to the clinical team normally involved in their
1455 care.
- 1456 • Subjects will benefit from additional discussions regarding the trial, which could
1457 increase their understanding of prostate cancer and help them to make a more
1458 informed decision about their health.
- 1459 • Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will
1460 remove any risk of post-biopsy infection. MRI-randomized subjects may also
1461 benefit from a reduced probability of having a clinically insignificant prostate
1462 cancer diagnosed. Clinically insignificant prostate cancer is often treated
1463 definitively per patient preference despite the lack of evidence supporting the
1464 need. All definitive local therapies for prostate cancer carry the risk of peri-
1465 operative complications as well as long-term risk of incontinence and erectile
1466 dysfunction.
1467

1468 **10.19 Concomitant medications**

1469 **10.19.1 Permitted Medications**

1470 All concomitant medications taken during the study will be recorded in the CRF with
1471 indication, dose information and dates of administration. The definition of which
1472 medication would be considered outside the routine medical practice is up to the
1473 discretion of the investigator. All dietary and herbal supplement usage will be
1474 recorded in the CRF.

1475 **10.19.2 Non-Drug Therapies**

1476 Any occurrence of prostate-related surgical and/or non-surgical (or minimally
1477 invasive) intervention during the conduct of the study will be recorded in the CRF.
1478

1479 **11. Schedule of Study Visits**

1480 **11.1 Visit 0 (Telephone Consult): Telephone consult**

1481 **For all subjects enrolled in trial**

1482 The purpose of this visit is to provide potential subject with the information about
1483 the study. Interested subjects will have an opportunity to discuss the study with
1484 their investigator.

1485
1486 This will occur any time from referral letter being received to the first hospital visit.
1487 Ideally, this will be performed as soon as possible following receipt of referral.
1488 Not all men have an opportunity to get a teleconsult prior to Visit 1. If this is the
1489 case, then these men may still be included in the study.

1490 **11.2 Visit 1 (Screening/Randomization): Screening, Consent,
1491 Randomization**

1492 **For all subjects enrolled in trial**

1493 Screening will occur any time following the referral of the subject. Ideally, this will be
1494 performed as soon as possible following receipt of referral.

1495 Subjects will be consented only after they have had time to consider the study. This
1496 may happen on the same visit as the screening visit.

1497 Randomization will happen immediately after the consent form is signed.

1498

1499 Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L
1500 questionnaire (Appendix 4), which is a validated 2-page questionnaire representing
1501 health related quality of life. It takes approximately 2 minutes to complete. This
1502 questionnaire should be completed at the screening visit before the subject leaves
1503 the clinic.

1504

1505 If a subject agrees to the optional informed consent, from randomization until any
1506 point prior to a biopsy, optional blood, urine and semen samples will be collected for
1507 correlative studies.

1508

1509 Even if PSA testing was done prior to Visit 1, PSA should be obtained at Visit 1.

1510

1511 **11.3 Visit 2 (MRI): ARM A, for men randomized to MRI**

1512 This will occur ideally within one week of randomization. Men will receive an MRI
1513 (see Section 10.2.) Men will complete an Immediate post MRI Questionnaire
1514 (Appendix 5) be completed within 24 hours of MRI, ideally immediately after MRI
1515 prior to leaving department and an EQ-5D-5L Questionnaire (Appendix 4) to be
1516 completed 24-48 hours post-MRI.

1517 **11.4 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate**

1518 **For men randomized to ARM A, who have a lesion identified by MRI.** This
1519 appointment will follow one-two weeks of MRI.

1520

1521 Depending on local Urology service structure, an appointment for a biopsy may need
1522 to be booked at the same time as the MRI is booked (i.e. immediately after
1523 randomization) in order for a biopsy to occur in timely fashion. If the results of the
1524 MRI show that a biopsy is not required, then the biopsy appointment can be used
1525 instead of Visit 4 for follow up of results and treatment decision.

1526
1527 Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy
1528 of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy
1529 Questionnaire (Appendix 7) ideally completed and returned immediately after a
1530 biopsy, before the subject leaves the department. In addition, subject needs to
1531 complete an EQ-5D-5L Questionnaire (Appendix 4) 24-48 hours post-biopsy.

1532
1533 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
1534 and complete as instructed on day 30 post-biopsy. This is to be returned by post or
1535 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
1536 biopsy then this questionnaire can be given to the research team when 30 days is
1537 finally complete. If Visit 4 is on or later than 30 days then this can be returned at the
1538 Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-
1539 biopsy, it will be acceptable, however, the questionnaire should be completed as
1540 close as possible to 30 days post-biopsy.

1541
1542 At 30-days post biopsy interval, a member of the research team will call the subject
1543 to remind them to complete and return the 30-day questionnaires.

1544 **11.5 Visit 3 (Biopsy): ARM B, for men randomized to a systematic** 1545 **TRUS-biopsy**

1546 **For men randomized to ARM B only.**

1547
1548 This will occur within four weeks of randomization. Men will receive a standardized
1549 TRUS-guided biopsy (see Section 10.7.) Men will complete an Immediate Post Biopsy
1550 Questionnaire (Appendix 7) ideally completed and returned immediately after the
1551 biopsy. In addition, subject needs to complete an EQ-5D-5L Questionnaire (Appendix
1552 4) 24-48 hours post-biopsy.

1553
1554 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
1555 and completed as instructed on day 30 post-biopsy. This is to be returned by post or
1556 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
1557 biopsy then this questionnaire can be given to the research team when 30 days is
1558 reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
1559 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it
1560 will be acceptable, however the questionnaire should be completed as close as
1561 possible to 30 days post-biopsy.

1562
1563 At 30-days post biopsy a member of the research team will call the subject to remind
1564 them to complete and return the 30-day questionnaires.

1565 **11.6 Visit 4 (Post-test follow up): ARM A, for men who did not receive a**
1566 **biopsy**

1567 This appointment will include a follow up meeting with the investigator to discuss
1568 the results of the MRI as well as treatment decisions. This follow up should occur
1569 after the availability of the MRI report. At this visit the subject will also complete a
1570 30-day post intervention EQ-5D-5L Questionnaire.

1571
1572 Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8), which has
1573 been posted to them by the research team. If Visit 4 is earlier than 30 days post MRI
1574 then this questionnaire can be given to the research team when 30-days is finally
1575 complete. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
1576 appointment. As long as questionnaire is completed at 30-60 days post-MRI, it will
1577 be acceptable, however the questionnaire should be completed as close as possible
1578 to 30 days post-MRI.

1579
1580 At 30-days post MRI, a member of the research team will call the subject to remind
1581 them to complete the 30-day questionnaires.

1582 **11.7 Visit 4 (Post-test follow up): For all men who received a biopsy**

1583 This appointment will include a follow up meeting with the investigator to discuss
1584 the results of the biopsy as well as treatment decisions. This should be completed as
1585 soon as possible following the availability of any pathology results. The follow up
1586 appointment should be within 1 month of the biopsy. Depending on local Urology
1587 service structure, these results may need to be discussed at an MDT meeting to
1588 inform treatment decision.

1589

1590 The research team should record the treatment decision in the patient file.

1591

1592 Possibilities for treatment decision include but are not limited to:

- 1593 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 1594 • Active Surveillance
- 1595 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 1596 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 1597 • Hormone therapy

1598

1599 At this visit the subject will also receive a 30-day post intervention EQ-5D-5L
1600 Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy
1601 questionnaire (Appendix 8), which has been posted to them by the research team.
1602 The questionnaire needs to be completed on the 30th day post-intervention (i.e. post
1603 biopsy). However it will be accepted if completed up to 72 hours prior to or after the
1604 30th day. A telephone reminder from the research team to the subject can take
1605 place.

1606

1607 **11.8 Visit 5 (1 year follow up): 52 week follow up**

1608 All subjects are planned to have a 52 week follow up visit.

1609 Subjects will be followed to obtain the following information on an annual basis:

-
- 1610
- time to cancer diagnosis;
- 1611
- Gleason score progression;
- 1612
- time to intervention on active surveillance;
- 1613
- time on active surveillance;
- 1614
- results of PSA tests.
- 1615
- Time to followup biopsy and/or mpMRI if performed (see followup
- 1616
- guidelines)
- 1617
- Indication for followup biopsy
- 1618
- Was MRI performed prior to followup biopsy
- 1619
- Was the biopsy systematic, targeted only or both systematic + targets, not
- 1620
- done because of negative MRI

1621

1622 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy

1623 will have an additional MRI at Visit 6 (year 2).

1624 **11.9 Visit 6 (2 year follow up): End of study**

1625 All study participants will be followed for up to two years or until they undergo

1626 radical treatment

1627 Subjects will be followed to obtain the following information on an annual basis:

- 1628
- time to cancer diagnosis;
- 1629
- Gleason score progression;
- 1630
- time to intervention on active surveillance;
- 1631
- time on active surveillance;
- 1632
- results of PSA tests.
- 1633
- Time to followup biopsy and/or mpMRI if performed (see followup
- 1634
- guidelines)
- 1635
- Indication for followup biopsy
- 1636
- Was MRI performed prior to followup biopsy
- 1637
- Was the biopsy systematic, targets only or both systematic + targets,
- 1638
- not done because of negative mpMRI

1639

1640

1641 Follow-up will cease once treatment beyond active surveillance is undertaken

1642 (prostatectomy, radiation therapy, focal therapy, etc.).

1643

1644 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy

1645 will have an additional MRI at Visit 6.

1646

1647 **12. Randomization**

1648 **12.1 Randomization Procedure**

1649 Written informed consent will be obtained from all eligible subjects prior to

1650 commencing any study related procedures. The Ontario Clinical Oncology Group

1651 (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre,

1652 Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate

1653 subject randomization. Subjects will be allocated to the two treatment arms in an
1654 approximate 1:1 ratio by use of a dynamic allocation scheme [47].

1655

1656 After documentation of written informed consent and confirmation of subject
1657 eligibility, clinical centres will randomize the subject by accessing the CMC's web-
1658 based Interactive Registration/Randomization System (IRIS). Prior to randomization
1659 and treatment allocation, the subjects' individualized risk of high-grade prostate
1660 cancer, obtained using the PCPTRC 2.0 calculator found at
1661 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> must be determined.

1662 **12.2 Stratification**

1663 Eligible, consenting subjects will be stratified by: (1) individualized risk of high-grade
1664 prostate cancer (5% to 25%, >25%); and (2) clinical centre

1665 **12.3 Blinding and measures taken to avoid bias**

1666 This study is unblinded, and all subjects will be aware of the treatment that they are
1667 receiving. As the MRI scan is unique to one of the arms it will not be possible to blind
1668 the participants or investigators as to what intervention is being received. Therefore,
1669 participants will be informed which arm they have been allocated to. Where
1670 possible, the data will be coded so as to blind individuals analyzing the data from
1671 which of the groups the data was from. Summary details of randomized allocation
1672 and outcomes will not be made available (unless specifically authorized by the Trial
1673 Steering Committee and/or Data Monitoring Committee) in order to maintain the
1674 overall blind of the trial.

1675

1676 Radiologists will not be blinded to patient information (e.g. PSA level) as
1677 international guidelines recommend that this should be available to them [48].

1678 Radiologists will be aware that the patient is part of the trial. Radiology images are
1679 stored on the hospital database.

1680

1681 Pathologists will be blinded to the cohort allocation. Concealment may be
1682 challenging due to the different number of cores in the two groups, but this is
1683 unavoidable. This is unlikely to represent a significant source of bias.

1684

1685

1686 **13. Data**

1687

1688 Type of data to be collected:

- 1689 • EQ-5D–5L questionnaires. These will measure quality of life and will be measured
1690 continuously throughout the trial.
- 1691 • Systematic TRUS guided biopsy – pathology – categorical (e.g. Gleason grade)
1692 and continuous data (e.g. maximum cancer core length)
- 1693 • MRI – diagram representing MRI; categorical data for areas and scores of
1694 suspicion (e.g. Sector 1p, score of suspicion 4/5)
- 1695 • MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and
1696 continuous data (e.g. maximum cancer core length)

-
- 1697 • Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers
 - 1698 yes/no)
 - 1699 • Treatment decisions – categorical data (e.g. radical treatment)
 - 1700 • PSA – continuous data (e.g. value of PSA in ng/ml)

1701

1702 Please see **Appendix 1** for the time window for data collection.

1703

1704 **14. Statistical Considerations**

1705 **14.1 Sample Size Calculation**

1706 **STATISTICAL methods**

1707 **Primary Analysis**

1708 Absolute differences in the proportion of clinically significant cancer detected
1709 between arms will be calculated and compared using the Clopper-Pearson method.
1710 If the lower boundary of an one-sided, 97.5% confidence interval for the difference
1711 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less
1712 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower
1713 bound is greater than zero, superiority can be claimed.

1714

1715 A supportive analysis will be performed by using a logistic regression model,
1716 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification
1717 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of
1718 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower
1719 bound was calculated to approximate an absolute 5% difference of interest (NOTE:
1720 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

1721

1722 **Secondary Analyses**

1723 For each secondary outcome, where appropriate, a difference in proportions with
1724 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.
1725 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for
1726 time-to-event outcomes.

1727

1728 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
1729 differences between allocation arms in secondary outcomes. Logistic regression and
1730 Cox proportional hazards regression will be used to examine the effect of allocation
1731 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
1732 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
1733 adjustments will be made due to multiple testing, however, results for secondary
1734 outcomes will be interpreted cautiously, acknowledging that tests were performed
1735 on secondary outcomes and numerous secondary tests were performed. Figures and
1736 tables will be used to illustrate results of interest.

1737

1738 **Treatment Allocation and Stratification**

1739 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
1740 use of a dynamic allocation scheme. Specifically, the first 20 patients will be
1741 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 patients, a
1742 biased coin method will be used, whereby the number of patients within each

1743 stratum will be calculated, and the next eligible patient will be allocated (with
1744 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
1745 allocation to each arm will occur with probability $p=0.5$.

1746

1747 Stratification

1748 For treatment allocation, the subjects' individualized risk of high-grade prostate
1749 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
1750 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
1751 subjects will be stratified by:

- 1752 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);
1753 (2) clinical centre.

1754

1755 **Sample Size**

1756 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
1757 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
1758 50% from another study [36].

1759

1760 Rates of clinically significant cancer detection from one the largest studies of
1761 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
1762 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will
1763 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
1764 systematic TRUS guided biopsy.

1765

1766 For this study, it will be conservatively hypothesized that systematic TRUS guided
1767 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
1768 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
1769 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
1770 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
1771 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
1772 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
1773 choice of 5% as the margin of non-inferiority represents a difference that would be
1774 considered clinically important.

1775

1776 Thus total men required in study = **422**.

1777

1778 To account potential withdrawal / loss to follow up and the effect of stratification,
1779 the sample size will be inflated by 5%, and a target of **450 men** will be recruited.

1780

1781 Note that the rate of clinically significant cancers is very dependent on the
1782 population registered for this study. It is possible that fewer (or more) subjects will
1783 have clinically significant cancers than what is initially hypothesized. However, if the
1784 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
1785 biopsy detection rate is <30%) and other statistical assumptions remain as stated
1786 previously, the statistical power will increase. The minimum statistical power would
1787 be obtained if the clinically significant cancer detection rate was 45% for systematic
1788 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
1789 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
1790 rate of clinically significant cancer in the population is miss-specified, assuming an

1791 absolute difference of 10% between targeted and systematic TRUS guided biopsy
1792 detection rates, and a 5% margin of non-inferiority.

1793

1794 **Statistical Conventions**

1795 For categorical data, tables will be presented showing the n and percentage
1796 (n/N*100%) of patients. Analyses will be presented by study allocation arm
1797 separately.

1798

1799 Duration of time will be described in either years, months or weeks, and calculated
1800 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or
1801 X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date –
1802 date of birth + 1)/365.25.

1803

1804 Transformations of the data in order to meet statistical assumptions may be
1805 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
1806 assess any of the model fittings. All the statistical analysis will be carried out using
1807 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. ([www.r-](http://www.r-project.org)
1808 [project.org](http://www.r-project.org)) or higher.

1809

1810 **Missing Data**

1811 Missing values for the primary endpoint will be examined closely. Sources and
1812 reasons for the absence of data incurred as a result of subjects lost-to-follow up,
1813 dropouts, and intermittent missing values will be described and explored by various
1814 summary statistics as well as graphical displays between the two allocation arms.
1815 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
1816 those subjects will be described by allocation arm and tested using Fisher's exact
1817 tests or Wilcoxon rank sum tests.

1818

1819 Missing data for secondary endpoints will be described. The methods for evaluating
1820 missing data of the primary endpoint may be employed for endpoints of interest. For
1821 summarization of baseline data, the following conventions will be used for partial
1822 missing date information occurring prior to randomization (e.g. for medical history
1823 or prior treatment). If year is missing, the date will be set at missing. If year is
1824 available, but month and date is missing, the month and date will be set to July 1st
1825 of the respective year. If date is missing, but year and month available, the day will be
1826 set to the 15th of the respective month.

1827 **14.2 Interim Analyses**

1828

1829 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
1830 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
1831 conduct if there are concerns about patient safety or futility. Unless otherwise
1832 specified by one of these bodies, a futility analysis will be performed after
1833 approximately 200 subjects are enrolled and have their primary outcome
1834 ascertained. Simulation will be used to estimate the conditional probability of futility
1835 assuming the study was to continue to completion, and assuming the clinically
1836 significant cancer detection rate is 30% in both arms. If the conditional probability is
1837 0.95 or higher that continuation of the study will result in a negative result, the

1838 DSMC will recommend a suspension of recruitment to the trial, and initiation of a
1839 quality assurance review. A decision to permanently close the study or continue with
1840 accrual will be determined by the Steering Committee, based on the results of the
1841 quality assurance review, and the recommendation of the DSMC.

1842

1843 **Timing of Final Analysis**

1844 A single, final, analysis will occur after all patients have undergone their initial biopsy
1845 and all data related to the initial biopsy is documented and validated. Follow-up
1846 analyses will be conducted after all patients have completed two years of follow-up.

1847 **14.3 Populations:**

1848 The per protocol, study population will consist of all subjects who satisfy all eligibility
1849 criteria and are randomized to the study, who undergo MPMRI-TB or systematic
1850 TRUS guided biopsy and have their primary outcome measured. This population will
1851 be used for the primary analysis of non-inferiority.

1852 The intent-to-treat (ITT) population will consist of all subjects randomized to the
1853 study, regardless of any protocol violations or if they do not complete the study as
1854 defined in the protocol. The ITT population will be used as a supportive analysis of
1855 the primary analysis, for all safety analyses, and for any analysis investigating
1856 superiority.

1857 **14.4 Primary Outcome**

1858 **14.4.1 Detection rate of clinically significant cancer**

1859 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will
1860 be calculated based on histology results from biopsy procedures. Analysis will be on
1861 the intention to treat population.

1862

1863 Absolute differences in proportion of clinically significant cancer detected between
1864 arms will be calculated and compared. If the lower boundary of the 97.5%
1865 confidence interval for the difference in detection rates of MPMRI-TB compared to
1866 systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-
1867 inferior. In the event that the lower bound is greater than zero, superiority can be
1868 claimed.

1869

1870 The primary analysis will be conducted once all patients have completed visit 4,
1871 when the results of the biopsy or MRI are given to the patient.

1872

1873 **14.5 Secondary Outcomes**

1874 For each secondary outcome, where appropriate, a difference in proportions with
1875 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

1876

1877 **14.5.1 Proportion of men in each arm with clinically insignificant 1878 cancer detected**

1879 The proportion of men in each arm with clinically insignificant cancer (Gleason < 7)
1880 will be calculated based on histology results from biopsy procedures. In addition, the

1881 numbers with clinically insignificant cancer identified by MRI alone will also be
1882 included.

1883

1884 **14.5.2 Proportion of men in each arm with Gleason $\geq 4+3$ detected**

1885 The proportion of men in each arm with Gleason $\geq 4+3$ will be calculated based on
1886 histology results from biopsy procedures. In addition, the numbers with clinically
1887 insignificant cancer identified by MRI alone will also be included.

1888

1889 **14.5.3 Proportion of men in MPMRI arm who avoid biopsy.**

1890

1891 **14.5.4 Proportion of men in the MRI arm whom the PI-RADS score for 1892 suspicion of clinically significant cancer was 3, 4 or 5 but no clinically 1893 significant cancer was detected.**

1894 The proportion of men in each arm whom the PI-RADS score for suspicion of
1895 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
1896 detected, will be calculated based on histology results from biopsy procedures.

1897

1898 **14.5.5 Proportion of men in each arm who go on to definitive local 1899 treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or 1900 systemic treatment (e.g. hormone therapy, chemotherapy)**

1901

1902 **14.5.6 Maximal cancer core length of the most involved biopsy core 1903 (maximum cancer core length, MCCL) in each arm**

1904 This measurement is routinely conducted, and will be determined by the pathologist.

1905

1906 **14.5.7 Total contiguous cancer core length of the most involved biopsy 1907 core (contiguous maximum cancer core length, CMCCL) excluding 1908 intervening normal regions**

1909 This measurement is routinely conducted, and will be determined by the pathologist.

1910

1911 **14.5.8 Proportion of men with a negative MRI who progress within 24 1912 months after their study MRI, or who are upgraded within 24 months**

1913 Men with a negative MRI who do not undergo a biopsy will have a follow-up MRI 2
1914 years after their study MRI. We will determine the proportion of men whose
1915 subsequent MRI shows a PI-RADS 3 or greater lesion. The results of targeted biopsy
1916 of those lesions will be recorded and analyzed. The number of men who are
1917 upgraded to Gleason ≥ 7 due to an off-protocol biopsy will also be recorded.

1918

1919 **14.5.9 Proportion of men with post-biopsy adverse events**

1920 Immediate post-biopsy discomfort and pain will be characterized by intensity using
1921 the numerical analogue score. Scores for each arm will be compared. 30-day biopsy
1922 specific complications and adverse events will be characterized according to their
1923 presence, absence, duration and how much of a problem the symptoms caused the
1924 subject. Whether the subject had contact with health care providers/system will also
1925 be recorded. The proportion of individuals experiencing each symptom, proportion

1926 in whom that symptom caused a problem and proportion who had contact with
1927 healthcare providers/system will be calculated and compared qualitatively between
1928 arms utilizing classification systems validated in previous studies [39]. The biopsy
1929 specific complications that will be compared include pain, urinary retention, fever,
1930 pain, erectile dysfunction, urinary incontinence, haematuria, haematochezia and
1931 haemotospermia.

1932
1933 Any post-biopsy complications up to 30-days post biopsy procedure will be tabulated
1934 and listed by duration and management.

1935

1936 **14.5.10 Health related quality of life**

1937 EQ-5D-5L descriptive domain summary indices and visual analogue scores will be
1938 assessed at baseline, 24-48 hours post intervention and at 30-days and changes will
1939 be compared between arms.

1940

1941 EQ-5D was selected as a simple, low burden quality of life instrument that will
1942 provide validated information on symptoms, particularly anxiety, that could be
1943 compared across disease states and studies. Other patient-reported outcomes
1944 directly linked to the interventions will be captured in the post-biopsy surveys. Since
1945 it provides utilities, these will be incorporated into a secondary economic analysis if
1946 the results permit.

1947

1948 **14.5.11 Proportion Gleason score upgrading in men undergoing radical 1949 prostatectomy**

1950 Of the men who undergo radical prostatectomy, the proportion who have cancer
1951 upgraded from the biopsy histopathology to the radical prostatectomy
1952 histopathology in each arm will be calculated and compared.

1953

1954 **14.5.12 Cost Outcomes**

1955 As the study design for clinical outcomes is one of non-inferiority, the primary
1956 economic analysis will be **cost minimization analysis**. The perspective of the
1957 economic analysis will be that of the public payer. The primary goal of the analysis
1958 will be to support arguments for public funding. Thus the costs of participant
1959 burden, logistical challenges, and expense of obtaining societal costs, will not be
1960 evaluated.

1961

1962 **14.5.12.1 Data collection:**

1963 As part of the informed consent process, participants will also consent to
1964 having their Ontario Health Insurance Number recorded, to be later
1965 transferred to the Institute for Clinical Evaluative Sciences (ICES) where it will
1966 be linked to a number of administrative claims databases recording health
1967 system resource utilization such as physician billing [Ontario Health Insurance
1968 Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization and
1969 surgery [Discharge Abstract Database (DAD)]; medications [Ontario Drug
1970 Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity
1971 Level Reporting (ALR)]; clinic and emergency department visits [National
1972 Ambulatory Care Reporting System (NACRS), Emergency Department visits];

1973 radiation (ALR); homecare (Home Care databases) and a few additional ones
1974 as determined necessary (e.g., Long-term care, Mental Health, Diabetes. The
1975 overall, number and proportion of health system resources will be
1976 determined. In this way we can capture comprehensive resource utilization
1977 related to on-trial management including any adverse events.

1978 **14.5.12.2 Sample consent form language:**

1979 *I understand that my Ontario Health Insurance Plan (OHIP) number*
1980 *will be collected and it, with information collected about me in this*
1981 *trial, will be transferred to the Institute for Clinical Evaluative Sciences*
1982 *and linked with routinely-collected information about my health care*
1983 *found in health-related databases (e.g., Ontario Health Insurance Plan*
1984 *(OHIP) physician claims database, Ontario Cancer Registry) for the*
1985 *purpose of analyzing the health services I use (e.g., clinic visits,*
1986 *hospitalizations, medications) and their costs. I understand that my*
1987 *personal health information will be protected and my confidentiality*
1988 *maintained.*

1989 **14.5.12.3 Cost calculation**

1990 Once the utilization of health services is determined from those cases linked
1991 to administrative databases, publicly available costs (2016\$CAN) will be
1992 applied to health services. Costs for physician and laboratory services will be
1993 determined by applying that year's fee code. Costs for hospital care will be
1994 estimated using the Canadian Institute for Health Information (CIHI) Resource
1995 Intensity Weight method for the most recently available year. Outpatient
1996 prescription drug costs for participants not covered by ODB (those under age
1997 65 and not on social assistance) will be considered to be the same as the trial
1998 arm-specific average for those with coverage. Costs will then be inflated
1999 using the healthcare-specific Consumer Price Index reported by Statistics
2000 Canada into constant Canadian dollars for the year the study ends. Due to the
2001 short time horizon, discounting will not be applied.

2002 **14.5.12.4 Primary Analysis**

2003 A within-trial analysis will be conducted to calculate the total cost for each
2004 arm and mean cost per patient for each arm. Frequency distributions and
2005 measures of central tendency (e.g. means and medians) will be determined
2006 for each resource category (e.g. hospitalizations) for each arm of the study.
2007 Confidence intervals for the difference in costs and resource utilization
2008 between the strategies overall and for each resource category will also be
2009 calculated. Univariate comparisons between the groups will be made
2010 primarily using nonparametric tests, such as Wilcoxon rank-sum test. In the
2011 primary analysis, assuming equivalence in the primary outcome, an arm with
2012 significantly lower mean costs will be considered the economically most
2013 attractive approach.

2014
2015 Should the clinical trial find a difference between the two arms on the
2016 primary endpoint, an incremental cost-benefit analysis will be calculated by

2017 deriving the additional cost per case of clinically significant cancer diagnosed,
2018 according to the following equation:

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\text{Diagnoses}_{(\text{Arm A})} - \text{Diagnoses}_{(\text{Arm B})}}$$

2019 The cost of avoiding each additional case of clinically insignificant cancer
2020 diagnosed may also be similarly calculated. Consideration will be given to
2021 extending this analysis using economic modeling with incorporation of utility
2022 values from the EQ-5D to allow a lifetime perspective to be taken and the
2023 estimation of quality adjusted life years (QALYs).

2024 **14.5.12.5 Secondary Cost Analyses**

2025 One and multi-way sensitivity analyses will be carried out around major cost
2026 drivers by varying the costs over their observed ranges and conducting
2027 threshold analyses where appropriate. Sensitivity analyses will also be
2028 performed to evaluate potential limitations in the data, such as ODB costs as
2029 described above (though the proportion without ODB coverage should be
2030 similar in the two arms, and it is not expected to be a major cost-driver).
2031

2032 **14.5.13 Missing Data**

2033 The impact of missing data will be explored in all analyses; sensitivity
2034 analyses/multiple imputation will be performed as appropriate.
2035

2036 **15. Participant compliance and withdrawal**

2037
2038 The study will be completed when at least 422 subjects have been randomized, have
2039 undergone a diagnostic test and completed follow up. Compliance to randomized
2040 treatment will be assessed by monitoring the completed forms, e.g. the systematic
2041 TRUS guided biopsy form or the MRI-targeted biopsy form.
2042

2043 In consenting to the study, subjects are consenting to study monitoring, imaging and
2044 biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to
2045 withdraw consent at any stage and their care will not be affected in any way. All
2046 communication surrounding the withdrawal and its reasons should be noted in the
2047 patient's record. Such cases should be reported to the PRECISE Study Operations
2048 Office. Data up to the time of withdrawal can be included in the study.
2049

2050 As the study diagnostic tests are for suspected cancer it is not anticipated that there
2051 will be significant loss to follow up.
2052

2053 **15.1 Subject Withdrawal from Study**

2054 A subject may discontinue participation in this study at any time at the investigator's
2055 discretion or at the request of the subject.
2056

2057 If a subject discontinues at or before Visit 1 (randomization), he is not required to
2058 complete end of study assessments.

2059

2060 If a subject discontinues after Visit 1 (randomization) for any reason, the investigator
2061 should make every effort to complete the activities bulleted below.

2062

- 2063 • End of study assessments as outlined in **Section 10.17**.
2064 • Any occurrence of death, prostatic surgical intervention, non-surgical treatment
2065 for prostate cancer after study withdrawal should be documented in the CRF and
2066 source documents.

2067

2068 Subjects who are discontinued from the study after randomization will not be
2069 replaced. Subjects withdrawn from the study retain their subject number if already
2070 given. New subjects will be allocated a new subject number.

2071

2072 In the event that a subject is prematurely discontinued from the study at any time
2073 due to an AE, the procedures describe in **Section 16.3** must be followed.

2074

2075 Subjects should be withdrawn from the study for any of the following criteria:

- 2076 • Non-compliance with the requirements of the study.
2077 • Request to discontinue treatment. This request can be made by either the
2078 subject or the investigator.
2079 • Develops progressive disease.

2080

2081 **15.2 Study completion**

2082 The primary end point will be reached when the last patient entered has their
2083 systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be
2084 followed for up to 2 years following study entry or until they have radical treatment.
2085 Subjects who are found to have significant prostate cancer and are treated will not
2086 be included in follow up for this period. This includes subjects diagnosed as part of
2087 study protocol, and subjects diagnosed during the follow up period by standard-of-
2088 care procedures. However, post MRI/biopsy questionnaires will not be required
2089 following non-protocol based procedures.

2090

2091 **16. Data Monitoring, Quality Control and Safety**

2092 **16.1 Stopping / discontinuation rules**

2093 The study will be completed when 450 participants have been randomized,
2094 undergone a diagnostic test and completed follow up.

2095

2096 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
2097 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
2098 conduct if there are concerns about patient safety or futility. See Section 14.2.1. for
2099 further details on the interim analysis. Appropriate documentation as per the PI's
2100 requirement will be completed if stopping the trial is necessary and the ethics
2101 committee will be informed.

2102

2103 As the study is unblinded there will be no need for randomization code breaks.

2104

2105 **16.2 Monitoring, quality control and assurance**

2106

2107 Members of the trial team will be Good Clinical Practice (or equivalent) trained.

2108

2109 An independent DSMC will be appointed to monitor patient safety and the rate of
2110 recruitment of subjects in the study. They will meet at least once a year whilst the
2111 trial is ongoing for routine review of safety data and trial progression. They have the
2112 power to call additional meetings and review data at any point in the trial should
2113 they wish to do so.

2114

2115 The PI may also arrange an independent trial monitor to review the study data.

2116 **16.3 Assessment of safety**

2117 The investigator is responsible for the detection and documentation of events

2118 meeting the criteria and definition of an AE or SAE as provided in this protocol.

2119 During this study, when there is a safety evaluation, the investigator or site staff will

2120 be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

2121 **16.3.1 Definition of an Adverse Event (AE)**

2122 Adverse events (AE) will be defined as “any untoward medical occurrence in a
2123 clinical trial subject undergoing any intervention in the trial, which does not
2124 necessarily have a causal relationship with this treatment”.

2125

2126 Only adverse events specific to biopsy-related complications including pain, fever,
2127 hematuria, hematochezia, hematospermia, urinary retention and urinary
2128 incontinence will be recorded. Any other adverse events will not be recorded. Please
2129 refer to section 16.3.6 of the protocol.

2130 **16.3.2 Definition of a Serious Adverse Event (SAE)**

2131 Serious adverse events (SAE) will be defined as “any untoward medical occurrence as
2132 a result of any intervention in the trial that:

2133 **(a) results in death**

2134 **(b) is life-threatening**

2135 The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which
2136 the subject was at risk of death at the time of the event. It does not refer to an
2137 event, which hypothetically might have caused death, if it were more severe.

2138 **(c) requires hospitalisation or prolongation of existing hospitalisation**

2139 In general, hospitalization signifies that the subject has been detained (usually
2140 involving at least an overnight stay) at a hospital or emergency ward for observation
2141 and/or treatment that would not have been appropriate in the physicians’ office or
2142 outpatient setting. Complications that occur during hospitalization are AEs. If a
2143 complication prolongs hospitalization or fulfils any other serious criteria, the event is
2144 serious. When in doubt as to whether ‘hospitalization’; occurred or was necessary,
2145 the AE should be considered serious. Hospitalization for elective treatment of a pre-
2146 existing condition that did not worsen form baseline is not considered an AE.

2147 **(d) results in disability / incapacity**

2148 The term disability means substantial disruption of a person's ability to conduct
2149 normal life functions. This definition is not intended to include experiences of
2150 relatively minor medical significance such as uncomplicated headache, nausea,
2151 vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may
2152 interfere or prevent everyday life functions but do not constitute a substantial
2153 disruption.

2154 **(e) is a congenital abnormality/birth defect.**

2155 Medical or scientific judgement should be exercised in deciding whether reporting is
2156 appropriate in other situations, such as important medical events that may not be
2157 immediately life threatening or result in death or hospitalization but may jeopardise
2158 the subject or may require medical or surgical intervention to prevent one of the
2159 outcomes listed in the above definition. These should also be considered serious.
2160 Examples of such events are invasive or malignant cancers, intensive treatment in an
2161 emergency room or at home for allergic bronchospasm, blood dyscrasias or
2162 convulsions that do not result in hospitalization, or development of drug
2163 dependence or drug abuse.

2164 **16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs**

2165 An event which is part of the natural course of the disease under study (i.e., disease
2166 progression) does not need to be reported as a serious adverse event. Progression of
2167 the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death
2168 due to progressive disease is to be recorded on 'Record of Death' CRF page and not
2169 as an SAE. However, if the progression of the underlying disease is greater than that
2170 which would normally be expected for the subject, or if the investigator considers
2171 that there was a causal relationship between treatment with study medication or
2172 protocol design/procedures and the disease progression, then this must be reported
2173 as an SAE. Any new primary cancer must be reported as an SAE.

2174 **16.3.4 Lack of Efficacy**

2175 "Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical
2176 sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE
2177 definition (including clarifications).

2178 **16.3.5 Clinical Laboratory Abnormalities and Other Abnormal**
2179 **Assessments as AEs and SAEs**

2180 Abnormal laboratory findings or other abnormal assessments that are judged by the
2181 investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet
2182 the definition of an AE or SAE. Clinically significant abnormal laboratory findings or
2183 other abnormal assessments that are detected during the study or are present at
2184 baseline and significantly worsen following the start of the study will be reported as
2185 AEs or SAEs. However, clinically significant abnormal findings or other abnormal
2186 assessments that are associated with the disease being studied, unless judged by the
2187 investigator as more severe than expected for the subject's condition or that are
2188 present or detected at the start of the study and do not worsen, will not be reported
2189 as AEs or SAEs.
2190

2191 The trial interventions are routinely carried out in clinical practice for investigation of
2192 suspected cancer and the risks of the interventions are therefore not any greater
2193 than if a man was not part of the trial. The risks of the procedures are relatively low,
2194 as detailed in Section 11.

2195
2196 The investigator will exercise his or her medical and scientific judgment in deciding
2197 whether an abnormal laboratory finding or other abnormal assessment is clinically
2198 significant.

2199 **16.3.6 Recording/Reporting AEs and SAEs**

2200 The first AE reporting period for this study begins at randomization and
2201 will be recorded until 30-days post-biopsy. In the event that the subject does not
2202 undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

2203
2204 Only adverse events specific to biopsy-related complications including pain, fever,
2205 hematuria, hematochezia, hematospermia, urinary retention and urinary
2206 incontinence will be recorded. Any other adverse events will not be recorded.

2207
2208 AEs will be recorded by a member of the research team or clinical team on an AE
2209 report form. All SAEs must be recorded on a SAE report form. Completed AEs and
2210 SAE report forms should be sent to the CTG who will keep a log of AEs and SAEs. AE
2211 and SAE logs will be reviewed by the DSMC.

2212
2213 For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or
2214 DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria
2215 as a SAE, will be collected and reported.

2216
2217 Expected AEs includes the following:

- 2218 • Pain
- 2219 • Blood in the urine
- 2220 • Blood in the semen
- 2221 • Blood in the stool or back passage
- 2222 • Erectile dysfunction
- 2223 • Urinary incontinence
- 2224 • Urinary tract infection
- 2225 • Fevers

2226
2227 In addition, small risks of allergic reactions are associated with the intravenous
2228 administration of gadolinium, the contrast agent used in MRI scans, as described in
2229 section 10.18.1.2. This contrast agent is used consistently in MRI scanning and is not
2230 limited to this trial.

2231
2232 If any of these symptoms are accompanied by events consistent with the definition
2233 of an SAE as specified above, then the event will be considered an SAE.

2234
2235 The Trial Coordinator, Principle Investigator or Chief Investigator should be informed
2236 of any SAE within 24 hours.

2237 All SAE report forms must be completed and the SAE logs updated. All SAEs must be
2238 followed up until a resolution is reached (i.e. recovered, recovering, recovered with
2239 sequelae, fatal, not recovered or unknown).

2240

2241 Local sites may have specific institutional protocols for reporting SAEs, which should
2242 be followed in addition.

2243

2244 When an AE/SAE occurs, it is the responsibility of the investigator to review all
2245 documentation relative to the event. The investigator will then record all relevant
2246 information regarding an AE/SAE on the CRF.

2247

2248 The investigator will attempt to establish a diagnosis of the event based on signs,
2249 symptoms and/or other clinical information. In such cases, the diagnosis should be
2250 documented as the AE/SAE and not the individual signs/symptoms.

2251 **16.3.7 Evaluating AEs and SAEs**

2252 **16.3.7.1 Assessment of Intensity**

2253

2254

2255

2256 The investigator will make an assessment of intensity for each AE and SAE reported
2257 during the study. Degree of severity and change in severity will be recorded by
2258 means of National Cancer Institute, Common Terminology Criteria for Adverse
2259 Events (NCI CTCAE), version 4.03.

2260

2261 If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on
2262 the investigator's clinical judgment. The intensity of each AE and SAE recorded in the
2263 CRF should be assigned to one of the following categories:

2264

2265 **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort
2266 and not interfering with everyday activities.

2267 **Moderate:** An event that is sufficiently discomfoting to interfere with normal
2268 everyday activities.

2269 **Severe:** An event that prevents normal everyday activities.

2270

2271 An event that is classified as severe should not be confused with a SAE. Severity is a
2272 category utilized for rating the intensity of an event; both AEs and SAEs can be
2273 assessed as severe.

2274 **16.3.7.2 Assessment of Causality**

2275 The investigator is obligated to assess the relationship between investigational
2276 product and the occurrence of each AE/SAE. The investigator will use clinical
2277 judgment to determine the relationship. Alternative causes and the temporal
2278 relationship of the event to the investigational product will be considered and
2279 investigated. The investigator will also consult the CIB and or Product Information,
2280 for marketed products, in the determination of his/her assessment.

2281 **16.3.8 Follow-up of AEs and SAEs**

2282 After the initial AE/SAE report, the investigator is required to proactively follow each
2283 subject and provide further information to the PI of the study, on the subject's
2284 condition.

2285

2286 All AEs and SAEs documented at a previous visit/contact and are ongoing, will be
2287 reviewed at subsequent visits/contacts.

2288

2289 All AEs and SAEs will be followed until resolution, until the condition stabilizes, until
2290 the event is otherwise explained or until the subject is lost to follow-up. Once
2291 resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will
2292 ensure that follow-up includes any supplemental investigations as may be indicated
2293 to elucidate the nature and/or causality of the AE or SAE.

2294

2295 The PI may request that the investigator perform or arrange for the conduct of
2296 supplemental measurements and/or evaluations to elucidate as fully as possible the
2297 nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a
2298 subject dies during participation in the study or during a recognized follow-up
2299 period, the PI will be provided with any post-mortem findings.

2300

2301 New or updated information will be recorded on the originally completed SAE CRF,
2302 with all changes signed and dated by the investigator or designate. The updated SAE
2303 CRF should be resent to the PI.

2304 **16.3.9 Prompt Reporting of SAEs**

2305 Once the investigator determines that an event meets the protocol definition of an
2306 SAE, the SAE will be reported to the PI (CURC) within 24 hours.

2307

2308 **16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI**

2309 The Site Investigator must immediately inform the PI (CURC) of all SAE (within 24
2310 hours) at the following fax number: 1-416-480-6121.

2311

2312 The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing
2313 addresses is as follows:

2314 Dr. Laurence Klotz

2315 c/o Marlene Kebabdjian

2316 Division of Urology

2317 Sunnybrook Health Sciences Centre

2318 2075 Bayview Avenue A304

2319 Toronto, Ontario M4N 3M5 Canada

2320 Phone: (416) 480-6100 ext 2890

2321 E-mail: Laurence.Klotz@sunnybrook.ca

2322 Marlene.kebabdjian@sunnybrook.ca

2323 **16.3.9.2 Completion and Transmission of the SAE Reports**

2324 Once an investigator becomes aware that an SAE has occurred in a study subject,
2325 she/he will report the information to the PI within 24 hours. The SAE CRF will always

2326 be completed as thoroughly as possible with all available details of the event, signed
2327 by the investigator (or designee), and forwarded to the PI within the designated time
2328 frames. If the investigator does not have all information regarding as SAE, he/she will
2329 not wait to receive additional information before notifying the PI of the event and
2330 completing the form. The form will be updated when additional information is
2331 received.

2332
2333 The investigator will always provide an assessment of causality at the time of the
2334 initial report as described in Section 16.3.6.2.

2335 **16.3.10 Post-study AEs and SAEs**

2336 If the investigator learns of any SAE at any time after a subject has been discharged
2337 from the study, and such event(s) is (are) reasonably related to the study
2338 intervention, the investigator should promptly notify the PI (CURC).

2339

2340 **17. Study Administration**

2341 **17.1 Regulatory and Ethical Considerations**

2342 An important consideration is that men are being randomized to one of two biopsy
2343 techniques when it is not known which will be more effective in diagnosing clinically
2344 significant prostate cancer. Both diagnostic tests are currently used in everyday
2345 clinical practice at the institutions involved in the trial. Though systematic TRUS
2346 guided biopsy could be considered standard of care, there is enough evidence to
2347 support the concept that MPMRI-targeted biopsy may be as effective, if not more so,
2348 than systematic TRUS guided biopsy [27]. This study aims to confirm this.

2349 **17.1.1 Ethical Conduct of the Study and Ethics Approval**

2350 The PI and each participating site will obtain approval to conduct the study from the
2351 Research Ethics Board (REB) prior to initiating the study.

2352

2353 This study will be conducted in accordance with 'good clinical practice' (GCP) and all
2354 applicable regulatory requirements, including where applicable, the 2013 version of
2355 the Declaration of Helsinki.

2356

2357 The investigator is responsible for ensuring that this protocol, the site's informed
2358 consent form and any other information that will be present to potential subjects
2359 are reviewed and approved by the appropriate REB. The investigator agrees to allow
2360 the REB direct access to all relevant regulatory documents. The PI will provide the
2361 site investigator(s) with relevant document(s)/data that are needed for REB review
2362 and approval of the study. Before CRFs can be shipped to the site, the PI must
2363 receive copies of the REB approval, the approved informed consent form and any
2364 other information that the REB has approved for presentation to potential subjects.

2365

2366 If the protocol, the informed consent form or any other information that the REB has
2367 approved for presentation to potential subjects is amended during the study, the
2368 site investigator(s) is responsible for ensuring the REB reviews and approves, where
2369 applicable, these amended documents. The site investigator(s) must follow all

2370 applicable regulatory requirements pertaining to the use of an amended informed
2371 consent form including obtaining the REB approval of the amended form before new
2372 subjects consent to take part in the study using this version of the form. Copies of
2373 the REB approval of the amended informed consent form/other information and the
2374 approved amended informed consent form/other information must be forwarded to
2375 the PI promptly.

2376 **17.1.2 Informed Consent**

2377 Informed consent will be obtained before the subject can participate in the study.
2378 The contents and process of obtaining informed consent will be in accordance with
2379 all applicable regulatory requirements.

2380

2381 The subject's consent to participate in the study should be obtained after a full
2382 explanation has been provided of the procedures to be given. Subjects should be
2383 given sufficient time (at least 24 hours) after being given the study patient
2384 information sheet to consider and discuss participation in the study with family and
2385 friends.

2386

2387 A contact number will be given to the subject should he wish to discuss any aspect of
2388 the study. Following this, the clinician will determine that the subject is fully
2389 informed of the study and their participation, in accordance with Good Clinical
2390 Practice Guidelines. Subjects will always be asked to sign a consent form. One copy
2391 will be given to the subject, one copy will be kept with subject's hospital notes and
2392 one copy should be kept in the local investigator's file.

2393 **17.1.3 Investigator Reporting Requirements**

2394 The investigator is responsible for reporting SAEs to the REB in accordance with all
2395 applicable regulations. Furthermore, the investigator may be required to provide
2396 periodic safety updates on the conduct of the study at his or her site and notification
2397 of study closure to the REB.

2398 **17.2 Study Monitoring**

2399 This study will be monitored by a CRA. The CRA will contact the sites by telephone
2400 on a predetermined basis and would conduct a monitoring visits based on the data
2401 entered in the EDC and queries.

2402

2403 During these contacts, the monitor will:

- 2404 • Check the progress of the study
- 2405 • Review study data collected
- 2406 • Conduct source document verification
- 2407 • Identify any issues and address their resolution

2408

2409 This will be done in order to verify that the:

- 2410 • Data are authentic, accurate and complete
- 2411 • Safety and rights of subjects are being protected
- 2412 • Study is conducted in accordance with the currently approved protocol (and
2413 any amendments), GCP and all applicable regulatory requirements

2414

2415 The investigator agrees to allow CRA personnel direct access to all relevant
2416 documents and to allocate his/her time and the time of his/her staff to CRA
2417 personnel to discuss findings and any relevant issues.

2418 **17.3 Quality Assurance**

2419 To ensure compliance with GCP and all applicable regulatory requirements,
2420 regulatory agencies may conduct a regulatory inspection of the study. Such
2421 audits/inspections can occur at any time during or after completion of the study. If
2422 an audit or inspection occurs, the investigator and institution agree to allow the
2423 auditor/inspector direct access to all relevant documents and to allocate his/her
2424 time and the time of his/her staff to the auditor/inspector to discuss findings and
2425 any relevant issues.

2426 **17.4 Study and Site Closure**

2427 Upon completion of the study, the site investigator(s) will conduct the following
2428 activities:

- 2429 • Return of all study data to the Sponsor (CURC)
- 2430 • Submission of all study data and data queries to OCOG
- 2431 • Review of site study records for completeness

2432

2433 In addition, the Principal Investigator has the right to temporarily suspend or
2434 prematurely discontinue this study either at a single site or at all sites at any time for
2435 reasons including but not limited to, safety or ethical issues or severe non-
2436 compliance. If the PI determines such action is needed, the PI will discuss this with
2437 the site investigator (including the reasons for taking such action) at that time. When
2438 feasible, the PI will provide advance notification to the site investigator of the
2439 impending action prior to it taking effect.

2440

2441 Individual site Investigators may also terminate their participation in the study at any
2442 time. If the investigator determines such action is needed, the investigator will
2443 discuss this with the PI (including the reasons for taking such action) at that time.
2444 When feasible, the investigator will provide advance notification to the PI of the
2445 impending action prior to it taking effect.

2446

2447 The PI will promptly inform all other investigators and/or institutions conducting the
2448 study if the study is suspended or terminated for safety reasons and will also inform
2449 the regulatory authorities of the suspension or termination of the study and the
2450 reason(s) for the action. If required by applicable regulations, the investigator must
2451 inform the REB promptly and provide the reason for the suspension or termination.

2452

2453 If the study is prematurely discontinued, all study data must be returned to the PI. In
2454 addition, the investigator has the responsibility to return any used/unused clinical
2455 supplies.

2456

2457 Financial compensation to investigators and/or institutions will be in accordance
2458 with the agreement established between the investigator and the PI.

2459 **17.5 Records Retention**

2460 Following closure of the study, the site investigator(s) must maintain all site study
2461 records in a safe and secure location. The records must be maintained to allow easy
2462 and timely retrieval when needed and whenever feasible, to allow any subsequent
2463 review of data in conjunction with assessment of the facility, supporting systems and
2464 staff.

2465
2466 The site investigator(s) will retain study records to comply with all applicable
2467 regulatory requirements. The minimum retention time will meet the strictest
2468 standard applicable to that site for the study as dictated by any institutional
2469 requirements or local laws or regulations of Health Canada standards/procedures;
2470 otherwise, the retention period will default to 25 years.

2471
2472 The site investigator(s) must inform the PI of any changes in the archival
2473 arrangements, including but not limited to the following: archival at an off-site
2474 facility, transfer of ownership of the records in the event the investigator leaves the
2475 site. The PI should be informed of this change if it affects their access to the
2476 information in case of an audit.

2477 **17.6 Data Management**

2478 Subject data are collected by the investigator or designee using the CRF within an
2479 Electronic Data Capture (EDC) system. Subject data necessary for analysis and
2480 reporting will be entered/transmitted into a validated database. Clinical data
2481 management will be performed in accordance with applicable standards and data
2482 cleaning procedures. Database lock will occur when data management quality
2483 control procedures are completed.

2484 **17.7 Publication**

2485 The results from the study will be analyzed and published as soon as possible and is
2486 appropriate. All study-related communications can only be presented or published
2487 after approval from all relevant members involved in the trial.

2488
2489 All publications shall include appropriate indication named authors as agreed on by
2490 the members involved in the trial. For the main study reports, senior and first
2491 authorship will be determined by agreement of the Chief Investigator, the Principle
2492 Investigator at time of manuscript drafting. Authorship will be based on
2493 recommendations of the International Committee of Medical Journal Editors
2494 (www.ICMJE.org) where all authors meet the following for criteria:

- 2495
2496 1. Substantial contributions to the conception or design of the work; or the
2497 acquisition, analysis, or interpretation of data for the work; AND
2498 2. Drafting the work or revising it critically for important intellectual content;
2499 AND
2500 3. Final approval of the version to be published; AND
2501 4. Agreement to be accountable for all aspects of the work in ensuring that
2502 questions related to the accuracy or integrity of any part of the work are
2503 appropriately investigated and resolved.

2504

2505 If there are no named authors (i.e. group authorship) then a writing committee will
2506 be identified that would usually include these people. The clinical trials.gov
2507 registration number that will be allocated to this trial will be attached to any
2508 publications resulting from this trial.

2509

2510 Trial funding agencies (OICR and others as appropriate) will be acknowledged in all
2511 publications.

2512

2513 The members of the trial steering committee will be listed with their affiliations in
2514 the acknowledgements/appendix of the main publication.

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2724 **Appendices**

2725 **Appendix 1: Time windows for data collection**

2726

2727 For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3

2728 For details on time windows permitted for each trial intervention to be completed
2729 please see Table 5 below.

2730

2731 Table 5: Details of time windows permitted for all trial interventions.

2732

Contact and Purpose if not clear	Time window permitted
<p>Visit 0</p> <p>Telephone consult</p> <p>Purpose: give information on study. Send interested subjects the information sheet</p>	<p>Any time from referral letter being received to 1st visit in hospital.</p> <p>Ideally perform as soon as possible following receipt of referral.</p> <p>It may be the case that not all men have an opportunity to get a teleconsult prior to Visit 1. If this is the case then these men may still be included in the study.</p>
<p>Visit 1</p> <p>Screening (eligibility review)</p>	<p>Any time following referral of subject.</p> <p>Ideally perform as soon as possible following receipt of referral.</p>
<p>Visit 1</p> <p>Consent</p> <p>Randomization</p> <p>EQ-5D-5L Questionnaire (baseline)</p> <p>Optional urine, semen and</p>	<p>Complete only once subject has had 24 hours after receiving the patient information leaflet to fully consider the study.</p> <p>Ideally on same visit as screening.</p> <p>Immediately after consent form signed.</p> <p>Complete immediately after consent form is signed</p> <p>If a subject is randomized to the MRI arm, a second EQ-5D-5L questionnaire should be given to the subject who is instructed to complete this 24-48 hours after the MRI.</p> <p>Complete after additional informed consent</p>

blood sample	signed, after randomization and up until any point prior to a biopsy.
Visit 2	
MRI	Only for men randomized to this arm. Any time following randomization. Ideally within 1 week of randomization.
EQ-5D-5L Questionnaire (post MRI)	To be completed 24-48 hours post-MRI as previously explained
Immediate post MRI/TRUS Fusion Biopsy Questionnaire	To be completed within 24 hours of MRI, ideally immediately after MRI prior to leaving department.
Visit 3	
MRI-Targeted Biopsy of Prostate	Only for men randomized to this arm who have a lesion on MRI that needs a biopsy. Any time following the MRI being reported, ideally within 1 week of MRI. Depending on local Urology service structure, an appointment for a biopsy may need to be booked at the same time as the MRI is booked (i.e. immediately after randomization) in order for a slot to be secured for a biopsy to occur in timely fashion. If it is determined from the MRI that a biopsy is not required then the biopsy appointment can be used instead of Visit 4 for follow up of results and treatment decision.
Visit 3	
Systematic TRUS guided biopsy	Only for men randomized to this arm. Any time following randomization. Ideally within 4 weeks of randomization.
Visit 3	
Immediate post-biopsy questionnaire	Should be completed and returned immediately after a biopsy, before the subject leaves the department. As long as questionnaire completed within 24 hours it will be acceptable.
30-day post-biopsy questionnaire	To be given to subject to take home after biopsy and completed as instructed on day 30 post-

<p>Telephone reminder</p>	<p>biopsy.</p> <p>To be returned by post or at follow up appointment (Visit 4).</p> <p>If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as possible to 30 days post-biopsy.</p> <p>At 30-days post biopsy a member of the research team will phone the subject to remind them to fill out the 30-day questionnaires</p>
<p>Visit 3</p> <p>EQ-5D-5L Questionnaire (post-biopsy)</p>	<p>Should be given to subject to take home after biopsy. To be completed 24-48 hours post-biopsy.</p> <p>Telephone call to remind to complete.</p>
<p>Visit 3</p> <p>Post-MRI/TRUS Fusion Biopsy 30-day questionnaire</p>	<p>Only for subjects in the MRI arm who do not undergo biopsy.</p> <p>In this case, the questionnaire will be posted to them by the research team or given to them when they obtain their results of the MRI.</p> <p>To be returned at follow up appointment (Visit 4) or by post.</p> <p>If Visit 4 is earlier than 30 days post MRI then this questionnaire can be given to the research team when 30-days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60</p>

Telephone Reminder	<p>days post-MRI, it will be acceptable. Ideally the questionnaire should be completed as close as possible to 30 days post-MRI.</p> <p>At 30-days post MRI, a member of the research team will ring the subject t to remind them to fill out the 30-day questionnaires</p>
<p>Visit 4</p> <p>Follow up for results And treatment Decision</p>	<p>Should be completed as soon as possible following the availability of any pathology results. Alternatively, if a man is in the MRI arm and the MRI is negative, this follow up should occur after the availability of the MRI report. Ideally the follow up appointment should be within 6 weeks of randomization.</p> <p>Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.</p>
<p>Visit 4</p> <p>30-day post intervention EQ-5D-5L Questionnaire</p>	<p>To be completed at 30 days post-biopsy or 30-days post MRI if no biopsy occurs.</p> <p>The questionnaire needs to be ideally completed on the 30th day post-intervention (i.e. post biopsy or post MRI if no biopsy). However it will be accepted if completed up to 72 hours prior to or after the 30th day.</p> <p>A telephone reminder from the research team to the subject can take place.</p>
<p>Visit 5</p> <p>52 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • results of any off protocol biopsies or MRI

<p>Visit 6</p> <p>104 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. <p>Those subjects randomized to ARM A but who did not have an MPMRI-targeted biopsy will have an additional MPMRI at Visit 6. This will be followed by a targeted-biopsy if results of MRI are positive (PI-RADS 3-5).</p> <p>Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).</p>
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2733

2734

Appendix 2: MPMRI Reporting Proforma

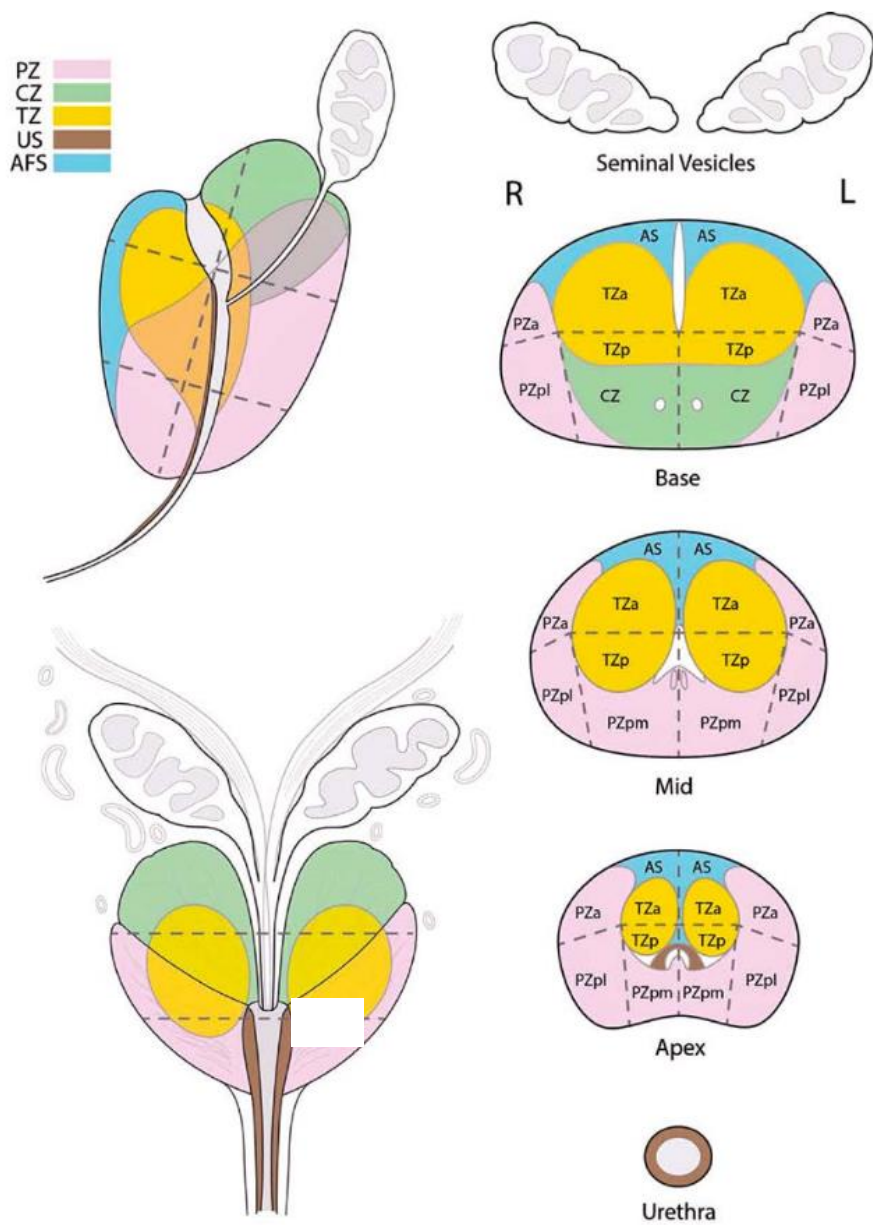
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Reporting radiologist Date of scan Date of report

Radiologists should annotate this diagram with up to 3 suspicious areas scoring 3 or greater on the PI-RADS v2 scale of suspicion.

The three most suspicious areas should be annotated, each with the score clearly marked.

“Target 1” should be the area with the greatest degree of suspicion. If applicable, “Target 2” should be the area with the next greatest degree of suspicion and finally if applicable, “Target 3” should be the area with the next greatest degree of suspicion. For each suspicious area biaxial measurements should be recorded using the pulse sequences that shows the tumor the best with all 3 measurements in orthogonal planes provided whenever possible and a minimum of two axial plane measurements provide for every lesion.



2786 Image quality: Good, Minor image quality issues, acceptable for diagnosis, unacceptable
 2787
 2788 If image quality is not good please comment: _____
 2789
 2790
 2791
 2792

2793
 2794 **Findings (intermediate (PI-Rads 3), high (PI-Rads 4) or very high (PI-Rads 5))**
 2795

2796
 2797 Number of candidate tumor sites (in order of dominance): 1
 2798

2799 Target 1:
 2800 Pi-Rads Score:
 2801 Size: x x mm
 2802 Location(s): (side)
 2803

2804 Target 2:
 2805 Pi-Rads Score:
 2806 Size: x x mm
 2807 Location(s): (side)
 2808

2809 Target 3:
 2810 Pi-Rads Score:
 2811 Size: x x mm
 2812 Location(s): (side)
 2813
 2814

2815 There are more than 3 targets seen: Y/N
 2816
 2817 There is a multifocal pattern raising a concern for multifocal small volume cancer
 2818 and a PSA Density >0.15 without a measurable focal lesion (3M pattern): Y/N
 2819

2820 Extraprostatic extension: Y/N/Equivocal
 2821 Seminal vesicle invasion: Left: Y/N/equivocal Right: y/n/equivocal
 2822 Adenopathy: no
 2823

	x		x		cm	Volume:		cc
PSA:		ng/ml		PSA Density:				ng/ml/cc

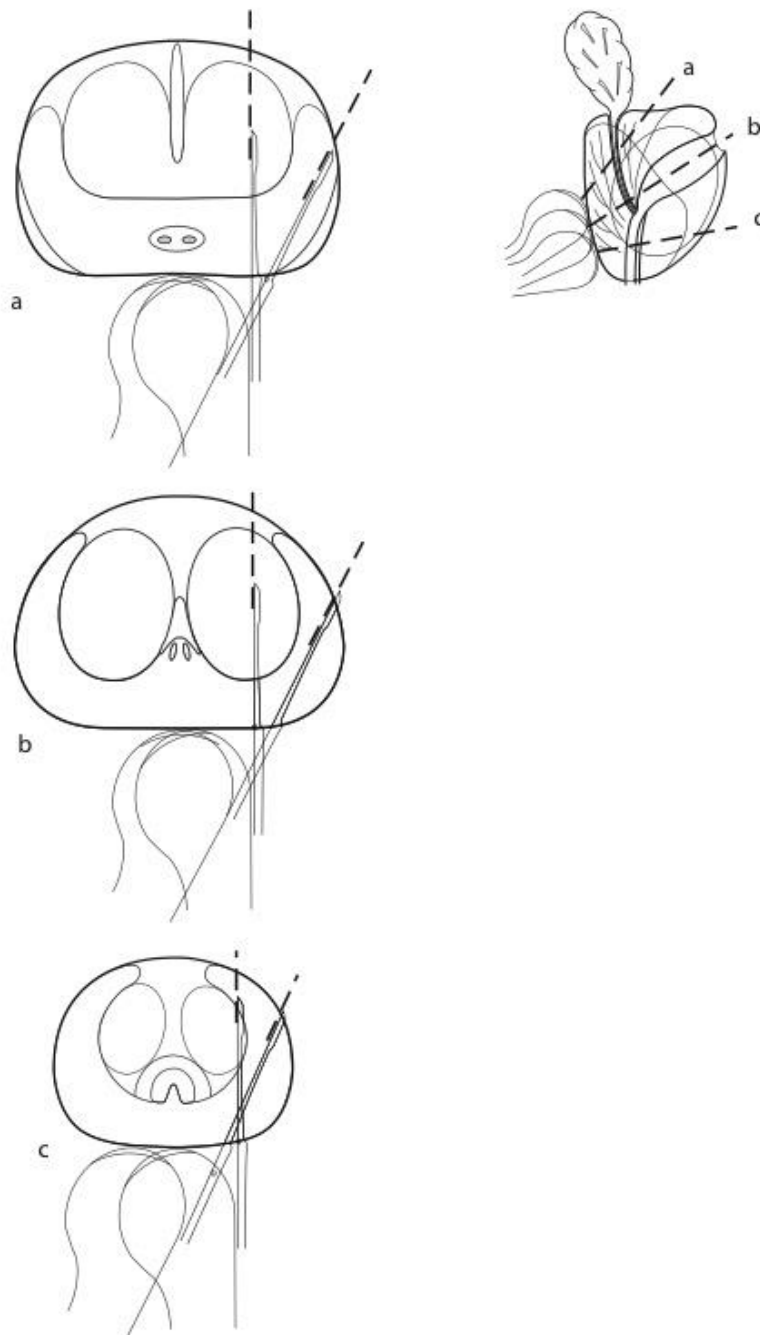
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Appendix 3: Example of systematic TRUS guided biopsy schema

2827

2828 Figure depicting 12-core systematic TRUS guided biopsy schema that sites are
2829 recommended to follow. Axial/coronal sections of a prostate gland (left) showing
2830 biopsy courses of the 12 biopsies performed under ultrasound guidance with an
2831 endfire probe. Upper right: axial planes in the sagittal view. a, base; b, mid-gland; c,
2832 apex. From Haffner *et al* [37].



2833

2834 **Appendix 4: 2-page EQ-5D-5L Questionnaire**

2835 Under each heading, please tick the ONE box that best describes your health TODAY

2836

2837 **MOBILITY**

2838 I have no problems in walking about

2839 I have slight problems in walking about

2840 I have moderate problems in walking about

2841 I have severe problems in walking about

2842 I am unable to walk about

2843

2844 **SELF-CARE**

2845 I have no problems washing or dressing myself

2846 I have slight problems washing or dressing myself

2847 I have moderate problems washing or dressing myself

2848 I have severe problems washing or dressing myself

2849 I am unable to wash or dress myself

2850

2851 **USUAL ACTIVITIES** (*e.g. work, study, housework,*

2852 *family or leisure activities*)

2853 I have no problems doing my usual activities

2854 I have slight problems doing my usual activities

2855 I have moderate problems doing my usual activities

2856 I have severe problems doing my usual activities

2857 I am unable to do my usual activities

2858

2859 **PAIN / DISCOMFORT**

2860 I have no pain or discomfort

2861 I have slight pain or discomfort

2862 I have moderate pain or discomfort

2863 I have severe pain or discomfort

2864 I have extreme pain or discomfort

2865

2866 **ANXIETY / DEPRESSION**

2867 I am not anxious or depressed

2868 I am slightly anxious or depressed

2869 I am moderately anxious or depressed

2870 I am severely anxious or depressed

2871 I am extremely anxious or depressed

2872

2873 © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

2874 • We would like to know how good or bad your health
2875 is TODAY.

The best health
you can imagine

2876 • This scale is numbered from 0 to 100.

2877 • 100 means the best health you can imagine.

2878 0 means the worst health you can imagine.

2879 • Mark an X on the scale to indicate how your health is
2880 TODAY.

2881 • Now, please write the number you marked on the
2882 scale in the box below.

2883

2884

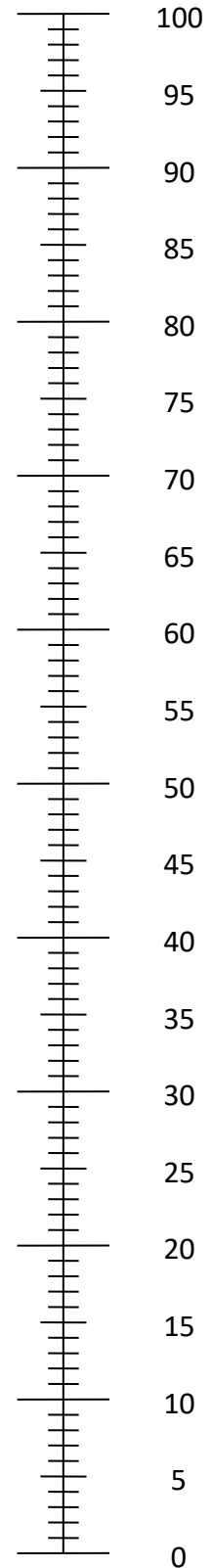
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2886

2887

2888

YOUR HEALTH TODAY =



The worst health
you can imagine

Did you experience any of the following in the month **before** your MRI. For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

Thank you for completing the questionnaire. Please give this to a member of the research team on your next hospital visit.

2893
2894
2895
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2897
2898
2899

Appendix 6: 30-day Post MRI/TRUS Fusion Biopsy Questionnaire

30-day post MRI questionnaire

30-days after the MRI, the patient should complete this 5-page questionnaire:

Did you experience the following problem in the 30-days after the MRI:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the MRI did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

2902

Did you experience the following problem in the 30-days after the MRI:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the MRI did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

Did you experience the following problem in the 30-days after the MRI:

25. Pain as a result of the MRI

Yes No
1 2

26. If you answered yes, specify on which days after the MRI you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem
1 2 3 4

2903

28. Please list any **new** medications that you have taken **since the MRI**. Do not list your regular medications but do list any **new** medications started related to the MRI. Think especially about any painkillers that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. paracetamol</i>	<i>1g</i>	<i>4</i>	<i>3</i>

29. Since the MRI, have you had contacts with hospital services for reasons related to the MRI, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

 1

No

 2

30. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over pain*)

(iii) manner of contact (*e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency*)

(iv) any treatment you received (please be as specific as possible *e.g. "I was seen in accident and emergency and discharged with 2 days of painkillers of oral paracetamol 1g four times a day"*):

2904

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the MRI, have you had contact with the community healthcare team for reasons related to the MRI?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over pain*)

(iii) manner of contact (*e.g. telephone/attendance at GP surgery/home visit*)

(iv) any treatment you received (please be as specific as possible *e.g. "I received 5 days of painkillers with paracetamol 1g four times a day"*):

2905

37. Have you felt unwell in any other way that we have not asked that you feel is due to the MRI?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the MRI did you have this for? (*tick one*)

Days:	0-2	3-5	6-10	11-15	16-20	21-30
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another MRI** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

?

Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

2906

Appendix 7: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

Please ask the patient to fill this out after the biopsy, before they leave the department.

Please tick the box corresponding to the number, which describes how you felt immediately after the biopsy procedure:

1. Overall, how much discomfort did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Discomfort			Moderate Discomfort					Worst Discomfort Possible		

2. Overall, how much pain did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Pain			Moderate Pain					Worst pain Possible		

-
-
-
-
-
-
-
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-
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-
-
-
-
-
-
-
-
-
-

Please complete the next page of questions

Did you experience any of the following in the month **before** your biopsy procedure.
For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

11. Pain at the site where the biopsies were taken from

Yes

1

No

2

Thank you for completing the questionnaire. Please hand this to a member of staff before you leave. Please ensure you are given the 30-day questionnaire for completion at 30 days following the biopsy.

2910

Appendix 8: 30-day post biopsy questionnaire

30-day post biopsy questionnaire

30-days after the biopsy procedure, the patient should complete this questionnaire:

Did you experience the following problem in the 30-days after the biopsy procedure:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the biopsy did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

2913

Did you experience the following problem in the 30-days after the biopsy procedure:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the biopsy did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

25. Pain at the site where the biopsies were taken from

Yes No
1 2

26. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

2914

28. Please list any **new** medications that you have taken **since the biopsy**. Do not list your regular medications but do list any **new** medications started related to the biopsy. Think especially about any painkillers or antibiotics that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. ciprofloxacin</i>	<i>500mg</i>	<i>2</i>	<i>3</i>

29. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

No

1

2

30. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over fevers*)

(iii) manner of contact (*e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency*)

(iv) any treatment you received (please be as specific as possible *e.g. "I was admitted to the ward and treated for an infection of the blood stream for 5 days of intravenous antibiotics with 1.2g co-amoxiclav three times a day and I had 2 days of painkillers with intravenous paracetamol 1g four times a day"*):

2915

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the biopsy, have you had contact with the community healthcare team for reasons related to the biopsy?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at GP surgery/home visit)

(iv) any treatment you received (please be as specific as possible e.g. "I received 5 days of oral antibiotics for a urinary tract infection- 625mg co-amoxiclav three times a day and I had 2 days of painkillers with paracetamol 1g four times a day"):

2916

2917

37. Have you felt unwell in any other way that we have not asked that you feel is due to the biopsy?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2	3-5	6-10	11-15	16-20	21-30
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another biopsy** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

?

Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

?

2918
2919
2920

2921 PRECISE Protocol: *revision date*: 30 January 2017
2922 Summary of Changes – Amendment 1
2923 **PROTOCOL CHANGES:**
2924 Protocol Version date change: 30January2017
2925 Revisions to the protocol were necessary as a result of the protocol review by the
2926 investigators involved in the trial. The following changes have been made to the
2927 protocol as part of Amendment 1:
2928 -Secondary Objectives: #7, #8 -page 3 -were omitted due to the challenges in
2929 obtaining this information due to site variability in pathology reporting
2930 -Secondary Objectives: addition of #12, #13 - page 4 -to determine impact Gd and
2931 reading of PI-rads by radiologist
2932 -Subject Inclusion Criteria clarification of #2, page 21 - no changes to the criteria
2933 were made. Clarification was added to instructions on how to enter subjects into the
2934 risk calculator.
2935 -Table 1, 2, 3 -Schedule of Assessment, page 24, 26, 28 - added 2 new visits (q6 mos),
2936 to obtain blood, and urine for correlative samples, if subject provided consent to
2937 optional sampling.
2938 -Table 1, 2, 3, -Schedule of Assessment, page 24, 26, 28 -clarification of how samples
2939 are to be obtained, and their timelines
2940 -Table 1, 2, 3 -Schedule of Assessment, page 24, 26, 28, -physical exam replaced with
2941 vital and DRE.
2942 -MRI Reporting -page 31, 32- clarification, revision of how MRI is to be reported by
2943 the attending radiologist
2944 -Pathology, page 34, removal of reporting of maximum cancer core length (MCCL)
2945 due to too much site variability on reporting.
2946 -Section 10.15.1 Optional Sample collection, page 37, -revision on the amount of
2947 samples to be collected, more detailed information added
2948 -removal of 2 questionnaires,- Appendix 5 and 6: 'Immediate post MRI
2949 questionnaire', and '30 Post MRI questionnaire'
2950 In addition to the above reference changes, minor administrative changes were
2951 made to revise typos, grammatical errors, and spacing.
2952 **INFORMED CONSENT CHANGES:**
2953 ICF date change change: 30January2017
2954 -Arm A: - page 3, 'approximately' added to clarify estimated timelines.
2955 -Non-Experimental Procedures, -page 3: physical exam replaced with vitals, DRE as
2956 per protocol change
2957 -Questionnaires- page 3: ommitted, clarity added to the timelines requiring select
2958 questionnaires
2959
2960 **OPTIONAL INFORMED CONSENT CHANGES:**
2961 Optional ICF date change: 30January2017
2962 -Purpose, page 1 - revised wording, no content change
2963 -Study Procedure: -page 2: -clarification/revision of sampe collection quantity, and
2964 timelines of collection.
2965 -Confidentiality, page 3: -inclusion of study collaborators,
2966 -Consent, page 5: order revised, no content change
2967

2968 **1. Title Page**
2969 *Full title:*
2970 **A phase III multi-centre open-label randomized controlled trial of**
2971 **multi-parametric magnetic resonance imaging (MRI)-targeted biopsy**
2972 **compared to systematic trans-rectal ultrasound (TRUS) guided biopsy**
2973 **for the diagnosis of prostate cancer in men without prior biopsy.**
2974
2975 1. **Short title: Prostate Evaluation for Clinically Important disease:**
2976 **MRI vs Standard Evaluation procedures. (PRECISE)**
2977
2978 **Date: 30 January 2017**
2979 **Version 2.0**
2980
2981 **Sponsor:**
2982 Canadian Urology Research Consortium (CURC)
2983
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Confidential

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2. Signature of Investigators

A phase III multi-centre open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.

Date: 30 January 2017
Version 2.0

The signatory agrees to the content of the final clinical study protocol as presented.

Signature: _____

Name: _____

Title: _____

Date: _____

Site name: _____

3. Synopsis

Title	A phase III multi-centre, open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.
Short Title	Prostate Evaluation for Clinically Important disease: MRI vs Standard Evaluation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	<p>Primary Objective</p> <p>To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.</p> <p>Secondary Objectives</p> <ol style="list-style-type: none"> 14. To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy. 15. Proportion of men in each arm with clinically insignificant cancer detected. 16. Proportion of men in each arm with Gleason $\geq 4+3$ detected. 17. Proportion of men in MRI arm who avoid biopsy. 18. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected. 19. Proportion of men in each arm who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy). 20. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer by 2 years. 21. Proportion of men with post-biopsy adverse events 22. Health-related quality of life scores. 23. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy. 24. To determine the cost per diagnosis of cancer. 25. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield 26. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone
Test procedures	Subjects will be randomized to either ARM A: multi-parametric magnetic resonance imaging (MRI)

	<p>which, depending on outcome, may be followed by (MRI)-targeted biopsy.</p> <p>ARM B: systematic trans-rectal ultrasound (TRUS) guided biopsy.</p> <p>Subjects in both arms will complete a number of different questionnaires and will have PSA measurements taken. If subjects consent to participate in correlative studies, they will also need to provide blood, urine, semen and tissue samples at pre-specified time points.</p>
Indication	Clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy.
Diagnosis and main criteria for inclusion	<p>In order to be eligible, <u>all</u> inclusion criteria must be met.</p> <p>6. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;</p> <p>7. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk assessment of prostate cancer calculator, PCPTRC 2.0, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp; For men under age 55, the default age of 55 should be entered on the risk calculator.</p> <p>8. Serum PSA ≤ 20ng/ml;</p> <p>9. Fit to undergo all procedures listed in protocol;</p> <p>10. Able to provide written informed consent.</p>
Exclusion Criteria	<p>Men who meet the following criteria at the time of screening will be excluded:</p> <p>7. Prior prostate biopsy;</p> <p>8. Prior treatment for prostate cancer;</p> <p>9. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min);</p> <p>10. Contraindication to prostate biopsy;</p> <p>11. Men in whom artifact would reduce the quality of the MRI; i.e, previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work;</p> <p>12. Unfit to undergo any procedures listed in protocol.</p>
Study Design	This is a multi-centre open-label, randomized two arm study. Men are either randomized to receive MRI or a systematic trans-rectal ultrasound (TRUS) guided biopsy.
Methodology	<p>Eligible subjects will be randomized in a 1:1 ratio to receive either (ARM A) multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy, or (ARM B) systematic trans-rectal ultrasound (TRUS) guided biopsy. The time frame for data collection is shown in Appendix 1.</p> <p><u>All subjects</u> will have a PSA test prior to, or at Visit 1, and will complete a baseline EQ-5D-5L questionnaire. In addition, they will contribute optional blood, urine, semen and tissue samples if they consent to correlative studies.</p>

	<p><u>All subjects in ARM A</u> will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI.</p> <p><u>Subjects in ARM A who do not receive a subsequent biopsy</u> will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (\pm 1 week) after the procedure. They will have another MRI and PSA test 2 years after the initial MRI. When they complete the study after 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>Subjects in ARM A who do receive a MRI-targeted biopsy</u> will complete and an immediate post-biopsy questionnaire at the time of the biopsy, another an EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>All subjects in ARM B</u> will complete an immediate post-biopsy questionnaire following the standardized TRUS-guided biopsy. They will complete another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p>
Type of control	This is an open-label randomized study.
Number of subjects	This study requires 422 subjects (211 in each arm). To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size will be inflated by 5%, and a target of 450 men will be recruited.
Primary endpoint	The proportion of men in each arm with clinically significant cancer (Gleason \geq 7) will be calculated based on histology results from biopsy procedures. Analysis will be on the per protocol study population.
Secondary endpoints	See section 7.4
Plan for statistical analysis	See section 14.0.
Funding	The total budget for this trial is \$3,000,000. (see attached). Ontario Institute for Cancer Research (OICR) has committed to \$1,500,000 in support of this study (letter appended). We hope to obtain the additional \$1,500,000 from the Movember Accelerated Translational Research Grant Competition

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3183 4. Abbreviations and definitions

3184 Abbreviations:

3185		
3186	ADC	Apparent diffusion coefficient
3187	CI	Confidence interval
3188	CRF	Case report form
3189	DSMC	Data Safety and Monitoring Committee
3190	DRE	Digital rectal examination
3191	DWI	Diffusion weighted imaging
3192	DCE	Dynamic contrast enhancement
3193	EDC	Electronic Data Capture
3194	ITT	Intention to treat
3195	MCCL	Maximum cancer core length
3196	MPMRI	Multi-parametric MRI, used interchangeably with MRI
3197		in this protocol.
3198	MPMRI-TB	Multi-parametric magnetic resonance image-targeted
3199		biopsy of the prostate
3200	MRI	Magnetic resonance imaging, used interchangeably
3201		with MPMRI in this protocol
3202	MRI-TB	Magnetic resonance imaging targeted biopsy
3203	MRS	Magnetic resonance spectroscopy
3204	PI	Principal Investigator
3205	PI-RADS	Prostate Imaging Reporting and Data System
3206	PTC	Permission to Contact
3207	PSA	Prostate specific antigen
3208	REB	Research Ethics Board
3209	STARD	Standards for the reporting of diagnostic studies
3210	TRUS	Trans-rectal ultrasound
3211	TSC	Trial Steering Committee
3212	T2W	T2-weighted imaging

3213

3214

3215 Definitions:

3216

3217	MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is
3218		used to determine the location of a suspicious
3219		target prior to biopsy.

3220

3221	Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure
3222		is not influenced by findings on MRI imaging.
3223		Currently this is the standard of care for
3224		prostate cancer in the province of Ontario.

3225

3226

3227

3228 **5. Trial summary**

3229

3230 **5.1 Aim and Rationale**

3231

3232 The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided
3233 (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is
3234 performed primarily for anatomic guidance as the ultrasound poorly discriminates
3235 between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are
3236 concentrated in areas of the peripheral zone, thought to harbor the majority of
3237 cancer.

3238

3239 An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to
3240 perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer.
3241 This information is used to direct a subsequent biopsy, known as an MRI-targeted
3242 biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a
3243 similar or greater amount of clinically significant cancer than systematic TRUS guided
3244 biopsy and has several other potential advantages including: the ability to
3245 differentiate between clinically significant and insignificant cancer, reducing
3246 unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related
3247 side-effects.

3248

3249 A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an
3250 individual's life expectancy and therefore does not warrant treatment. However
3251 when diagnosed with low grade cancer that is likely to be insignificant, a large
3252 proportion of subjects request treatment in case a more significant cancer is
3253 present[1]. A challenge in this area is that subjects are typically not aware that their
3254 cancer is clinically insignificant, and often view the early diagnosis and aggressive
3255 treatment they have been subjected to as life-saving.

3256 A prostate cancer detection procedure that differentiates clinically significant cancer
3257 from clinically insignificant cancer is therefore a major unmet need.

3258

3259 The potential implications of this trial include:

3260

- A redefinition of the prostate cancer diagnostic pathway;
- A reduction in the number of subjects undergoing prostate biopsy;
- A reduction in the number of biopsy cores taken per subject;
- A reduction in biopsy-related adverse events including sepsis and pain;
- A reduction in the over-diagnosis of clinically insignificant prostate cancer;
- A reduction in the economic burden of diagnosing and treating prostate cancer.

3267

3268

3269

5.2 Methods

3270

3271

3272 Men referred with clinical suspicion of prostate cancer who have had no prior biopsy

3273 are randomized to either systematic TRUS guided biopsy(standard of care) or to a

3274 multi-parametric MRI (MPMRI) arm (the investigational arm). In the MRI arm, areas

3275 of the prostate are scored on a 5-point scale of suspicion for clinically significant

3276 cancer based on the Prostate Imaging Reporting and Data System

3277 (PI-RADS) v2[2]:

3278 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
3279 present)

3280 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

3281 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
3282 equivocal)

3283 PI-RADS 4 – High (clinically significant cancer is likely to be present)

3284 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
3285 present)

3286

3287 Each suspicious area will be given a separate score as described by consensus

3288 meeting recommendations [2, 3]. Lesions scoring 3, 4 or 5 will undergo targeted

3289 biopsy; up to three suspicious areas will be targeted.

3290

3291 In the control arm, subjects will undergo a standard 12 core systematic TRUS guided

3292 biopsy as per standard recommendations[4]. Suspicious sono graphic lesions will be

3293 targeted (12 cores *in toto*).

3294

3295 Pathologic findings from all biopsies will be recorded and will undergo statistical
3296 analysis (see statistics section, 14.0).

3297

3298 In both arms, self-reported questionnaires to capture biopsy-specific side effects will

3299 be administered immediately post-procedure, and at the post-procedure

3300 appointment which will take place 3 weeks (\pm 1 week) after the procedure. Euro QOL

3301 group 5 domain EQ-5D-5L questionnaires or a comparable QOL instrument will also

3302 be completed at baseline (prior to MRI or TRUS biopsy), 24 hours post MRI and 24

3303 hours post-biopsy. Men will be followed up for 30-days post intervention and until a

3304 treatment decision is made and recorded. Pathology results from men requiring a

3305 radical prostatectomy will be recorded.

3306

3307 Men will complete the trial after they complete treatment for prostate cancer

3308 (radical prostatectomy) or the required follow-up procedures for each arm are met

3309 (see study timelines, section 9.3). Once men complete the trial, they revert to

3310 standard of care.

3311

3312 Annual questionnaires will be administered for all men with negative biopsy in both

3313 arms during a two-year follow-up period to determine cancer and treatment status.

3314

3315 No diagnostic test is perfect, and even with the best test some cancers may be

3316 missed. To minimize the risk of false negatives, men with negative biopsy results will

3317 be followed with serial PSA testing; PSA levels will increase if cancer is present. In
3318 addition to serial PSA testing, in this study men who had a negative MRI (defined as
3319 no cancer detected) and do not have a biopsy will have a follow up MRI at 24
3320 months.

3321
3322 As recruitment is expected to take up to 24 months (see section 7.6) and each
3323 subject will be followed up for two years, the estimated maximal duration of this
3324 study is four years in total. The primary endpoint will be reached at approximately 2
3325 years after study initiation.

3326 **5.3 Participating Sites**

3327 This is a multi-centre study. Institutions participating in the study must be able to
3328 perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able
3329 to randomize men to one of these two diagnostic tests.

3330

3331 We expect to recruit 3-6 subjects per month per site, based on recruitment rates
3332 from previous diagnostic trials performed by the centers involved. A typical centre
3333 sees 15-30 eligible men per month. We expect 5 recruitment sites, with 100 men to
3334 be recruited at each site over an 18-24 month period (see section 7.6).

3335 **5.4 Study outcomes**

3336 **5.4.1 Primary outcome**

3337 To determine whether the proportion of men with clinically significant cancer
3338 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
3339 guided biopsy.

3340 **5.4.2 Secondary outcomes**

3341 14. To determine whether the proportion of men with clinically significant cancer
3342 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
3343 guided biopsy.

3344 15. Proportion of men in each arm with clinically insignificant cancer detected.

3345 16. Proportion of men in each arm with Gleason $\geq 4+3$ detected.

3346 17. Proportion of men in MRI arm who avoid biopsy.

3347 18. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
3348 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
3349 detected.

3350 19. Proportion of men in each arm who go on to definitive local treatment (e.g.
3351 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
3352 hormone therapy, chemotherapy).

3353 20. Proportion of men with a negative MRI who develop a positive MRI and/ or
3354 Gleason ≥ 7 cancer by 2 years.

3355 21. Proportion of men with post-biopsy adverse events

3356 22. Health-related quality of life scores.

3357 23. Proportion with Gleason grade upgrading in men undergoing radical
3358 prostatectomy.

3359 24. To determine the cost per diagnosis of cancer.

-
- 3360 25. To determine the impact of the addition of Gd based contrast compared to a non
3361 contrast abbreviated MRI protocol on target yield
3362 26. To determine if a radiologist Likert score not based on Pi-Rads has a better target
3363 yield than Pi_Rads alone
3364
3365

3366 **6. Background**

3367 **6.1 Prostate cancer diagnosis**

3368 Prostate cancer is the most common male cancer in the Western world with an
3369 incidence of 24,000 new cases in Canada and 233,000 in the USA[5, 6]. It is the
3370 second most common cause of cancer death in European and North American men,
3371 with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe[5, 6].
3372 The incidence of the disease has increased by 22% over the last decade due to the
3373 widespread use of the prostate specific antigen (PSA) blood test; by 2030 the
3374 Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.As
3375 prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal
3376 digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one
3377 million prostate biopsies are performed in North America and Europe every year[7].
3378

3379 **6.2 Clinically significant versus clinically insignificant prostate cancer**

3380
3381 Clinically significant prostate cancer is cancer that is likely to progress and affect a
3382 man's life expectancy if left untreated. Though there is no universally agreed upon
3383 definition on what histological parameters define clinically significant cancer, most
3384 agree that larger volume cancers with a higher Gleason grade are more likely to be
3385 clinically significant; an historically accepted threshold is a tumour volume above
3386 0.5milliliters or any Gleason pattern 4 or 5 cancer[8-11].
3387

3388 This definition is likely overly stringent. An increasing consensus views all Gleason
3389 pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of
3390 pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate
3391 cancers fall into this category, and are unlikely to progress and affect a man's life
3392 expectancy if left untreated. The widespread use of PSA testing has led to more men
3393 being diagnosed with insignificant cancer that does not warrant any treatment [13];
3394 however they are typically monitored closely with active surveillance. This is
3395 associated with anxiety about harbouring untreated cancer, and the negative
3396 psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate
3397 cancer are also subjected to serial biopsies and other tests, requiring long term
3398 follow up. Further, many men with low risk disease receive radical treatment, either
3399 because their physicians are not advocates of surveillance or because of anxiety
3400 [15].These treatments may expose them to morbidity including urinary incontinence
3401 and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate
3402 clinically significant cancer from clinically insignificant cancer will help reduce patient
3403 anxiety, alleviate further testing, and avoid radical treatment and associated
3404 morbidities.

3406 **6.3 Current standard of care: systematic TRUS guided biopsy**

3407 The European association of Urology and NICE guidelines recommend systematic
3408 TRUS guided biopsy as the current standard of care for the diagnosis of prostate
3409 cancer [4, 17]. This procedure has several advantages: it can be delivered quickly in
3410 an outpatient clinic under local anesthetic, it can be offered at most Urology centres,
3411 and the expertise is widely distributed.

3412
3413 Limitations of systematic TRUS guided biopsy are as follows: the procedure requires
3414 the operator to take 10-12 samples in the peripheral zone, where it is thought that
3415 the majority of prostate cancer can be found (See Appendix 2)[18]. The ultrasound
3416 guidance used during the procedure is useful for visualizing the prostate and
3417 assessing the location of the needle within the prostate but has a poor ability to
3418 discriminate tumour from normal tissue [19], which means that the systematic TRUS
3419 guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has
3420 been shown to have a high false negative rate of 30-45% [20, 21]. As a systematic
3421 TRUS guided biopsy is not specifically targeted to the location of a suspected
3422 significant cancer, there is also a greater chance that a significant cancer may be
3423 missed.

3424 **6.4 The emerging role of MRI in prostate cancer diagnosis and** 3425 **treatment**

3426 **6.4.1 The role of imaging in prostate cancer diagnosis**

3427 Although used to diagnose many other solid organ cancers such as breast, renal and
3428 colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic
3429 pathway. Imaging in prostate cancer, is typically limited to stage the disease
3430 following histological diagnosis. Magnetic resonance imaging (MRI) is used in many
3431 centres to assess for extra-capsular extension during prostate cancer staging. In the
3432 past five years however, the possibility of using multi-parametric MRI (MPMRI) for
3433 diagnosing prostate cancer prior to biopsy, has generated tremendous interest[22].

3434 **6.4.2 Limitations of early MRI studies in prostate cancer**

3435 Early literature reported conflicting results on the ability of MRI to detect prostate
3436 cancer. A recent systematic review of the literature showed that the quality of
3437 studies evaluating MRI was disappointing [22]. Limitations of reported studies
3438 include:

- 3439 • **Poor reporting standards.** Many early studies failed to closely follow
3440 published guidelines for the standards of reporting of diagnostic studies
3441 (STARD) [23].
- 3442 • **Biopsy artifact.** The majority of early studies evaluated MRI after biopsy.
3443 Evidence has shown that post-biopsy hemorrhage can remain for several
3444 months and affect interpretation of the image [24].
- 3445 • **Poor reference standards.** Many early studies use systematic TRUS guided
3446 biopsy as a reference standard, which due to its limitations, can influence the
3447 validity of the index test of MRI. Using radical prostatectomy specimens as

3448 reference standards can lead to a selection bias, as MRI is only validated in
3449 men with disease characteristics that require radical prostatectomy. Further,
3450 correlation of radical prostatectomy specimen with an MRI image is not
3451 without difficulty given the shrinkage (10-20%), distortion, absent perfusion,
3452 orientation and tissue loss as a result of specimen trimming.

- 3453 • **Incomplete analysis of the prostate.** Many early studies only evaluate the
3454 validity of MRI in the peripheral zone, even though studies have shown that
3455 around 25% of prostate cancers may be located in the transition zone [18].
- 3456 • **Segmentation.** Many early studies artificially divide the prostate into a
3457 number of segments in order to increase the amount of data obtained and
3458 the power of the analysis. Segments should not be treated as independent
3459 regions of interest, and this should be factored into the analysis.

3460

3461 **6.4.3 Emerging role of MRI in the diagnosis of prostate cancer**

3462 Since the publication of these early reports, improvements in diagnostic technology
3463 have changed the field and more evidence supporting the role of pre-biopsy MRI has
3464 been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla
3465 and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image
3466 acquisition and the addition of functional sequences including magnetic resonance
3467 spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast
3468 enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for
3469 biopsy artifacts.

3470
3471 The combination of anatomical sequences (T2-weighted imaging) and functional
3472 sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI.
3473 Combining the sequences improves the validity of the test [25, 26].

3474
3475 A systematic review determined that 60% of men with a clinical suspicion of prostate
3476 cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI
3477 with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity,
3478 positive predictive value and negative predictive value of 90%, 88%, 77% and 95%
3479 respectively for the identification of prostate tumours greater than 0.5ml [28].
3480 Systematic reviews and meta-analysis of recent studies have demonstrated
3481 sensitivity and specificity consistently between 70-90% for the detection of clinically
3482 significant prostate cancer[26, 29-31].

3483
3484 As a result of this accumulating evidence, MRI is increasingly used in clinical practice
3485 in the diagnostic pathway for prostate cancer. The results of MRI can influence the
3486 decision to perform a prostate biopsy, as well as the technique and targeting used
3487 during the biopsy.

3488
3489 MRI has tremendous potential to enhance the outcome of men on active
3490 surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA <
3491 10) harbor higher-grade disease. This occult high-grade disease "*the wolf in sheep's*
3492 *clothing*", is responsible for the 3-5% of prostate cancer deaths that have been
3493 reported in long term surveillance series that did not incorporate MRI[32, 33]. The
3494 early use of MRI in men on surveillance has the potential both to reduce the need

3495 for confirmatory biopsies, and to identify the *wolf in sheep's clothing* earlier, prior to
3496 the development of metastasis.

3497

3498 This was the rationale for the very successful ASIST study, which recently successfully
3499 completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in*
3500 *toto* by the Ontario Institute of Cancer Research. The project was managed by the
3501 Canadian Urology Research Consortium (CURC). It randomized 273 men recently
3502 diagnosed with low risk prostate cancer, on surveillance, between systematic
3503 confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end
3504 point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or
3505 higher prostate cancer. The study had numerous secondary end points and
3506 correlative science components. We expect to report the initial results by 3Q
3507 2016. We believe that the success and potential impact of the ASIST trial has created
3508 strong momentum to proceed with the PRECISE trial, which has even greater
3509 potential to substantially influence prostate cancer screening and diagnosis.

3510 **6.4.3.1 MRI can influence the decision to perform a prostate biopsy**

3511 With reported negative predictive values of 95% [28, 34,35], MRI can help determine
3512 whether a prostate biopsy is necessary; if the MRI does not identify a suspicious area
3513 the biopsy can be avoided. Using MRI, 40-50% of men referred with clinical suspicion
3514 of prostate cancer might avoid a biopsy [27]. The recent National Institute for Health
3515 Research (NIHR) Health Technology Assessment (HTA) report [11] acknowledged the
3516 value of MRI in this context. The NIHR HTA report suggests that using MRI to reduce
3517 the number of men who undergo biopsy, can be cost effective despite the costs
3518 associated with MRI[11]. Cost savings for the publically funded health care system
3519 accrue as a result of reduced number of biopsies and costs of attendant
3520 complications, and reduced treatment of clinically insignificant cancer.

3521 **6.4.3.2 MRI can influence the biopsy technique**

3522 For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI
3523 information is used to influence the prostate biopsy technique. This is known as MRI-
3524 targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of
3525 ways.

3526

3527 The biopsy operator can use the MRI images or report to direct biopsies into the
3528 area of the prostate where the tumour is located. The location of the tumour on the
3529 MRI (carried out in advance) is registered to the real-time ultrasound images with
3530 the use of software (software assisted registration or image-fusion) or without the
3531 use of software (visual registration or cognitive registration), while the prostate is
3532 visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted
3533 directly "in-bore", where the biopsy is conducted within an MRI scanner where the
3534 target identified on MRI during a prior diagnostic scan is biopsied using guidance
3535 from serial MRI scans during the biopsy procedure, performed in an open magnet.

3536

3537 For the PRECISE study, the biopsy will be performed using an image fusion-targeting
3538 device. Two devices have been FDA approved: the Artemis, made by Eigen, and the
3539 Urostation, made by Koelis. These devices import the MR target into the TRUS
3540 image, and direct the biopsy needle into the target.

3541 **6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are**
3542 **similar to other methods**

3543 A systematic review determined that 60% of men with a clinical suspicion of prostate
3544 cancer will have a suspicious area identified on MRI [27]. One study found that a
3545 prostate biopsy strategy using only MPMRI-targeted cores resulted in the same
3546 detection rate of clinically significant cancer as 20-sector transperineal biopsies[36].
3547 Other studies also show that a targeted-alone approach would detect a similar
3548 amount of clinically significant cancer when compared to a 10-12 core systematic
3549 TRUS guided biopsy[37]. A targeted-alone approach detects 17% less clinically
3550 insignificant cancer compared to systematic TRUS guided biopsy[38].

3551
3552 The detection rates achieved with a targeted-alone biopsy strategy require fewer
3553 biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis,
3554 targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer
3555 detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores
3556 compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of
3557 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material
3558 for histopathological analysis as the maximum cancer core length obtained from
3559 targeted biopsies can be greater than that obtained from systematic biopsies[37].

3560
3561 Robust comparative evidence from randomized controlled trials is needed to
3562 determine if MRI scans can improve our ability over systematic TRUS guided biopsy
3563 to diagnose clinically significant cancer and our ability to avoid detecting clinically
3564 insignificant cancer.

3565

3566 **6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy**

3567 Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine
3568 clinical practice for prostate cancer diagnosis. Most existing studies have cohort
3569 study designs which make interpretation difficult as they do not conform well to
3570 STARD [23] recommendations [27]. Limitations of these studies include:

- 3571 • **Broad definition of the study population.** The cancer detection rates depend on
3572 the prevalence of the condition in the population being investigated. This varies
3573 amongst men with no prior biopsy, prior negative biopsy and prior positive
3574 biopsy. In many studies the detection rates are not attributable to a clearly
3575 defined population.
- 3576 • **MRI conduct and reporting.** The detail in which MRI is conducted and
3577 interpreted varies greatly amongst published studies.
- 3578 • **Reporting of cancer detection.** The cancer detection by systematic and targeted
3579 cores is not always presented separately and cancer detection is not always
3580 specified by clinical significance. These are both essential in order to evaluate the
3581 technique.

3582 There is a strong need for a randomized controlled trial comparing MRI-targeted
3583 biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical
3584 practice can be established.

3585 **6.5 Novelty of PRECISE**

3586 PRECISE is the first randomized study in biopsy-naïve men in which men are
3587 randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal
3588 areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic
3589 TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-
3590 targeted biopsy approach in the detection of clinically significant cancer. In order to
3591 evaluate a biopsy technique that could replace standard of care, the standard of care
3592 test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to
3593 allow a direct comparison.

3594

3595 Other constituencies with an interest in MRI in prostate cancer (University College,
3596 London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New
3597 York) have considered similar studies, however in these centres MRI has largely
3598 replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to
3599 date. As a result, these centres have acknowledged that randomization to a standard
3600 biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as
3601 equipoise has been lost.

3602

3603 In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not
3604 recommended for the indication of an elevated PSA in men who have not had a
3605 biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed
3606 to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a
3607 biopsy will make entry into this trial very appealing to potential candidates. Further,
3608 the barriers, both financial and physical, to obtaining a quality MRI outside of the
3609 health care system are substantial. Thus we believe men who are randomized to the
3610 systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant
3611 contamination (i.e. men randomized to the systematic biopsy arm seeking out an
3612 MRI instead).

3613

3614 **7. Trial objectives**

3615 **7.1 Overall aim**

3616 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
3617 standard of care systematic TRUS guided biopsy in the detection of clinically
3618 significant and clinically insignificant prostate cancer in men without prior biopsy.
3619 The implication of this trial is that MRI-targeted biopsy could replace systematic
3620 TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

3621 **7.2 Hypotheses**

3622 The proportion of men with clinically significant cancer detected by MRI-targeted
3623 biopsy will be no less than that detected by systematic TRUS guided biopsy.

3624 **7.3 Primary Objective**

3625 To determine whether the proportion of men with clinically significant cancer
3626 (Gleason \geq 7) detected by MRI-targeted biopsy is no less than systematic TRUS
3627 guided biopsy.

3628 **7.4 Secondary Objectives**

- 3629 27. To determine whether the proportion of men with clinically significant cancer
3630 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
3631 guided biopsy.
- 3632 28. Proportion of men in each arm with clinically insignificant cancer detected.
- 3633 29. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 3634 30. Proportion of men in MRI arm who avoid biopsy.
- 3635 31. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
3636 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
3637 detected.
- 3638 32. Proportion of men in each arm who go on to definitive local treatment (e.g.
3639 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
3640 hormone therapy, chemotherapy).
- 3641 33. Proportion of men with a negative MRI who develop a positive MRI and/ or
3642 Gleason ≥ 7 cancer by 2 years.
- 3643 34. Proportion of men with post-biopsy adverse events
- 3644 35. Health-related quality of life scores.
- 3645 36. Proportion with Gleason grade upgrading in men undergoing radical
3646 prostatectomy.
- 3647 37. To determine the cost per diagnosis of cancer.
- 3648 38. To determine the impact of the addition of Gd based contrast compared to a non
3649 contrast abbreviated MRI protocol on target yield
- 3650 39. To determine if a radiologist Likert score not based on Pi-Rads has a better target
3651 yield than Pi_Rads alone
- 3652
- 3653

3654 **7.5 Explanation for non-inferiority hypothesis**

3655 Due to the putative advantages of MRI-TB in reducing the number of men who
3656 require a biopsy, reducing the number of cores required in each man who is
3657 biopsied, more accurate representation of disease burden, less insignificant disease
3658 detected and reducing the number of men at risk of complications of biopsy, the
3659 primary outcome of detection of clinically significant cancer in each arm will be
3660 compared using a non-inferiority hypothesis. Even if a similar amount of clinically
3661 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these
3662 advantages would support the use of MRI-TB instead of systematic TRUS guided
3663 biopsy in clinical practice.

3664

3665 **7.6 Anticipated timeline of study progression**

3666 The study will commence once sponsorship, ethical approval and local approvals
3667 have been obtained at a participating site and once site initiation training has
3668 occurred and a letter of site activation has been issued from the coordinating centre.
3669 Additional sites may join after the study has commenced. At this time, five sites will
3670 participate. Assuming a minimum recruitment rate of 3-6 men per site per month,
3671 recruitment will be complete by 24 months, if not sooner. If accrual is slower than
3672 expected, an additional 1-2 sites will be recruited for year 2.

3673

Month	Number of Sites	Total recruitment
0	2	0
3	4	18-36
6	5	54-108
9	5	99-198
12	5	144-288
15	5	189-378
18	5	234-468
21	5	279-558
24	5	324-648

3674

3675 **8.Study Population**

3676 **8.1 Number of Subjects**

3677 Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or
3678 results of digital rectal exam, with no prior biopsy will be eligible for participation.
3679 Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be
3680 enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

3681 **8.2 Subject inclusion criteria**

3682 In order to be eligible, all inclusion criteria must be met:

- 3683 7. Men at least 18 years of age referred with clinical suspicion of prostate cancer
3684 who have been advised to have a prostate biopsy;
- 3685 8. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk
3686 assessment of prostate cancer calculator, PCPTRC 2.0, found at
3687 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> For men under age 55,
3688 the default age of 55 should be entered on the risk calculator.
- 3689 9. Serum PSA ≤ 20 ng/ml within 3 months of randomization
- 3690 10. Fit to undergo all procedures listed in protocol;
- 3691 11. Able to provide written informed consent.

3692 **8.3 Subject exclusion criteria**

3693 Men who meet the following criteria at the time of screening will be excluded:

- 3694 7. Prior prostate biopsy
- 3695 8. Prior treatment for prostate cancer
- 3696 9. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR
3697 ≤ 50 mls/min)
- 3698 10. Contraindication to prostate biopsy
- 3699 11. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip
3700 replacement surgery, metallic hip replacement or extensive pelvic orthopaedic
3701 metal work
- 3702 12. Unfit to undergo any procedures listed in protocol.
- 3703

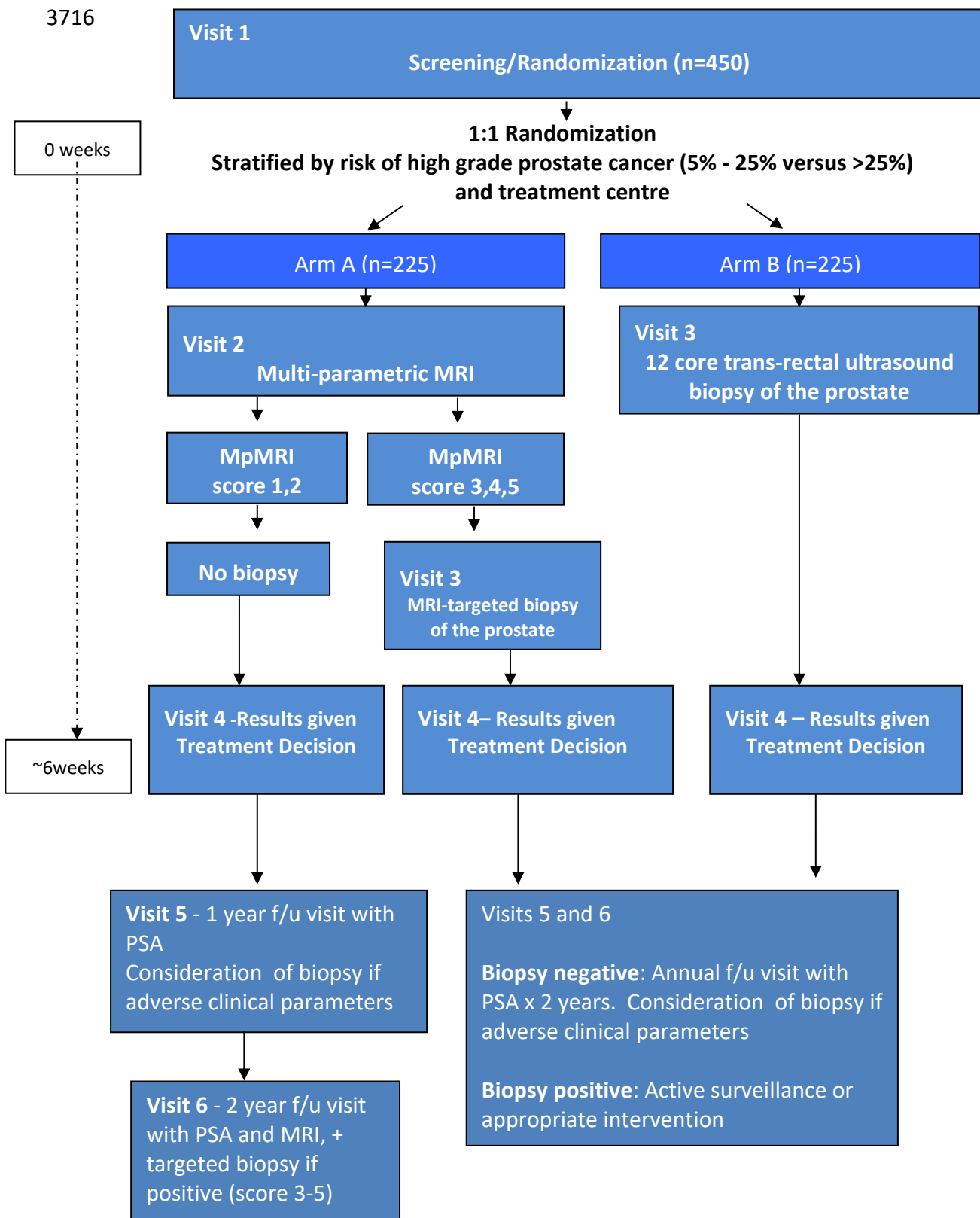
3704 **9. Study design**

3705 **9.1 Study design**

3706 The study is a multi-centre, open-label randomized controlled trial, with men
3707 randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in
3708 Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or
3709 will be followed for two years if there is no suspicious areas identified by MRI. The
3710 unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-
3711 core systematic TRUS guided biopsy. All men in the study will be followed for two
3712 years or until they have had radical treatment (whichever comes first).
3713

3714
3715
3716

9.2 Study Trial Schema



3717 **9.3 Timeline of subject contact**

3718 Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial.

3719 The individual pathway that each subject experiences is dependent on both the arm
3720 he is randomized to and results of the tests.

3721

3722 **Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require**
3723 **a biopsy**

	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3 N/A	Visit 4 Post- Test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	5	26	52	78	104
Consent	X							
Screening (eligibility review, med hx,	X							
Vitals, DRE ¹	X				X	X	X	X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue- NA								
Creatinine	X							
PSA ⁴	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI		X						X ⁵
MRI-Targeted Biopsy								X if target
Immediate post- biopsy questionnaire								
Follow up for results of tests				X				
Treatment decision ⁶				X				
30-day post- biopsy questionnaire								
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

3724 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
3725 Science component. See correlative manual for instruction.
3726 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
3727 catch' and post-DRE samples. See the Correlative Science Manual for further details on
3728 collection and processing.
3729 ³Collected at baseline, and annually.
3730 ⁴PSA will have been done prior to visit 1 as part of screening.
3731 ⁵ If MRI indicates a target, biopsy must be done
3732 ⁶After treatment decision men revert to standard of care.
3733

3734
3735

Table 2: ARM A: Men randomized to MRI arm who have a lesion on MRI and require a biopsy

	Visit 1 Screening / Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post- test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follo w up
Weeks:	0	1	2	6	26	52	78	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals, DRE ¹	X				X	X	X	X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue ⁴			X					X
Creatinine	X							
PSA ⁵	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI ⁶		X						
MRI-Targeted Biopsy			X					
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁷				X				
30-day post- biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds From	Complete as required at any time following registration							

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¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First catch' and post-DRE samples. See the Correlative Science Manual for further details on collection and processing.

³Collected at baseline, and annually.

⁴ tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

⁵PSA will have been done prior to visit 1 as part of screening.

⁶ If MRI indicates a target, biopsy must be done, and tissue obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.⁷After treatment decision men revert to standard of care.

Table 3: ARM B: Men randomized to systematic TRUS guided biopsy arm

	Visit 1 Screening/ Randomization	Visit 2	Visit 3 Biopsy	Visit 4 Post- test visit	Visit 5 6 mos	Visit 6 1 year follo w up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	6	26	52	52	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals, DRE ¹								
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue			X					
Creatinine	X							
PSA	X				X	X	X	X
Systematic TRUS guided biopsy			X					
MRI								
MRI-Targeted Biopsy								
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁴				X				
30-day post- biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

3788 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
3789 Science component. See correlative manual for instruction.
3790 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
3791 catch' and post-DRE samples. See the Correlative Science Manual for further details on
3792 collection and processing.
3793 ³Collected at baseline, and annually.
3794 ⁴PSA will have been done prior to visit 1 as part of screening.
3795 ⁵If MRI indicates a target, biopsy must be done, and tissue must be obtained if subject has
3796 agreed to the Correlative Science component. See correlative manual for instruction.⁶After
3797 treatment decision men revert to standard of care.
3798
3799

3800 **10. Trial Interventions and procedures**

3801
3802 The following procedures will be applied as necessary to subjects enrolled in both
3803 arm of the trial.

3804 **10.1 EQ-5D-5L Questionnaires**

3805

3806 **For all subjects enrolled in trial**

3807 Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L
3808 questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to
3809 evaluate health related quality of life. It takes approximately 2 minutes to complete.

- 3810 • All subjects should complete the baseline questionnaire at the screening visit
3811 before leaving the department.
- 3812 • Subjects will be given the questionnaire before they leave the department and
3813 the subject should take this home. Subjects can return the completed
3814 questionnaire to the investigator by post in a pre-addressed envelope provided
3815 by the investigator. It cannot be filled out immediately after the procedure in the
3816 department as it assesses domains such as washing, dressing and carrying out
3817 usual activities, which cannot be established immediately after the biopsy.
3818 Subjects will be reminded by the biopsy operator to complete the questionnaire
3819 at home and may be given a phone call by the research team to remind them to
3820 complete the questionnaire.
- 3821 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
3822 be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date
3823 that the subject should fill out the questionnaires should be written on top of the
3824 questionnaire. (This can also be done at Visit 4).
- 3825 • All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up
3826 visit.

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3833 **10.2 Multiparametric MRI imaging procedure**

3834 **For subjects in Arm A only**

3835

3836 **10.2.1 MRI Protocol**

3837 A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic
3838 phased array coil and an automated injector system with the subject in the supine
3839 position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast
3840 enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS
3841 v2.

3842

3843 Within the specified PiRads-2 framework a common protocol will be formulated by a
3844 consensus of the radiologists involved in the trial at each site at a startup meeting.
3845 The highest agreed upon b-value image for DWI (at least 1400s/mm²) will be
3846 selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast
3847 media, injection rates and dynamic scanning temporal resolution will be matched for
3848 all sites. An optional multi b value DWI acquisition will be undertaken as well to
3849 allow for ancillary studies into non log linear apparent diffusion coefficient (ADC)
3850 models for tumor characterization. This is summarized in an MRI Operations Manual

3851

3852

3853 Subjects will be asked to follow their local standard of care MRI examination
3854 preparation instructions for the MRI procedure.

3855 **10.2.2 MRI reporting**

3856 The MRI will be reported by an experienced radiologist using the MRI Reporting
3857 Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored
3858 based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5
3859 point Likert score for purposes of comparison. . Biopsy decisions will be based on the
3860 PiRads scores.

3861

3862

3863 Lesions in the prostate will be scored on the following scale:

3864 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
3865 present)

3866 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

3867 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
3868 equivocal)

3869 PI-RADS 4 – High (clinically significant cancer is likely to be present)

3870 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
3871 present)

3872

3873 The location of the suspicious areas in the prostate should be marked on a diagram
3874 of the prostate (see Appendix2) and the sector numbers containing each suspicious
3875 area should be recorded in the case report form.

3876

3877 Radiologists will be blinded to the PSA.

3878

3879

3880 Imaging interpretation will be carried out at each site, however ensuring consistency
3881 and quality of imaging interpretation is crucial. A central imaging site will be
3882 designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site
3883 will perform the interpretation of all images for that site. The designated radiologist
3884 must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A
3885 startup meeting involving all radiologists will be held prior to start of accrual where
3886 each site will bring 5 MRI cases performed at their site for consensus review, scoring
3887 and discussion. This will provide a commonality of approach to interpretation among
3888 the radiologists before the study begins. After this startup meeting each site will
3889 send one set of MRI images and its interpretation for central review for site
3890 qualification.

3891

3892 A copy of all images will be sent on CD/DVD to the central site for archiving.

3893 **10.3 No target identified on MPMRI (PiRads 1 or 2)**

3894 **For subjects in Arm A only, who do not require a biopsy**

3895 Men who have MRIs that do not identify any suspicious lesion will not receive a
3896 biopsy. These subjects will benefit from being part of the trial as a result of not
3897 having to undergo an invasive biopsy procedure, avoiding the discomfort associated
3898 with the procedure, the risk of being diagnosed with clinically insignificant cancer
3899 and the risk of sepsis associated with the biopsy procedure. Studies suggest that if
3900 the MRI does not identify areas suspicious for cancer there is an 85-95% chance that
3901 clinically significant cancer is not present[28, 34, 35].

3902

3903 As soon as the results of the MRI are discussed with the subject, their treatment
3904 decision will be recorded and they will return to standard of care management. As
3905 part of standard of care these subjects can undergo further PSA surveillance and / or
3906 prostate biopsies if indicated.

3907 **10.4 MRI-Targeted biopsy**

3908 **For subjects in Arm A who do require a biopsy**

3909 **10.4.1 MRI choice of targets for targeted biopsy**

3910 Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will
3911 subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in
3912 MRI-targeted biopsy. Operator experience (number of targeted biopsies performed
3913 to date) will be recorded before each procedure. The number of biopsy operators
3914 should be kept to the minimum number possible.

3915

3916 Targets will be stratified by PI-RADS score and if the same score then by size and
3917 labeled T1, T2, T3...etc. If there are more than 3 lesions with a score of 3 or more
3918 only T1-T3 will be targeted. The radiologist should record the sectors involved with
3919 tumor in order of most to least involved using the PI-RADS v2 sector scheme.

3920 The number of biopsy operators should be kept to the minimum number possible.

3921

3922 Subjects in the MRI cohort will not have systematic biopsies, with one exception.
3923 Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small
3924 volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core
3925 biopsy will be conducted.

3926 **10.4.2 MRI Biopsy**

3927 The procedure will be performed in the outpatient departments of sites possessing
3928 the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An
3929 operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI
3930 fusion system at their institution before they are qualified to participate as an
3931 operator in the study.

3932
3933 Coumarin anticoagulant, clopidogrel treatment and other relevant
3934 anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and
3935 advice sought as to appropriate substitutes if indicated. Aspirin will be continued at
3936 the discretion of the physician doing the biopsy.

3937
3938 Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will
3939 be performed via the trans-rectal route or via the trans-perineal route depending
3940 upon local practice.

3941
3942 Targeted biopsies should be performed by software-assisted fusion devices
3943 (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This
3944 software is safe and poses no risks to the subject since the same CE-marked
3945 ultrasound probes that are designed to perform the biopsy when performed as
3946 standard of care biopsy are used during targeted biopsy. Should the operator wish to
3947 not use the information provided by the software registration system and use
3948 cognitive (visual) registration alone they can do so, but should indicate this on the
3949 subject's case report form.

3950
3951 The samples per target will be 4cores spread across the target region for a maximum
3952 total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be
3953 conducted in order meaning T1 then T2 then T3.

3954
3955 Biopsy cores from different suspicious areas will be aliquoted separately. The vials
3956 will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there
3957 are) which should match the assignment of suspicious areas by the radiologist on the
3958 MRI report. The order of lettering a-d should match the order in which the biopsies
3959 were performed in each region. The first biopsy should be at the center of the target
3960 and the remaining fanning out from the center. Each core from the same suspicious
3961 area must be submitted separately. Alternative methods of storing cores that allow
3962 identification of the order of score samples from each target are acceptable.

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- 3966 **10.5 Systematic TRUS guided biopsy**
- 3967 **For all subjects in Arm B**
- 3968 Systematic TRUS guided biopsy is the current standard of care for the diagnosis of
3969 prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local
3970 site of recruitment.
- 3971
- 3972 A clinician competent in systematic TRUS guided biopsy will perform the procedure.
3973 The experience of the operator (number of systematic TRUS guided biopsies
3974 performed to date) will be recorded prior to each procedure. Software that guides
3975 clinicians in placing biopsy cores should not be used.
- 3976
- 3977 Coumarin anticoagulant, clopidogrel treatment and other relevant
3978 anticoagulant/antiplatelet medication will be discontinued 5 to 10 days before biopsy
3979 and advice sought as to appropriate substitutes if indicated. Aspirin will be continued
3980 at the discretion of the physician doing the biopsy.
- 3981
- 3982 The subject will be positioned in left lateral position. 10-12 core biopsies will be
3983 taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed
3984 to the peripheral zone (See Appendix 3 for standardized method for conducting 12-
3985 core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be
3986 given as per local guidelines.
- 3987 **10.6 Pathology**
- 3988 The 2005 International Society of Urological Pathology guidelines for Gleason
3989 Grading of Prostatic Carcinoma will be followed [43].
- 3990
- 3991 For men undergoing MRI-targeted biopsy it is required that pathology reported per
3992 suspicious area targeted and per targeted core. For systematic TRUS guided biopsy,
3993 each core will be reported and graded.
- 3994 **10.7 Post-procedural care**
- 3995 **For all subjects in ARMS A and B receiving a biopsy**
- 3996 After a biopsy procedure the subject can be discharged. within 2-3 weeks for results
3997 of the histopathology and treatment options to be discussed.
- 3998 **10.8 Immediate post-biopsy questionnaire**
- 3999 **For all subjects in ARMS A and B receiving a biopsy**
- 4000 A modified version of a self-reported questionnaire validated previously [39] in the
4001 assessment of post-biopsy complications will be completed immediately post-biopsy
4002 after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject
4003 should complete the immediate post-biopsy questionnaire before they leave the
4004 department. It aims to assess intensity of discomfort and pain associated with the
4005 procedure.
- 4006 **10.9 30-day post-biopsy questionnaire**
- 4007 **For all subjects in ARMS A and B receiving a biopsy**

4008 A modified version of a self-reported questionnaire validated previously [39] in the
4009 assessment of post-biopsy complications at 30 days post-biopsy should be given to
4010 all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home
4011 (Appendix 8). The subject should fill this out on day 30 following the procedure. It
4012 should take 5 minutes to fill out. The date that the participant should complete the
4013 questionnaire should be written on top of the questionnaire. Data on specific biopsy-
4014 related complications including pain, fever, hematuria, hematochezia,
4015 hematospermia, urinary retention and urinary incontinence will be recorded. Any
4016 other adverse events will not be recorded. Contact with healthcare and resource
4017 used data following the biopsy will also be ascertained. The completed questionnaire
4018 can be returned to the investigator in a pre-addressed envelope.

4019

4020 Subjects should be reminded at 30 days to complete this questionnaire.

4021 **10.10 Results and treatment decision (Visit 4)**

4022 The results of the biopsies and/or MRI will be explained to the subject by the clinical
4023 care team during this visit, which is approximately 2-3 weeks after the biopsy.

4024 The research team should record the treatment decision in the subject file.

4025 Possibilities for treatment decision include but are not limited to:

- 4026 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 4027 • Active Surveillance
- 4028 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 4029 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 4030 • Hormone therapy

4031 **10.11 Follow up period**

4032 All study participants will be followed up for up to two years or until they have
4033 radical treatment. Each year, subjects will be surveyed to obtain the following
4034 information:

- 4035 • time to cancer diagnosis
- 4036 • Gleason score progression
- 4037 • time to intervention on active surveillance
- 4038 • time on active surveillance
- 4039 • PSA

4040

4041 **10.11.1 Indications for biopsies off protocol**

4042 For subjects who are not biopsied due to a negative MRI, have negative or non-
4043 significant systematic biopsies, or who have a positive MRI but no or non-significant
4044 cancer on targeted biopsy, the following are guidelines for subjects management
4045 during the 2 year follow up period.

4046 It is an accepted standard of care in Ontario for subjects on active surveillance or
4047 with a prior negative biopsy who have a worsening risk profile to undergo mpMRI
4048 followed by targeted biopsy. We propose the following guidelines for risk profile
4049 assessment and consideration of repeat biopsy

4050 Subjects should continue to be followed with semi-annual PSA and DRE. A biopsy
4051 should be considered under one or more of the following circumstances:

- 4052 1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.
- 4053 2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase
4054 in PSA in 1 year.
- 4055 3. Biopsy if a doubling of the risk of high grade cancer according to the NCI
4056 nomogram.
- 4057 4. Biopsy if development of a suspicious nodule on DRE.
4058
- 4059 5. For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy
4060 which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or
4061 more increase in PSA over 1 year or a PSA density > 0.15.
4062
- 4063 12. For men on the systematic biopsy arm which was negative or showed only
4064 Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or
4065 a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these
4066 subjects.

4067

4068

4069 These are guidelines and should be interpreted with clinical judgment.

4070

4071 Follow-up will cease once treatment beyond active surveillance is undertaken
4072 (prostatectomy, radiation therapy, focal therapy, etc.)

4073 PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI
4074 identifies a target.

4075 **10.12 Additional tests for biomarker discovery - Optional**

4076 Though not related to the primary outcome of this study, this cohort represents a
4077 unique opportunity to obtain human samples for future biomarker discovery studies.
4078 Participants will be consented to provide a blood, urine, semen, and tissue sample
4079 after the consent and screen visit, and subsequent visits for storage and use in future
4080 biomarker studies. In addition, men will be consented for use of the prostate biopsy
4081 tissue in the biomarker discovery studies.

4082

4083 We propose two initial biomarker analyses for men recruited to the PRECISE study.
4084 First we propose testing the utility of existing validated tests, these potentially
4085 include the Genomic Prostate Score (OncotypeDx) [44] and a recently developed
4086 multiple Kallikrein biomarker test[45]. We will test the hypothesis that alongside
4087 conventional PSA measurements, the multiple Kallikrein test or other serum
4088 biomarker test, may identify subjects whose MRI was initially negative for prostate
4089 cancer, but who are at high risk of harboring clinically significant disease as detected
4090 by the secondary MRI at 2 years. We will also test the association between serum
4091 biomarkers and clinically significant or clinically insignificant prostate cancer
4092 detected during the PRECISE study. We will also explore the potential for the

4093 Genomic Prostate Score to provide additional information over and above Gleason
4094 grade. These studies will be separately funded from PRECISE.
4095
4096 Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will
4097 be planned to assess markers which might identify men at higher risk of developing
4098 prostate cancer.

4099 **10.12.1 Samples to be collected for future biomarker discovery work**
4100 **(Optional)**

4101 Participants will be asked to consent to provide a blood, urine, semen, and tissue
4102 sample after the consent and screen visit and subsequent visits for storage and use
4103 in future biomarker studies. This will involve a separate consent form.

4104 Samples include:

- 4105 • Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- 4106 • Urine – 75 mls urine
- 4107 • Semen-1-5 cc (single ejaculate)
- 4108 • Tissue-unstained biopsy sections -15 unstained slides from cancer, and
4109 -15 unstained slide from non-cancer cores
4110 (if possible)

4111 **10.13 Long-term data linkage – Permission to Contact**

4112 The cohort of men who consent to participate in this study represent a uniquely
4113 characterized group. Their long-term outcomes will contribute to our understanding
4114 of the epidemiology of prostate cancer beyond the questions being addressed in this
4115 study.

4116

4117 Permission to Contact (PTC) is a feasible mechanism to engage subjects in research
4118 programs. This will allow researchers to contact study participants in the future to
4119 assess their willingness to respond to questionnaires. This potentially enables
4120 research that would complement the planned long-term follow up in terms of health
4121 status, for obtaining information about future biopsies not included in the study, and
4122 allow assessment of quality of life.

4123 **10.14 End of Study**

4124 The end of study assessment comprises an essential safety evaluation that should be
4125 completed prior to discharging any subject from the study.

- 4126 • Adverse events;
- 4127 • PSA measurement;
- 4128 • EQ-5D-5L questionnaire;
- 4129 • An MRI in those who did NOT have a biopsy;
- 4130 • Complete CRF.

4131 **10.15 Risks and Benefits to Participants**

4132 An important consideration of this study is that men are being randomized to one of
4133 two biopsy techniques when it is not known which will be more effective. Both
4134 diagnostic tests are currently used in clinical practice at the institutions involved in

4135 the trial. Though systematic TRUS guided biopsy could be considered standard of
4136 care, there is enough evidence to support the concept that MRI-targeted biopsy may
4137 be at least as effective as systematic TRUS guided biopsy[27].

4138 **10.15.1 Risks to subjects**

4139 The intervention proposed in this trial (MRI-biopsy) do not offer participants any
4140 more risk than if they underwent standard of care (systematic TRUS guided biopsy)
4141 for the diagnosis of prostate cancer.

4142 **10.15.1.1 Risk of Systematic TRUS guided biopsy**

4143 Systematic TRUS guided biopsy can be associated with discomfort, haematuria,
4144 haematospermia and dysuria in a large proportion of subjects, which is self-resolving
4145 (See Table 4). There is a 4% risk of systemic urosepsis[46].

4146 **10.15.1.2 Risks of MPMRI**

4147 MRI is associated with few risks. It is a safe procedure used in everyday clinical
4148 practice (See Table 4). Small risks of allergic reactions are associated with the
4149 intravenous administration of gadolinium, the contrast agent used in MRI scans. The
4150 study uses a low molecular weight Gd chelate as a contrast agent (Gadovist, Bayer,
4151 gadobutrol – generic). This contrast agent is used routinely for contrast enhanced
4152 MRI and is approved by Health Canada. Subjects will be screened for any
4153 contraindications to Gd injection or to MRI as per current clinical Dept of Medical
4154 Imaging protocols at each institution. The commonest reported sides effects are of
4155 limited duration and mild to moderate in intensity and include headache,
4156 vasodilation, injection site pain, nausea, dizziness, rash, and dyspnea. The incidence
4157 of these are <1%. Severe life threatening reactions such as severe anaphylaxis occur
4158 very rarely, about 1:10,000-1: 100,000. These are treatable with epinephrine and
4159 steroids. The risk of death is <1:100,000. There is a known risk of nephrogenic
4160 systemic fibrosis, a potentially fatal condition in subjects with impaired renal
4161 function, with an eGFR <30ml/min/1.73m². These subjects are ineligible for this
4162 study.

4163 **10.15.1.3 Risks of MRI-targeted biopsy**

4164 MRI-targeted biopsy is associated with similar risks to the standard of care
4165 systematic TRUS guided biopsy. As fewer biopsy cores are being taken with MRI-
4166 targeted biopsy, the theoretical risk of adverse events associated may be less than
4167 that of systematic TRUS guided biopsy. In addition, as a proportion of men may not
4168 require a biopsy (approximately 30%) on a group level there will be reduced number
4169 of men experiencing these complications, which is one of the major advantages of an
4170 MRI-based approach.

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Table 4: Adverse events associated with procedures

Procedure Side Effect	Systematic TRUS guided biopsy(Standard of care)	MRI	MRI-targeted biopsy
Pain / discomfort	Some have discomfort Some have pain	Intravenous cannulation (to allow contrast administration) can cause minimal discomfort	Similar / reduced compared to systematic TRUS guided biopsy
Dysuria	Majority have dysuria (self-resolving in 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematuria	Majority (self-resolving, 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haemospermia	Majority (self-resolving, 1-2 weeks)	No	Similar / reduced compared to systematic TRUS guided biopsy
Erectile dysfunction	30% (self resolving after 1-2 months)	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary Tract infection	1-8 %	No	Similar / reduced compared to systematic TRUS guided biopsy
Systemic urosepsis	2-4%	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary retention	1%	No	Similar / reduced compared to systematic TRUS guided biopsy
Contrast allergy	N/A	Rare < 1 in 10000 – severe allergic reaction (breathing problems) < 1 in 2000 – moderate allergic reaction (nausea and vomiting) < 1 in 250 – mild allergic reaction (rash, itching)	N/A
Adverse effects of antibiotics	Rare <1%	N/A	Rare <1%

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4188 **10.15.2 Benefits to subjects**

4189 Subjects enrolled in this trial will benefit from the following:

- 4190 • Subjects in both arms may benefit from receiving a diagnostic test for suspected
4191 prostate cancer and will receive further treatment if required. The research team
4192 will also ensure streamlined diagnostic investigations to promptly conduct the
4193 diagnostic test and communicate the test outcome for the subject.
- 4194 • Subjects enrolled in the trial will benefit from the dedicated research team
4195 involved in their care in addition to the clinical team normally involved in their
4196 care.
- 4197 • Subjects will benefit from additional discussions regarding the trial, which could
4198 increase their understanding of prostate cancer and help them to make a more
4199 informed decision about their health.
- 4200 • Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will
4201 remove any risk of post-biopsy infection. MRI-randomized subjects may also
4202 benefit from a reduced probability of having a clinically insignificant prostate
4203 cancer diagnosed. Clinically insignificant prostate cancer is often treated
4204 definitively per subject preference despite the lack of evidence supporting the
4205 need. All definitive local therapies for prostate cancer carry the risk of peri-
4206 operative complications as well as long-term risk of incontinence and erectile
4207 dysfunction.

4208

4209 **10.16 Concomitant medications**

4210 **10.16.1 Permitted Medications**

4211 All concomitant medications taken during the study will be recorded in the CRF with
4212 indication, dose information and dates of administration. The definition of which
4213 medication would be considered outside the routine medical practice is up to the
4214 discretion of the investigator. All dietary and herbal supplement usage will be
4215 recorded in the CRF.

4216 **10.16.2 Non-Drug Therapies**

4217 Any occurrence of prostate-related surgical and/or non-surgical (or minimally
4218 invasive) intervention during the conduct of the study will be recorded in the CRF.

4219

4220 **11. Schedule of Study Visits**

4221 **11.1 Visit 1 (Screening/Randomization): Screening, Consent,**
4222 **Randomization**

4223 **For all subjects enrolled in trial**

4224 Screening will occur any time following the referral of the subject. Ideally, this will be
4225 performed as soon as possible following receipt of referral.

4226 Subjects will be consented only after they have had time to consider the study. This
4227 may happen on the same visit as the screening visit.

4228 Randomization can happen immediately after the consent form is signed and
4229 eligibility is confirmed.
4230
4231 Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L
4232 questionnaire (Appendix 4), which is a validated 2-page questionnaire representing
4233 health related quality of life. It takes approximately 2 minutes to complete. This
4234 questionnaires should be completed at the screening visit before the subject leaves
4235 the clinic.
4236
4237 If a subject agrees to the optional informed consent, from randomization until any
4238 point prior to a biopsy, optional blood, urine, semen and tissue samples will be
4239 collected for correlative studies.
4240
4241 Even if PSA testing was done prior to Visit 1, PSA should be obtained at Visit 1.
4242

4243 **11.2 Visit 2 (MRI): ARM A, for men randomized to MRI**

4244 This will occur approximately within one week of randomization. Men will receive an
4245 MRI (see Section 10.2.)

4246 **11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate**

4247 **For men randomized to ARM A, who have a lesion identified by MRI.** This
4248 appointment will follow approximately one-two weeks of MRI.

4249
4250 Depending on local Urology service structure, an appointment for a biopsy may need
4251 to be booked at the same time as the MRI is booked (i.e. immediately after
4252 randomization) in order for a biopsy to occur in timely fashion. If the results of the
4253 MRI show that a biopsy is not required, then the biopsy appointment can be used
4254 instead of Visit 4 for follow up of results and treatment decision.
4255

4256 Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy
4257 of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy
4258 Questionnaire (Appendix 7) ideally completed and returned immediately after a
4259 biopsy, before the subject leaves the department. In addition, subject needs to
4260 complete an EQ-5D-5L Questionnaire (Appendix 4) 24-48 hours post-biopsy.
4261

4262 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
4263 and complete as instructed on day 30 post-biopsy. This is to be returned by post or
4264 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
4265 biopsy then this questionnaire can be given to the research team when 30 days is
4266 finally complete. If Visit 4 is on or later than 30 days then this can be returned at the
4267 Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-
4268 biopsy, it will be acceptable, however, the questionnaire should be completed as
4269 close as possible to 30 days post-biopsy.
4270

4271 At 30-days post biopsy interval, a member of the research team will call the subject
4272 to remind them to complete and return the 30-day questionnaires.

4273 **11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic**
4274 **TRUS-biopsy**

4275 **For men randomized to ARM B only.**

4276
4277 Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will
4278 complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed
4279 and returned immediately after the biopsy.

4280 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
4281 and completed as instructed on day 30 post-biopsy. This is to be returned by post or
4282 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
4283 biopsy then this questionnaire can be given to the research team when 30 days is
4284 reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
4285 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it
4286 will be acceptable, however the questionnaire should be completed as close as
4287 possible to 30 days post-biopsy.

4288
4289 At 30-days post biopsy a member of the research team will call the subject to remind
4290 them to complete and return the 30-day questionnaires.

4291 **11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a**
4292 **biopsy**

4293 This appointment will include a follow up meeting with the investigator to discuss
4294 the results of the MRI as well as treatment decisions. This follow up should occur
4295 after the availability of the MRI report. At this visit the subject will also complete a
4296 30-day post intervention EQ-5D-5L Questionnaire.

4297
4298 Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8),which has been
4299 posted to them by the research team. If Visit 4 is earlier than 30 days post MRI then
4300 this questionnaire can be given to the research team when 30-days is finally
4301 complete. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
4302 appointment. As long as questionnaire is completed at 30-60 days post-MRI, it will
4303 be acceptable, however the questionnaire should be completed as close as possible
4304 to 30 days post-MRI.

4305
4306 At 30-days post MRI, a member of the research team will call the subject to remind
4307 them to complete the 30-day questionnaires.

4308 **11.6 Visit 4 (Post-test follow up): For all men who received a biopsy**

4309 This appointment will include a follow up meeting with the investigator to discuss
4310 the results of the biopsy as well as treatment decisions. This should be completed as
4311 soon as possible following the availability of any pathology results. The follow up
4312 appointment should be within 1 month of the biopsy. Depending on local Urology
4313 service structure, these results may need to be discussed at an MDT meeting to
4314 inform treatment decision.

4315
4316 The research team should record the treatment decision in the subject file.
4317

-
- 4318 Possibilities for treatment decision include but are not limited to:
- 4319 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 4320 • Active Surveillance
- 4321 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 4322 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 4323 • Hormone therapy
- 4324
- 4325 At this visit the subject will also receive a 30-day post intervention EQ-5D-5L
- 4326 Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy
- 4327 questionnaire (Appendix 8), which has been posted to them by the research team.
- 4328 The questionnaire needs to be completed on the 30th day post-intervention (i.e. post
- 4329 biopsy). However it will be accepted if completed up to 72 hours prior to or after the
- 4330 30th day. A telephone reminder from the research team to the subject can take
- 4331 place.
- 4332
- 4333 **11.7 Visit 5 (6 month follow up):26 week follow up**
- 4334 All subjects will have a 26 week visit
- 4335 Subjects will have the following:
- 4336 • PSA
- 4337 • Optional sample collection (blood, urine)
- 4338 **11.8 Visit 6(1 year follow up): 52 week follow up**
- 4339 All subjects are planned to have a 52 week follow up visit.
- 4340 Subjects will be followed to obtain the following information on an annual basis:
- 4341 • time to cancer diagnosis;
- 4342 • Gleason score progression;
- 4343 • time to intervention on active surveillance;
- 4344 • time on active surveillance;
- 4345 • results of PSA tests.
- 4346 • Time to follow up biopsy and/or mpMRI if performed (see follow up
- 4347 guidelines)
- 4348 • Indication for follow up biopsy
- 4349 • Was MRI performed prior to follow up biopsy
- 4350 • Was the biopsy systematic, targeted only or both systematic + targets, not
- 4351 done because of negative MRI
- 4352 • Optional sample collection (blood, urine)
- 4353
- 4354 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
- 4355 will have an additional MRI at Visit 6 (year 2).
- 4356 **11.9 Visit 7 (18 month follow up): 78 week follow up**
- 4357 All subjects will have a 78 week visit
- 4358 Subjects will have the following:
- 4359 • PSA
- 4360 • Optional sample collection (blood, urine)

4361

4362 **11.10 Visit 8 (2 year follow up): End of study**

4363 All study participants will be followed for up to two years or until they undergo
4364 radical treatment

4365 Subjects will be followed to obtain the following information on an annual basis:

- 4366 • time to cancer diagnosis;
- 4367 • Gleason score progression;
- 4368 • time to intervention on active surveillance;
- 4369 • time on active surveillance;
- 4370 • results of PSA tests.
- 4371 • Optional sample collection (blood, urine)
- 4372
- 4373 • Time to follow up biopsy and/or mpMRI if performed (see follow up
4374 guidelines)
 - 4375 ○ Indication for follow up biopsy
 - 4376 ○ Was MRI performed prior to follow up biopsy
 - 4377 ○ Was the biopsy systematic, targets only or both systematic + targets,
4378 not done because of negative mpMRI
- 4379
- 4380

4381 Follow-up will cease once treatment beyond active surveillance is undertaken
4382 (prostatectomy, radiation therapy, focal therapy, etc.).

4383

4384 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
4385 will have an additional MRI at Visit 8.

4386

4387 **12. Randomization**

4388 **12.1 Randomization Procedure**

4389 Written informed consent will be obtained from all eligible subjects prior to
4390 commencing any study related procedures. The Ontario Clinical Oncology Group
4391 (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre,
4392 Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate
4393 subject randomization. Subjects will be allocated to the two treatment arms in an
4394 approximate 1:1 ratio by use of a dynamic allocation scheme[47].

4395

4396 After documentation of written informed consent and confirmation of subject
4397 eligibility, clinical centres will randomize the subject by accessing the CMC's web-
4398 based Interactive Registration/Randomization System (IRIS). Prior to randomization
4399 and treatment allocation, the subjects' individualized risk of high-grade prostate
4400 cancer, obtained using the PCPTRC 2.0 calculator found at
4401 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> must be determined.

4402 **12.2 Stratification**

4403 Eligible, consenting subjects will be stratified by: (1) individualized risk of high-grade
4404 prostate cancer (5% to 25%, >25%); and (2) clinical centre

4405 **12.3 Blinding and measures taken to avoid bias**

4406 This study is unblinded, and all subjects will be aware of the treatment that they are
4407 receiving. As the MRI scan is unique to one of the arms it will not be possible to blind
4408 the participants or investigators as to what intervention is being received. Therefore,
4409 participants will be informed which arm they have been allocated to. Where
4410 possible, the data will be coded so as to blind individuals analyzing the data from
4411 which of the groups the data was from. Summary details of randomized allocation
4412 and outcomes will not be made available (unless specifically authorized by the Trial
4413 Steering Committee and/or Data Monitoring Committee) in order to maintain the
4414 overall blind of the trial.

4415

4416 Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be
4417 aware that the subject is part of the trial.

4418 Pathologists will be blinded to the cohort allocation. Concealment may be
4419 challenging due to the different number of cores in the two groups, but this is
4420 unavoidable. This is unlikely to represent a significant source of bias.

4421

4422

4423 **13. Data**

4424

4425 Type of data to be collected:

- 4426 • EQ-5D–5L questionnaires. These will measure quality of life and will be measured
4427 continuously throughout the trial.
- 4428 • Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and
4429 continuous data (e.g. maximum cancer core length)
- 4430 • MRI – diagram representing MRI; categorical data for areas and scores of
4431 suspicion (e.g. Sector 1p, score of suspicion 4/5)
- 4432 • MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and
4433 continuous data (e.g. maximum cancer core length)
- 4434 • Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers
4435 yes/no)
- 4436 • Treatment decisions – categorical data (e.g. radical treatment)
- 4437 • PSA – continuous data (e.g. value of PSA in ng/ml)

4438

4439 Please see **Appendix1** for the time window for data collection.

4440

4441 **14. Statistical Considerations**

4442 **14.1 Sample Size Calculation**

4443 **STATISTICAL methods**

4444 **Primary Analysis**

4445 Absolute differences in the proportion of clinically significant cancer detected
4446 between arms will be calculated and compared using the Clopper-Pearson method.
4447 If the lower boundary of an one-sided, 97.5% confidence interval for the difference
4448 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less
4449 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower
4450 bound is greater than zero, superiority can be claimed.

4451

4452 A supportive analysis will be performed by using a logistic regression model,
4453 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification
4454 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of
4455 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower
4456 bound was calculated to approximate an absolute 5% difference of interest (NOTE:
4457 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

4458

4459 **Secondary Analyses**

4460 For each secondary outcome, where appropriate, a difference in proportions with
4461 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.
4462 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for
4463 time-to-event outcomes.

4464

4465 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
4466 differences between allocation arms in secondary outcomes. Logistic regression and
4467 Cox proportional hazards regression will be used to examine the effect of allocation
4468 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
4469 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
4470 adjustments will be made due to multiple testing, however, results for secondary
4471 outcomes will be interpreted cautiously, acknowledging that tests were performed
4472 on secondary outcomes and numerous secondary tests were performed. Figures and
4473 tables will be used to illustrate results of interest.

4474

4475 **Treatment Allocation and Stratification**

4476 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
4477 use of a dynamic allocation scheme. Specifically, the first 20 subjects will be
4478 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a
4479 biased coin method will be used, whereby the number of subjects within each
4480 stratum will be calculated, and the next eligible subject will be allocated (with
4481 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
4482 allocation to each arm will occur with probability $p=0.5$.

4483

4484 Stratification

4485 For treatment allocation, the subjects' individualized risk of high-grade prostate

4486 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
4487 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
4488 subjects will be stratified by:
4489 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);
4490 (2) clinical centre.

4491

4492 **Sample Size**

4493 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
4494 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
4495 50% from another study [36].

4496

4497 Rates of clinically significant cancer detection from one the largest studies of
4498 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
4499 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will
4500 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
4501 systematic TRUS guided biopsy.

4502

4503 For this study, it will be conservatively hypothesized that systematic TRUS guided
4504 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
4505 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
4506 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
4507 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
4508 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
4509 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
4510 choice of 5% as the margin of non-inferiority represents a difference that would be
4511 considered clinically important.

4512

4513 Thus total men required in study = **422**.

4514

4515 To account potential withdrawal / loss to follow up and the effect of stratification,
4516 the sample size will be inflated by 5%, and a target of **450 men** will be recruited.

4517

4518 Note that the rate of clinically significant cancers is very dependent on the
4519 population registered for this study. It is possible that fewer (or more) subjects will
4520 have clinically significant cancers than what is initially hypothesized. However, if the
4521 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
4522 biopsy detection rate is <30%) and other statistical assumptions remain as stated
4523 previously, the statistical power will increase. The minimum statistical power would
4524 be obtained if the clinically significant cancer detection rate was 45% for systematic
4525 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
4526 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
4527 rate of clinically significant cancer in the population is miss-specified, assuming an
4528 absolute difference of 10% between targeted and systematic TRUS guided
4529 biopsy detection rates, and a 5% margin of non-inferiority.

4530

4531 **Statistical Conventions**

4532 For categorical data, tables will be presented showing the n and percentage
4533 (n/N*100%) of subjects. Analyses will be presented by study allocation arm
4534 separately.

4535

4536 Duration of time will be described in either years, months or weeks, and calculated
4537 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or
4538 X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date –
4539 date of birth + 1)/365.25.

4540

4541 Transformations of the data in order to meet statistical assumptions may be
4542 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
4543 assess any of the model fittings. All the statistical analysis will be carried out using
4544 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-
4545 project.org) or higher.

4546

4547 **Missing Data**

4548 Missing values for the primary endpoint will be examined closely. Sources and
4549 reasons for the absence of data incurred as a result of subjects lost-to-follow up,
4550 dropouts, and intermittent missing values will be described and explored by various
4551 summary statistics as well as graphical displays between the two allocation arms.
4552 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
4553 those subjects will be described by allocation arm and tested using Fisher's exact
4554 tests or Wilcoxon rank sum tests.

4555

4556 Missing data for secondary endpoints will be described. The methods for evaluating
4557 missing data of the primary endpoint may be employed for endpoints of interest. For
4558 summarization of baseline data, the following conventions will be used for partial
4559 missing date information occurring prior to randomization (e.g. for medical history
4560 or prior treatment). If year is missing, the date will be set at missing. If year is
4561 available, but month and date is missing, the month and date will be set to July 1st of
4562 the respective year. If date is missing, but year and month available, the day will be
4563 set to the 15th of the respective month.

4564 **14.2 Interim Analyses**

4565

4566 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
4567 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
4568 conduct if there are concerns about subject safety or futility. Unless otherwise
4569 specified by one of these bodies, a futility analysis will be performed after
4570 approximately 200 subjects are enrolled and have their primary outcome
4571 ascertained. Simulation will be used to estimate the conditional probability of futility
4572 assuming the study was to continue to completion, and assuming the clinically
4573 significant cancer detection rate is 30% in both arms. If the conditional probability is
4574 0.95 or higher that continuation of the study will result in a negative result, the
4575 DSMC will recommend a suspension of recruitment to the trial, and initiation of a
4576 quality assurance review. A decision to permanently close the study or continue with

4577 accrual will be determined by the Steering Committee, based on the results of the
4578 quality assurance review, and the recommendation of the DSMC.

4579

4580 **Timing of Final Analysis**

4581 A single, final, analysis will occur after all subjects have undergone their initial biopsy
4582 and all data related to the initial biopsy is documented and validated. Follow-up
4583 analyses will be conducted after all subjects have completed two years of follow-up.

4584 **14.3 Populations:**

4585 The per protocol, study population will consist of all subjects who satisfy all eligibility
4586 criteria and are randomized to the study, who undergo MPMRI-TB or systematic
4587 TRUS guided biopsy and have their primary outcome measured. This population will
4588 be used for the primary analysis of non-inferiority.

4589 The intent-to-treat (ITT) population will consist of all subjects randomized to the
4590 study, regardless of any protocol violations or if they do not complete the study as
4591 defined in the protocol. The ITT population will be used as a supportive analysis of
4592 the primary analysis, for all safety analyses, and for any analysis investigating
4593 superiority.

4594 **14.4 Primary Outcome**

4595 **14.4.1 Detection rate of clinically significant cancer**

4596 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will
4597 be calculated based on histology results from biopsy procedures. Analysis will be on
4598 the intention to treat population.

4599

4600 Absolute differences in proportion of clinically significant cancer detected between
4601 arms will be calculated and compared. If the lower boundary of the 97.5%
4602 confidence interval for the difference in detection rates of MPMRI-TB compared to
4603 systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-
4604 inferior. In the event that the lower bound is greater than zero, superiority can be
4605 claimed.

4606

4607 The primary analysis will be conducted once all subjects have completed visit 4,
4608 when the results of the biopsy or MRI are given to the subject.

4609

4610 **14.5 Secondary Outcomes**

4611 For each secondary outcome, where appropriate, a difference in proportions with
4612 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

4613

4614 **14.5.1 Proportion of men in each arm with clinically insignificant 4615 cancer detected**

4616 The proportion of men in each arm with clinically insignificant cancer (Gleason < 7)
4617 will be calculated based on histology results from biopsy procedures. In addition, the
4618 numbers with clinically insignificant cancer identified by MRI alone will also be
4619 included.

4620

4621 **14.5.2 Proportion of men in each arm with Gleason $\geq 4+3$ detected**

4622 The proportion of men in each arm with Gleason $\geq 4+3$ will be calculated based on
4623 histology results from biopsy procedures. In addition, the numbers with clinically
4624 insignificant cancer identified by MRI alone will also be included.

4625

4626 **14.5.3 Proportion of men in MPMRI arm who avoid biopsy.**

4627

4628 **14.5.4 Proportion of men in the MRI arm whom the PI-RADS score for
4629 suspicion of clinically significant cancer was 3, 4 or 5 but no clinically
4630 significant cancer was detected.**

4631 The proportion of men in each arm whom the PI-RADS score for suspicion of
4632 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
4633 detected, will be calculated based on histology results from biopsy procedures.

4634

4635 **14.5.5 Proportion of men in each arm who go on to definitive local
4636 treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or
4637 systemic treatment (e.g. hormone therapy, chemotherapy)**

4638

4639

4640

4641 **14.5.8 Proportion of men with a negative MRI who progress within 24
4642 months after their study MRI, or who are upgraded within 24 months**

4643 Men with a negative MRI who do not undergo a biopsy will have a follow-up MRI 2
4644 years after their study MRI. We will determine the proportion of men whose
4645 subsequent MRI shows a PI-RADS 3 or greater lesion. The results of targeted biopsy
4646 of those lesions will be recorded and analyzed. The number of men who are
4647 upgraded to Gleason ≥ 7 due to an off-protocol biopsy will also be recorded.

4648

4649 **14.5.9 Proportion of men with post-biopsy adverse events**

4650 Immediate post-biopsy discomfort and pain will be characterized by intensity using
4651 the numerical analogue score. Scores for each arm will be compared. 30-day biopsy
4652 specific complications and adverse events will be characterized according to their
4653 presence, absence, duration and how much of a problem the symptoms caused the
4654 subject. Whether the subject had contact with health care providers/system will also
4655 be recorded. The proportion of individuals experiencing each symptom, proportion
4656 in whom that symptom caused a problem and proportion who had contact with
4657 healthcare providers/system will be calculated and compared qualitatively between
4658 arms utilizing classification systems validated in previous studies [39]. The biopsy
4659 specific complications that will be compared include pain, urinary retention, fever,
4660 pain, erectile dysfunction, urinary incontinence, haematuria, haematochezia and
4661 haemotospermia.

4662

4663 Any post-biopsy complications up to 30-days post biopsy procedure will be tabulated
4664 and listed by duration and management.

4665

4666 **14.5.10 Health related quality of life**

4667 EQ-5D-5L descriptive domain summary indices and visual analogue scores will be
4668 assessed at baseline, 24-48 hours post intervention and at 30-days and changes will
4669 be compared between arms.

4670
4671 EQ-5D was selected as a simple, low burden quality of life instrument that will
4672 provide validated information on symptoms, particularly anxiety, that could be
4673 compared across disease states and studies. Other subject-reported outcomes
4674 directly linked to the interventions will be captured in the post-biopsy surveys. Since
4675 it provides utilities, these will be incorporated into a secondary economic analysis if
4676 the results permit.

4677

4678 **14.5.11 Proportion Gleason score upgrading in men undergoing radical**
4679 **prostatectomy**

4680 Of the men who undergo radical prostatectomy, the proportion who have cancer
4681 upgraded from the biopsy histopathology to the radical prostatectomy
4682 histopathology in each arm will be calculated and compared.

4683

4684 **14.5.12 Cost Outcomes**

4685 As the study design for clinical outcomes is one of non-inferiority, the primary
4686 economic analysis will be **cost minimization analysis**. The perspective of the
4687 economic analysis will be that of the public payer. The primary goal of the analysis
4688 will be to support arguments for public funding. Thus the costs of participant
4689 burden, logistical challenges, and expense of obtaining societal costs, will not be
4690 evaluated.

4691

4692 **14.5.12.1 Data collection:**

4693 As part of the informed consent process, participants in Ontario will also
4694 consent to having their Ontario Health Insurance Number recorded, to be
4695 later transferred to the Institute for Clinical Evaluative Sciences (ICES) where
4696 it will be linked to a number of administrative claims databases recording
4697 health system resource utilization such as physician billing [Ontario Health
4698 Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization
4699 and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug
4700 Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity
4701 Level Reporting (ALR)]; clinic and emergency department visits [National
4702 Ambulatory Care Reporting System (NACRS), Emergency Department visits];
4703 radiation (ALR); homecare (Home Care databases) and a few additional ones
4704 as determined necessary (e.g., Long-term care, Mental Health, Diabetes. The
4705 overall, number and proportion of health system resources will be
4706 determined. In this way we can capture comprehensive resource utilization
4707 related to on-trial management including any adverse events.

4708 **14.5.12.2 Health Insurance number handling and security**

4709 As the economic implications of this study are of prime importance to some
4710 of the funders, the request for data linkage will be part of the main consent
4711 form. If a participant indicates to the study team that they decline or

4712 withdraw consent, the OHIP number will be recorded as 9999-999-999-XX.
4713 The OHIP numbers will stay with the participating institution until after
4714 accrual is complete, and then they will all be transferred at one time under
4715 data sharing agreements between ICES and each institution. Data will be
4716 transferred using a secure electronic file transfer system established by ICES
4717 and managed by authorized ICES personnel responsible for receiving
4718 data. The file transfer system uses security safeguards including encryption
4719 and authentication.

4720
4721 ICES is a Prescribed Entity under the Personal Health Information Protection
4722 Act (PHIPA), and can receive and use personal health information for
4723 purposes of analysis and compiling statistical information and other research.
4724 Its policies and procedures for privacy protection and data security have been
4725 approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-
4726 monitored and requiring passkeys to access private offices and
4727 computers. ICES has extensive experience in the protection of confidentiality
4728 when using such data. It has a UNIX-based network that cannot be accessed
4729 externally. ICES data facilities are fully 'moated' (no connections to other
4730 computers). At ICES, routine procedures for data backup are instituted by a
4731 data management team. The data is burned onto a CD or placed on an
4732 external hard drive and placed in a locked vault. All ICES staff and scientific
4733 affiliates are required to sign agreements of confidentiality annually. Internal
4734 audits are conducted to monitor compliance with ICES policies, standards and
4735 procedures.

4736
4737 Study data with direct personal identifiers such as OHIP numbers will
4738 reside on a dedicated and secure server at ICES and will only be
4739 accessible by a named Data Covenantor. The Covenantor will encode
4740 the OHIP number, replacing it with an ICES key number (IKN) (a code)
4741 and transferring it to a "moated" server for the study project. (The
4742 Data Covenantor is an ICES person named in our data sharing
4743 agreements and identified to the Office of the Information and
4744 Privacy Commissioner, who can access personal health information at
4745 ICES for the purposes of receiving, coding, transferring or destroying
4746 personal health information.) The coded study data will only be made
4747 available to the Principal Investigator and project staff directly
4748 responsible for data analysis (under the supervision of the
4749 investigator). No subject, physician or institution will be identified in
4750 the reporting of results

4752 **14.5.12.3 Cost calculation**

4753 Once the utilization of health services is determined from those cases linked
4754 to administrative databases, publicly available costs (2016\$CAN) will be
4755 applied to health services. Costs for physician and laboratory services will be
4756 determined by applying that year's fee code. Costs for hospital care will be
4757 estimated using the Canadian Institute for Health Information (CIHI) Resource
4758 Intensity Weight method for the most recently available year. Outpatient

4759 prescription drug costs for participants not covered by ODB (those under age
4760 65 and not on social assistance) will be considered to be the same as the trial
4761 arm-specific average for those with coverage. Costs will then be inflated
4762 using the healthcare-specific Consumer Price Index reported by Statistics
4763 Canada into constant Canadian dollars for the year the study ends. Due to the
4764 short time horizon, discounting will not be applied.

4765 **14.5.12.4 Primary Analysis**

4766 A within-trial analysis will be conducted to calculate the total cost for each
4767 arm and mean cost per subject for each arm. Frequency distributions and
4768 measures of central tendency (e.g. means and medians) will be determined
4769 for each resource category (e.g. hospitalizations)for each arm of the study.
4770 Confidence intervals for the difference in costs and resource utilization
4771 between the strategies overall and for each resource category will also be
4772 calculated. Univariate comparisons between the groups will be made
4773 primarily using nonparametric tests, such as Wilcoxon rank-sum test. In the
4774 primary analysis, assuming equivalence in the primary outcome, an arm with
4775 significantly lower mean costs will be considered the economically most
4776 attractive approach.

4777
4778 Should the clinical trial find a difference between the two arms on the
4779 primary endpoint, an incremental cost-benefit analysis will be calculated by
4780 deriving the additional cost per case of clinically significant cancer diagnosed,
4781 according to the following equation:

4782

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\text{Diagnoses}_{(\text{Arm A})} - \text{Diagnoses}_{(\text{Arm B})}}$$

4783 The cost of avoiding each additional case of clinically insignificant cancer
4784 diagnosed may also be similarly calculated. Consideration will be given to
4785 extending this analysis using economic modeling with incorporation of utility
4786 values from the EQ-5D to allow a lifetime perspective to be taken and the
4787 estimation of quality adjusted life years (QALYs).

4788 **14.5.12.5 Secondary Cost Analyses**

4789 One and multi-way sensitivity analyses will be carried out around major cost
4790 drivers by varying the costs over their observed ranges and conducting
4791 threshold analyses where appropriate. Sensitivity analyses will also be
4792 performed to evaluate potential limitations in the data, such as ODB costs as
4793 described above (though the proportion without ODB coverage should be
4794 similar in the two arms, and it is not expected to be a major cost-driver).

4795

4796 **14.5.13 Missing Data**

4797 The impact of missing data will be explored in all analyses; sensitivity
4798 analyses/multiple imputation will be performed as appropriate.

4799

4800 **15. Participant compliance and withdrawal**

4801

4802 The study will be completed when at least 422 subjects have been randomized, have
4803 undergone a diagnostic test and completed follow up. Compliance to randomized
4804 treatment will be assessed by monitoring the completed forms, e.g. the systematic
4805 TRUS guided biopsy form or the MRI-targeted biopsy form.

4806

4807 In consenting to the study, subjects are consenting to study monitoring, imaging and
4808 biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to
4809 withdraw consent at any stage and their care will not be affected in any way. All
4810 communication surrounding the withdrawal and its reasons should be noted in the
4811 subject's record. Such cases should be reported to the PRECISE Study Operations
4812 Office. Data up to the time of withdrawal can be included in the study.

4813

4814 As the study diagnostic tests are for suspected cancer it is not anticipated that there
4815 will be significant loss to follow up.

4816

4817 **15.1 Subject Withdrawal from Study**

4818 A subject may discontinue participation in this study at any time at the investigator's
4819 discretion or at the request of the subject.

4820

4821 If a subject discontinues at or before Visit 1 (randomization), he is not required to
4822 complete end of study assessments.

4823

4824 If a subject discontinues after Visit 1 (randomization) for any reason, the investigator
4825 should make every effort to complete the activities bulleted below.

4826

- 4827 • End of study assessments as outlined in **Section 10.17**.
4828 • Any occurrence of death, prostatic surgical intervention, non-surgical treatment
4829 for prostate cancer after study withdrawal should be documented in the CRF and
4830 source documents.

4831

4832 Subjects who are discontinued from the study after randomization will not be
4833 replaced. Subjects withdrawn from the study retain their subject number if already
4834 given. New subjects will be allocated a new subject number.

4835

4836 In the event that a subject is prematurely discontinued from the study at any time
4837 due to an AE, the procedures describe in **Section 16.3** must be followed.

4838

4839 Subjects should be withdrawn from the study for any of the following criteria:

- 4840 • Non-compliance with the requirements of the study.
4841 • Request to discontinue treatment. This request can be made by either the
4842 subject or the investigator.
4843 • Develops progressive disease.

4844

4845 **15.2 Study completion**

4846 The primary end point will be reached when the last subject entered has their
4847 systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be
4848 followed for up to 2 years following study entry or until they have radical treatment.
4849 Subjects who are found to have significant prostate cancer and are treated will not
4850 be included in follow up for this period. This includes subjects diagnosed as part of
4851 study protocol, and subjects diagnosed during the follow up period by standard-of-
4852 care procedures. However, post MRI/biopsy questionnaires will not be required
4853 following non-protocol based procedures.

4854

4855 **16. Data Monitoring, Quality Control and Safety**

4856 **16.1 Stopping / discontinuation rules**

4857 The study will be completed when 450 participants have been randomized,
4858 undergone a diagnostic test and completed follow up.

4859

4860 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
4861 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
4862 conduct if there are concerns about subject safety or futility. See Section 14.2.1 for
4863 further details on the interim analysis. Appropriate documentation as per the PI's
4864 requirement will be completed if stopping the trial is necessary and the ethics
4865 committee will be informed.

4866

4867 As the study is unblinded there will be no need for randomization code breaks.

4868

4869 **16.2 Monitoring, quality control and assurance**

4870

4871 Members of the trial team will be Good Clinical Practice (or equivalent) trained.

4872

4873 An independent DSMC will be appointed to monitor subject safety and the rate of
4874 recruitment of subjects in the study. They will meet at least once a year whilst the
4875 trial is ongoing for routine review of safety data and trial progression. They have the
4876 power to call additional meetings and review data at any point in the trial should
4877 they wish to do so.

4878

4879 The PI may also arrange an independent trial monitor to review the study data.

4880 **16.3 Assessment of safety**

4881 The investigator is responsible for the detection and documentation of events
4882 meeting the criteria and definition of an AE or SAE as provided in this protocol.
4883 During this study, when there is a safety evaluation, the investigator or site staff will
4884 be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

4885 **16.3.1 Definition of an Adverse Event (AE)**

4886 Adverse events (AE) will be defined as “any untoward medical occurrence in a
4887 clinical trial subject undergoing any intervention in the trial, which does not
4888 necessarily have a causal relationship with this treatment”.

4889

4890 Only adverse events specific to biopsy-related complications including pain, fever,
4891 hematuria, hematochezia, hematospermia, urinary retention and urinary
4892 incontinence will be recorded. Any other adverse events will not be recorded. Please
4893 refer to section 16.3.6 of the protocol.

4894 **16.3.2 Definition of a Serious Adverse Event (SAE)**

4895 Serious adverse events (SAE) will be defined as “any untoward medical occurrence as
4896 a result of any intervention in the trial that:

4897 **(a) results in death**

4898 **(b) is life-threatening**

4899 The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which
4900 the subject was at risk of death at the time of the event. It does not refer to an
4901 event, which hypothetically might have caused death, if it were more severe.

4902 **(c) requires hospitalisation or prolongation of existing hospitalisation**

4903 In general, hospitalization signifies that the subject has been detained (usually
4904 involving at least an overnight stay) at a hospital or emergency ward for observation
4905 and/or treatment that would not have been appropriate in the physicians’ office or
4906 outpatient setting. Complications that occur during hospitalization are AEs. If a
4907 complication prolongs hospitalization or fulfils any other serious criteria, the event is
4908 serious. When in doubt as to whether ‘hospitalization’; occurred or was necessary,
4909 the AE should be considered serious. Hospitalization for elective treatment of a pre-
4910 existing condition that did not worsen from baseline is not considered an AE.

4911 **(d) results in disability / incapacity**

4912 The term disability means substantial disruption of a person’s ability to conduct
4913 normal life functions. This definition is not intended to include experiences of
4914 relatively minor medical significance such as uncomplicated headache, nausea,
4915 vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may
4916 interfere or prevent everyday life functions but do not constitute a substantial
4917 disruption.

4918 **(e) is a congenital abnormality/birth defect.**

4919 Medical or scientific judgement should be exercised in deciding whether reporting is
4920 appropriate in other situations, such as important medical events that may not be
4921 immediately life threatening or result in death or hospitalization but may jeopardise
4922 the subject or may require medical or surgical intervention to prevent one of the
4923 outcomes listed in the above definition. These should also be considered serious.

4924 Examples of such events are invasive or malignant cancers, intensive treatment in an
4925 emergency room or at home for allergic bronchospasm, blood dyscrasias or
4926 convulsions that do not result in hospitalization, or development of drug
4927 dependence or drug abuse.

4928 **16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs**

4929 An event which is part of the natural course of the disease under study (i.e., disease
4930 progression) does not need to be reported as a serious adverse event. Progression of
4931 the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death
4932 due to progressive disease is to be recorded on 'Record of Death' CRF page and not
4933 as an SAE. However, if the progression of the underlying disease is greater than that
4934 which would normally be expected for the subject, or if the investigator considers
4935 that there was a causal relationship between treatment with study medication or
4936 protocol design/procedures and the disease progression, then this must be reported
4937 as an SAE. Any new primary cancer must be reported as an SAE.

4938 **16.3.4 Lack of Efficacy**

4939 "Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical
4940 sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE
4941 definition (including clarifications).

4942 **16.3.5 Clinical Laboratory Abnormalities and Other Abnormal**
4943 **Assessments as AEs and SAEs**

4944 Abnormal laboratory findings or other abnormal assessments that are judged by the
4945 investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet
4946 the definition of an AE or SAE. Clinically significant abnormal laboratory findings or
4947 other abnormal assessments that are detected during the study or are present at
4948 baseline and significantly worsen following the start of the study will be reported as
4949 AEs or SAEs. However, clinically significant abnormal findings or other abnormal
4950 assessments that are associated with the disease being studied, unless judged by the
4951 investigator as more severe than expected for the subject's condition or that are
4952 present or detected at the start of the study and do not worsen, will not be reported
4953 as AEs or SAEs.

4954
4955 The trial interventions are routinely carried out in clinical practice for investigation of
4956 suspected cancer and the risks of the interventions are therefore not any greater
4957 than if a man was not part of the trial. The risks of the procedures are relatively low,
4958 as detailed in Section 11.

4959
4960 The investigator will exercise his or her medical and scientific judgment in deciding
4961 whether an abnormal laboratory finding or other abnormal assessment is clinically
4962 significant.

4963 **16.3.6 Recording/Reporting AEs and SAEs**

4964 The first AE reporting period for this study begins at randomization and
4965 will be recorded until 30-days post-biopsy. In the event that the subject does not
4966 undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

4967
4968 Only adverse events specific to biopsy-related complications including pain, fever,
4969 hematuria, hematochezia, hematospermia, urinary retention and urinary
4970 incontinence will be recorded. Any other adverse events will not be recorded.
4971

4972 AEs will be recorded by a member of the research team or clinical team on an AE
4973 report form. All SAEs must be recorded on a SAE report form. Completed AEs and
4974 SAE report forms should be sent to the CTG who will keep a log of AEs and SAEs. AE
4975 and SAE logs will be reviewed by the DSMC.

4976
4977 For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or
4978 DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria
4979 as a SAE, will be collected and reported.

4980
4981 Expected AEs includes the following:

- 4982 • Pain
- 4983 • Blood in the urine
- 4984 • Blood in the semen
- 4985 • Blood in the stool or back passage
- 4986 • Erectile dysfunction
- 4987 • Urinary incontinence
- 4988 • Urinary tract infection
- 4989 • Fevers

4990
4991 In addition, small risks of allergic reactions are associated with the intravenous
4992 administration of gadolinium, the contrast agent used in MRI scans, as described in
4993 section 10.18.1.2. This contrast agent is used consistently in MRI scanning and is not
4994 limited to this trial.

4995
4996 If any of these symptoms are accompanied by events consistent with the definition
4997 of an SAE as specified above, then the event will be considered an SAE.

4998
4999 The Trial Coordinator, Principle Investigator or Chief Investigator should be informed
5000 of any SAE within 24 hours.

5001 All SAE report forms must be completed and the SAE logs updated. All SAEs must be
5002 followed up until a resolution is reached (i.e. recovered, recovering, recovered with
5003 sequelae, fatal, not recovered or unknown).

5004
5005 Local sites may have specific institutional protocols for reporting SAEs, which should
5006 be followed in addition.

5007
5008 When an AE/SAE occurs, it is the responsibility of the investigator to review all
5009 documentation relative to the event. The investigator will then record all relevant
5010 information regarding an AE/SAE on the CRF.

5011
5012 The investigator will attempt to establish a diagnosis of the event based on signs,
5013 symptoms and/or other clinical information. In such cases, the diagnosis should be
5014 documented as the AE/SAE and not the individual signs/symptoms.

5015 **16.3.7 Evaluating AEs and SAEs**

5016 **16.3.7.1 Assessment of Intensity**

5017

5018

5019

5020 The investigator will make an assessment of intensity for each AE and SAE reported
5021 during the study. Degree of severity and change in severity will be recorded by
5022 means of National Cancer Institute, Common Terminology Criteria for Adverse
5023 Events (NCI CTCAE), version 4.03.

5024

5025 If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on
5026 the investigator's clinical judgment. The intensity of each AE and SAE recorded in the
5027 CRF should be assigned to one of the following categories:

5028

5029 **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort
5030 and not interfering with everyday activities.

5031 **Moderate:** An event that is sufficiently discomforting to interfere with normal
5032 everyday activities.

5033 **Severe:** An event that prevents normal everyday activities.

5034

5035 An event that is classified as severe should not be confused with a SAE. Severity is a
5036 category utilized for rating the intensity of an event; both AEs and SAEs can be
5037 assessed as severe.

5038 **16.3.7.2 Assessment of Causality**

5039 The investigator is obligated to assess the relationship between investigational
5040 product and the occurrence of each AE/SAE. The investigator will use clinical
5041 judgment to determine the relationship. Alternative causes and the temporal
5042 relationship of the event to the investigational product will be considered and
5043 investigated. The investigator will also consult the CIB and or Product Information,
5044 for marketed products, in the determination of his/her assessment.

5045 **16.3.8 Follow-up of AEs and SAEs**

5046 After the initial AE/SAE report, the investigator is required to proactively follow each
5047 subject and provide further information to the PI of the study, on the subject's
5048 condition.

5049

5050 All AEs and SAEs documented at a previous visit/contact and are ongoing, will be
5051 reviewed at subsequent visits/contacts.

5052

5053 All AEs and SAEs will be followed until resolution, until the condition stabilizes, until
5054 the event is otherwise explained or until the subject is lost to follow-up. Once
5055 resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will
5056 ensure that follow-up includes any supplemental investigations as may be indicated
5057 to elucidate the nature and/or causality of the AE or SAE.

5058

5059 The PI may request that the investigator perform or arrange for the conduct of
5060 supplemental measurements and/or evaluations to elucidate as fully as possible the
5061 nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a
5062 subject dies during participation in the study or during a recognized follow-up
5063 period, the PI will be provided with any post-mortem findings.

5064
5065 New or updated information will be recorded on the originally completed SAE CRF,
5066 with all changes signed and dated by the investigator or designate. The updated SAE
5067 CRF should be resent to the PI.

5068 **16.3.9 Prompt Reporting of SAEs**

5069 Once the investigator determines that an event meets the protocol definition of an
5070 SAE, the SAE will be reported to the PI (CURC) within 24 hours.
5071

5072 **16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI**

5073 The Site Investigator must immediately inform the PI (CURC) of all SAE (within 24
5074 hours) at the following fax number: 1-416-480-6121.

5075
5076 The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing
5077 addresses is as follows:

5078 Dr. Laurence Klotz
5079 c/o Marlene Kebabdjian
5080 Sunnybrook Health Sciences Centre
5081 2075 Bayview Avenue A304
5082 Toronto, Ontario M4N 3M5 Canada
5083 Phone: (416) 480-6100 ext 2890
5084 E-mail: Laurence.Klotz@sunnybrook.ca
5085 Marlene.kebabdjian@sunnybrook.ca

5086 **16.3.9.2 Completion and Transmission of the SAE Reports**

5087 Once an investigator becomes aware that an SAE has occurred in a study subject,
5088 she/he will report the information to the PI within 24 hours. The SAE CRF will always
5089 be completed as thoroughly as possible with all available details of the event, signed
5090 by the investigator (or designee), and forwarded to the PI within the designated time
5091 frames. If the investigator does not have all information regarding as SAE, he/she will
5092 not wait to receive additional information before notifying the PI of the event and
5093 completing the form. The form will be updated when additional information is
5094 received.

5095
5096 The investigator will always provide an assessment of causality at the time of the
5097 initial report as described in Section 16.3.6.2.

5098 **16.3.10 Post-study AEs and SAEs**

5099 If the investigator learns of any SAE at any time after a subject has been discharged
5100 from the study, and such event(s) is (are) reasonably related to the study
5101 intervention, the investigator should promptly notify the PI (CURC).
5102

5103 **17. Study Administration**

5104 **17.1 Regulatory and Ethical Considerations**

5105 An important consideration is that men are being randomized to one of two biopsy
5106 techniques when it is not known which will be more effective in diagnosing clinically
5107 significant prostate cancer. Both diagnostic tests are currently used in everyday
5108 clinical practice at the institutions involved in the trial. Though systematic TRUS
5109 guided biopsy could be considered standard of care, there is enough evidence to
5110 support the concept that MPMRI-targeted biopsy may be as effective, if not more so,
5111 than systematic TRUS guided biopsy[27]. This study aims to confirm this.

5112 **17.1.1 Ethical Conduct of the Study and Ethics Approval**

5113 The PI and each participating site will obtain approval to conduct the study from the
5114 Research Ethics Board (REB) prior to initiating the study.

5115

5116 Participating sites from Ontario will use the Ontario Cancer Research Ethics Board
5117 (OCREB) as their Board of Record.

5118 This study will be conducted in accordance with 'good clinical practice' (GCP) and all
5119 applicable regulatory requirements, including where applicable, the 2013 version of
5120 the Declaration of Helsinki.

5121

5122 The investigator is responsible for ensuring that this protocol, the site's informed
5123 consent form and any other information that will be present to potential subjects
5124 are reviewed and approved by the appropriate REB. The investigator agrees to allow
5125 the REB direct access to all relevant regulatory documents. The PI will provide the
5126 site investigator(s) with relevant document(s)/data that are needed for REB review
5127 and approval of the study. Before CRFs can be shipped to the site, the PI must
5128 receive copies of the REB approval, the approved informed consent form and any
5129 other information that the REB has approved for presentation to potential subjects.

5130

5131 If the protocol, the informed consent form or any other information that the REB has
5132 approved for presentation to potential subjects is amended during the study, the
5133 site investigator(s) is responsible for ensuring the REB reviews and approves, where
5134 applicable, these amended documents. The site investigator(s) must follow all
5135 applicable regulatory requirements pertaining to the use of an amended informed
5136 consent form including obtaining the REB approval of the amended form before new
5137 subjects consent to take part in the study using this version of the form. Copies of
5138 the REB approval of the amended informed consent form/other information and the
5139 approved amended informed consent form/other information must be forwarded to
5140 the PI promptly.

5141 **17.1.2 Informed Consent**

5142 Informed consent will be obtained before the subject can participate in the study.
5143 The contents and process of obtaining informed consent will be in accordance with
5144 all applicable regulatory requirements.

5145

5146 The subject's consent to participate in the study should be obtained after a full
5147 explanation has been provided of the procedures to be given. Subjects should be
5148 given sufficient time (at least 24 hours) after being given the study subject
5149 information sheet to consider and discuss participation in the study with family and
5150 friends.

5151
5152 A contact number will be given to the subject should he wish to discuss any aspect of
5153 the study. Following this, the clinician will determine that the subject is fully
5154 informed of the study and their participation, in accordance with Good Clinical
5155 Practice Guidelines. Subjects will always be asked to sign a consent form. One copy
5156 will be given to the subject, one copy will be kept with subject's hospital notes and
5157 one copy should be kept in the local investigator's file.

5158 **17.1.3 Investigator Reporting Requirements**

5159 The investigator is responsible for reporting SAEs to the REB in accordance with all
5160 applicable regulations. Furthermore, the investigator may be required to provide
5161 periodic safety updates on the conduct of the study at his or her site and notification
5162 of study closure to the REB.

5163 **17.2 Study Monitoring**

5164 This study will be monitored by a CRA. The CRA will contact the sites by telephone
5165 on a predetermined basis and would conduct a monitoring visits based on the data
5166 entered in the EDC and queries.

5167
5168 During these contacts, the monitor will:

- 5169 • Check the progress of the study
- 5170 • Review study data collected
- 5171 • Conduct source document verification
- 5172 • Identify any issues and address their resolution

5173

5174 This will be done in order to verify that the:

- 5175 • Data are authentic, accurate and complete
- 5176 • Safety and rights of subjects are being protected
- 5177 • Study is conducted in accordance with the currently approved protocol (and
5178 any amendments), GCP and all applicable regulatory requirements

5179

5180 The investigator agrees to allow CRA personnel direct access to all relevant
5181 documents and to allocate his/her time and the time of his/her staff to CRA
5182 personnel to discuss findings and any relevant issues.

5183 **17.3 Quality Assurance**

5184 To ensure compliance with GCP and all applicable regulatory requirements,
5185 regulatory agencies may conduct a regulatory inspection of the study. Such
5186 audits/inspections can occur at any time during or after completion of the study. If
5187 an audit or inspection occurs, the investigator and institution agree to allow the
5188 auditor/inspector direct access to all relevant documents and to allocate his/her

5189 time and the time of his/her staff to the auditory/inspector to discuss findings and
5190 any relevant issues.

5191 **17.4 Study and Site Closure**

5192 Upon completion of the study, the site investigator(s) will conduct the following
5193 activities:

- 5194 • Return of all study data to the Sponsor (CURC)
- 5195 • Submission of all study data and data queries to OCOG
- 5196 • Review of site study records for completeness

5197

5198 In addition, the Principal Investigator has the right to temporarily suspend or
5199 prematurely discontinue this study either at a single site or at all sites at any time for
5200 reasons including but not limited to, safety or ethical issues or severe non-
5201 compliance. If the PI determines such action is needed, the PI will discuss this with
5202 the site investigator (including the reasons for taking such action) at that time. When
5203 feasible, the PI will provide advance notification to the site investigator of the
5204 impending action prior to it taking effect.

5205

5206 Individual site Investigators may also terminate their participation in the study at any
5207 time. If the investigator determines such action is needed, the investigator will
5208 discuss this with the PI(including the reasons for taking such action) at that time.
5209 When feasible, the investigator will provide advance notification to the PI of the
5210 impending action prior to it taking effect.

5211

5212 The PI will promptly inform all other investigators and/or institutions conducting the
5213 study if the study is suspended or terminated for safety reasons and will also inform
5214 the regulatory authorities of the suspension or termination of the study and the
5215 reason(s) for the action. If required by applicable regulations, the investigator must
5216 inform the REB promptly and provide the reason for the suspension or termination.

5217

5218 If the study is prematurely discontinued, all study data must be returned to the PI. In
5219 addition, the investigator has the responsibility to return any used/unused clinical
5220 supplies.

5221

5222 Financial compensation to investigators and/or institutions will be in accordance
5223 with the agreement established between the investigator and the PI.

5224 **17.5 Records Retention**

5225 Following closure of the study, the site investigator(s) must maintain all site study
5226 records in a safe and secure location. The records must be maintained to allow easy
5227 and timely retrieval when needed and whenever feasible, to allow any subsequent
5228 review of data in conjunction with assessment of the facility, supporting systems and
5229 staff.

5230

5231 The site investigator(s) will retain study records to comply with all applicable
5232 regulatory requirements. The minimum retention time will meet the strictest
5233 standard applicable to that site for the study as dictated by any institutional

5234 requirements or local laws or regulations of Health Canada standards/procedures;
5235 otherwise, the retention period will default to 25 years.

5236

5237 The site investigator(s) must inform the PI of any changes in the archival
5238 arrangements, including but not limited to the following: archival at an off-site
5239 facility, transfer of ownership of the records in the event the investigator leaves the
5240 site. The PI should be informed of this change if it affects their access to the
5241 information in case of an audit.

5242 **17.6 Data Management**

5243 Subject data are collected by the investigator or designee using the CRF within an
5244 Electronic Data Capture (EDC) system. Subject data necessary for analysis and
5245 reporting will be entered/transmitted into a validated database. Clinical data
5246 management will be performed in accordance with applicable standards and data
5247 cleaning procedures. Database lock will occur when data management quality
5248 control procedures are completed.

5249 **17.7 Publication**

5250 The results from the study will be analyzed and published as soon as possible and is
5251 appropriate. All study-related communications can only be presented or published
5252 after approval from all relevant members involved in the trial.

5253

5254 All publications shall include appropriate indication named authors as agreed on by
5255 the members involved in the trial. For the main study reports, senior and first
5256 authorship will be determined by agreement of the Chief Investigator, the Principle
5257 Investigator at time of manuscript drafting. Authorship will be based on
5258 recommendations of the International Committee of Medical Journal Editors
5259 (www.ICMJE.org) where all authors meet the following for criteria:

5260

- 5261 5. Substantial contributions to the conception or design of the work; or the
5262 acquisition, analysis, or interpretation of data for the work; AND
- 5263 6. Drafting the work or revising it critically for important intellectual content;
5264 AND
- 5265 7. Final approval of the version to be published; AND
- 5266 8. Agreement to be accountable for all aspects of the work in ensuring that
5267 questions related to the accuracy or integrity of any part of the work are
5268 appropriately investigated and resolved.

5269

5270 If there are no named authors (i.e. group authorship) then a writing committee will
5271 be identified that would usually include these people. The clinical trials.gov
5272 registration number that will be allocated to this trial will be attached to any
5273 publications resulting from this trial.

5274

5275 Trial funding agencies (OICR, PCC and collaborators as appropriate) will be
5276 acknowledged in all publications.

5277

5278 The members of the trial steering committee will be listed with their affiliations in
5279 the acknowledgements/appendix of the main publication.
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5489 **Appendices**

5490 **Appendix 1: Time windows for data collection**

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5492 For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3

5493 For details on time windows permitted for each trial intervention to be completed
5494 please see Table 5 below.

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5496 Table 5: Details of time windows permitted for all trial interventions.

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Contact and Purpose if not clear	Time window permitted +/-30 days of scheduled visit
Visit 1 Screening (eligibility review, med hx,)	Any time following referral of subject. Ideally perform as soon as possible following receipt of referral.
Visit 1 Consent Vitals, DRE Randomization EQ-5D-5L Questionnaire (baseline) Optional blood, urine, semen and tissue sample	Complete only once subject has had 24 hours after receiving the patient information to fully consider the study. Ideally on same visit as screening. Complete at screening Immediately after consent form signed and eligibility is confirmed. Complete immediately after consent form is signed Complete after additional informed consent signed, after randomization and up until any point prior to a biopsy.
Visit 2 MRI EQ-5D-5L Questionnaire (post MRI)	Only for men randomized to this arm. Any time following randomization. Ideally within 1 week of randomization. To be completed 24-48 hours post-MRI as previously explained

<p>Visit 3</p> <p>MRI-Targeted Biopsy of Prostate</p>	<p>Only for men randomized to this arm who have a lesion on MRI that needs a biopsy.</p> <p>Any time following the MRI being reported, ideally within 1 week of MRI.</p> <p>Depending on local Urology service structure, an appointment for a biopsy may need to be booked at the same time as the MRI is booked (i.e. immediately after randomization) in order for a slot to be secured for a biopsy to occur in timely fashion.</p> <p>If it is determined from the MRI that a biopsy is not required then the biopsy appointment can be used instead of Visit 4 for follow up of results and treatment decision.</p>
<p>Visit 3</p> <p>Systematic TRUS guided biopsy</p>	<p>Only for men randomized to this arm.</p> <p>Any time following randomization. Ideally within 4 weeks of randomization.</p>
<p>Visit 3</p> <p>Immediate post-biopsy questionnaire</p> <p>30-day post-biopsy questionnaire</p>	<p>Should be completed and returned immediately after a biopsy, before the subject leaves the department. As long as questionnaire completed within 24 hours it will be acceptable.</p> <p>To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy.</p> <p>To be returned by post or at follow up appointment (Visit 4).</p> <p>If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60</p>

Telephone reminder	<p>days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as possible to 30 days post-biopsy.</p> <p>At 30-days post biopsy a member of the research team will phone the subject to remind them to fill out the 30-day questionnaires</p>
<p>Visit 4</p> <p>Follow up for results And treatment Decision</p>	<p>Should be completed as soon as possible following the availability of any pathology results. Alternatively, if a man is in the MRI arm and the MRI is negative, this follow up should occur after the availability of the MRI report. Ideally the follow up appointment should be within 6 weeks of randomization.</p> <p>Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.</p>
<p>Visit 5</p> <p>26 week follow up</p>	<ul style="list-style-type: none"> • DRE • PSA • Optional blood, urine
<p>Visit6</p> <p>1 year follow up 52 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
<p>Visit 7</p> <p>78 week follow up</p>	<ul style="list-style-type: none"> • DRE • PSA • Optional blood, urine

<p>Visit 8</p> <p>104 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • Optional sample collection (blood, urine) <p>Those subjects randomized to ARM A but who did not have an MPMRI-targeted biopsy will have an additional MPMRI at Visit 8. This will be followed by a targeted-biopsy if results of MRI are positive (PI-RADS 3-5).</p> <p>Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).</p>
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Appendix 2: MPMRI Reporting Proforma

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day			month			year		

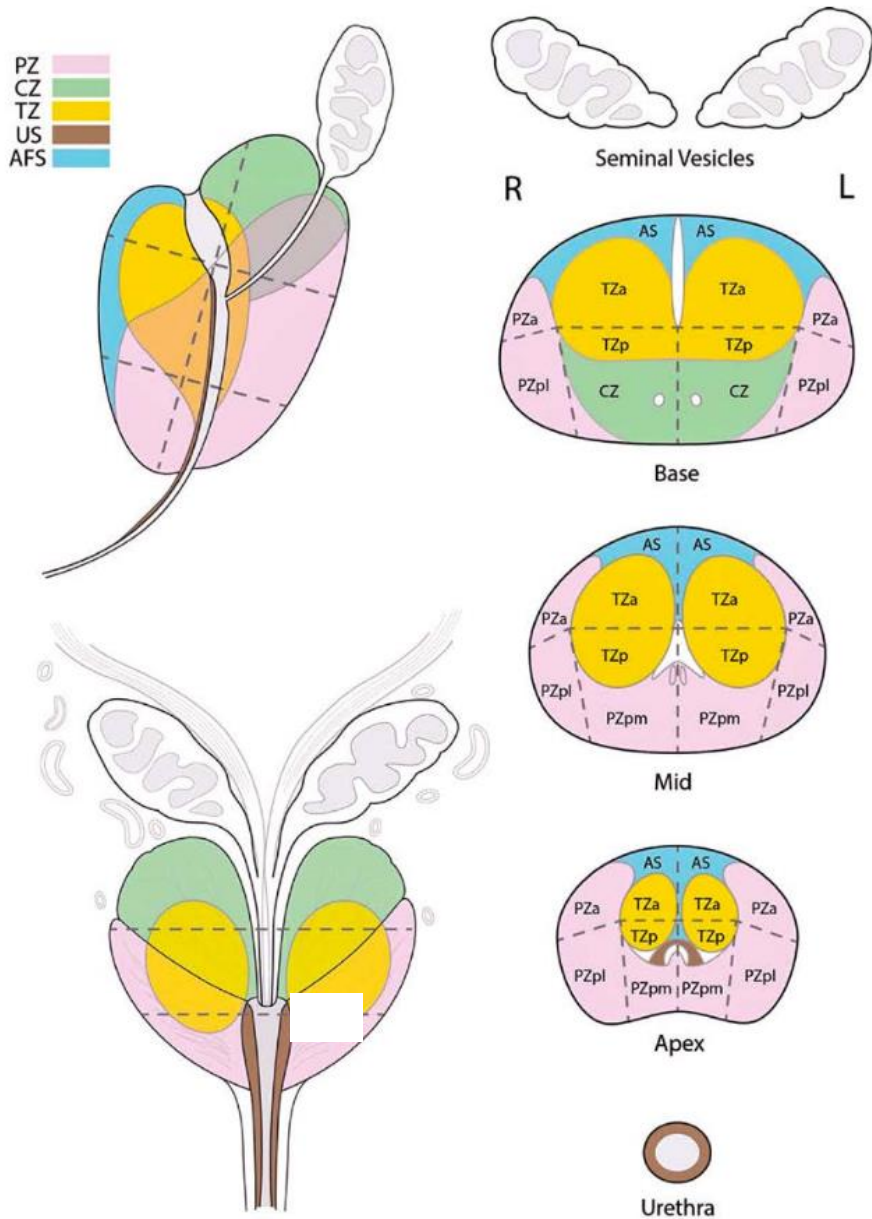
Reporting Radiologist:

Radiologists should annotate this diagram with up to 3 suspicious areas scoring 3 or greater on the PI-RADS v2 scale of suspicion. The three most suspicious areas should be annotated, each with the score clearly marked. "T1" should be the area with the greatest degree of suspicion. If applicable, "T2" should be the area with the next greatest degree of suspicion and finally if applicable, "T3" should be the area with the next greatest degree of suspicion. For each suspicious area, triaxial measurements should be recorded with all 3 measurements in orthogonal planes provided whenever possible. In the PZ, lesions should be measured on ADC. In the TZ, lesions should be measured on T2W. If lesion measurement is difficult or compromised on ADC (for PZ) or T2W (for TZ), measurement should be made on the sequence that show the lesion best. For example, coronal measurements may be best performed in the peripheral zone on T2 images.

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NO DCE (Part 1 or 2) – T2/DWI/ADC
DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE PSA

Draw lesions on diagram below annotating each with the T index (i.e T1; T2...)



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NO DCE (Part 1 or 2) – T2/DWI/ADC
**DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE
PSA**

- Image quality:** **Good**
 Minor image quality issues
 Acceptable for diagnosis
 Unacceptable

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If image quality is not good please comment:

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How to record locations

5599 **Location Code Format:** (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ,
5600 PZa, PZpl, PZpm)

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5602 Number of candidate tumor sites: _____

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5604 Target 1 (Highest Pi-Rads score and then largest):

5605 Present (Y/N): _____

5606 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

5607 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

5608 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
5609 x10⁻⁶

5610 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

5611 Location(s) (largest to smallest area involved):

5612 _____/_____/_____/_____

5613 _____/_____/_____/_____ (as per location code

5614 format above)

5615 Extraprostatic extension (Y/N/E-equivocal): _____

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5617 Target 2:

5618 Present (Y/N): _____

5619 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

5620 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

5621 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
5622 x10⁻⁶

5623 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

5624 Location(s) (largest to smallest area involved):

5625 _____/_____/_____/_____

5626 _____/_____/_____/_____ (as per location code

5627 format above)

5628 Extraprostatic extension (Y/N/E-equivocal): _____

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 5671
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Target 3:

Present (Y/N): _____
 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____
 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____
 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
 x10⁻⁶
 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)
 Location(s) (largest to smallest area involved):
 _____, _____, _____, _____
 _____, _____, _____, _____ (as per location code
 format above)
 Extraprostatic extension (Y/N/E-equivocal): _____
 There are more than 3 targets seen (Y/N): _____
 If yes give describe:

 LSV invasion (Y/N/E): _____ RSV invasion (Y/N/E): _____
 Adenopathy (Y/N): _____
 Worst Pi-Rads Score: _____
 Other Findings:

_____	(SI)	_____	(AP)	_____	(LR)	Volume:	_____	cc
cm	x	cm	x	cm				

5674
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DCE (Part 2 or 2) – T2/DWI/ADC/DCE
VIEW DCE – YOU SHOULD NOT KNOW THE PSA

- Image quality (including DCE):**
- Good
 - Minor image quality issues (still acceptable)
 - Acceptable for diagnosis
 - Unacceptable

5681
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5685
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If image quality is not good please comment:

5688
5689

Number of candidate tumor sites: _____

5690
5691

There was a change in lesions number or rank when adding DCE sequence
(Y/N):_____

5692
5693
5694
5695

If Yes, please give the correspondence between Target numbers with and without DCE (i.e. Target 1 without DCE = Target x with DCE) and **fill in all fields below to avoid confusion. Also draw lesions on diagram below again**

5696
5697
5698
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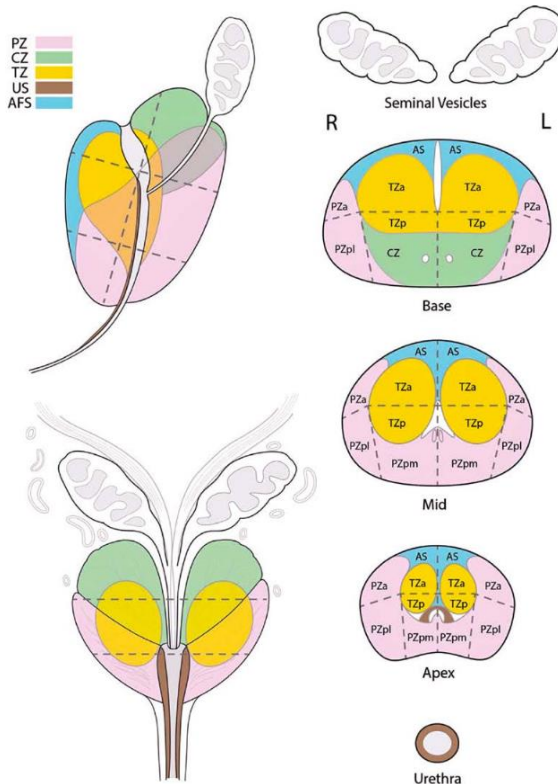
Correspondence:

Old T1 = New T____ Old T2 = New T____ Old T3 = New T____

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If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2...)



5722

5723 Target 1:

5724 Present (Y/N): _____

5725 Change from Part 1 (Y/N): _____,

5726 **If YES, complete ALL sections below**

5727 **If NO change in scores, ONLY complete DCE PiRads score below.**

5728 **All other entries are assumed = to Part 1**

5729 Overall Pi-Rads Score: _____ Your Likert Score: _____

5730 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE, 0,1): _____**

5732

5733 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
5734 x10⁻⁶

5735 Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

5736 Location(s) (largest to smallest area involved):

5737 _____ / _____ / _____ / _____

5738 _____ / _____ / _____ / _____

5739 Extraprostatic extension (Y/N/E-equivocal): _____

5740

5741 Target 2:

5742 Present (Y/N): _____

5743 Change from Part 1 (Y/N): _____

5744 **If YES, complete ALL sections below**

5745 **If NO change in scores, ONLY complete DCE PiRads score below.**

5746 **All other entries are assumed = to Part 1**

5747
5748
5749 Overall Pi-Rads Score: _____ Your Likert Score: _____
5750 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE,**
5751 **0,1):** _____
5752 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
5753 x10⁻⁶
5754 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)
5755 Location(s) (largest to smallest area involved):
5756 _____/_____/_____/_____
5757 _____/_____/_____/_____
5758 Extraprostatic extension (Y/N/E-equivocal): _____
5759
5760 Target 3:
5761 Present (Y/N): _____
5762 Change from Part 1 (Y/N): _____
5763 **If YES, complete ALL sections below**
5764 **If NO change in scores, ONLY complete DCE PiRads score below.**
5765 **All other entries are assumed = to Part 1**
5766 Overall Pi-Rads Score: _____ Your Likert Score: _____
5767 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE,**
5768 **0,1):** _____
5769 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
5770 x10⁻⁶
5771 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)
5772 Location(s) (largest to smallest area involved):
5773 _____/_____/_____/_____
5774 _____/_____/_____/_____
5775 Extraprostatic extension (Y/N/E-equivocal): _____
5776
5777 There are more than 3 targets seen (Y/N): _____
5778 If yes give describe:
5779 _____
5780 _____
5781 _____
5782 _____
5783
5784 LSV invasion (Y/N/E): _____ RSV invasion (Y/N/E): _____
5785
5786 Adenopathy (Y/N): _____
5787
5788 Worst Pi-Rads Score: _____
5789
5790 Other Findings:
5791 _____
5792 _____
5793 _____
5794 _____
5795
5796 **Safety:**
5797 Was there an immediate reaction to Gd contrast injection (Y/N): _____
5798

5799 If yes, please give details:

5800

5801

5802

**Will subject require an TRUS/MRI-fused No Yes
biopsy (Pi-Rads ≥ 3)?**

5803

5804 Please send this form and a DVD with the images AND completed MRI

5805 Report to:

5806

5807 Marlene Kebabdjian

5808 Sunnybrook Health Sciences Center

5809 *Urology Research, A304*

5810 2075 Bayview Avenue

5811 Toronto, Ontario M4N 3M5

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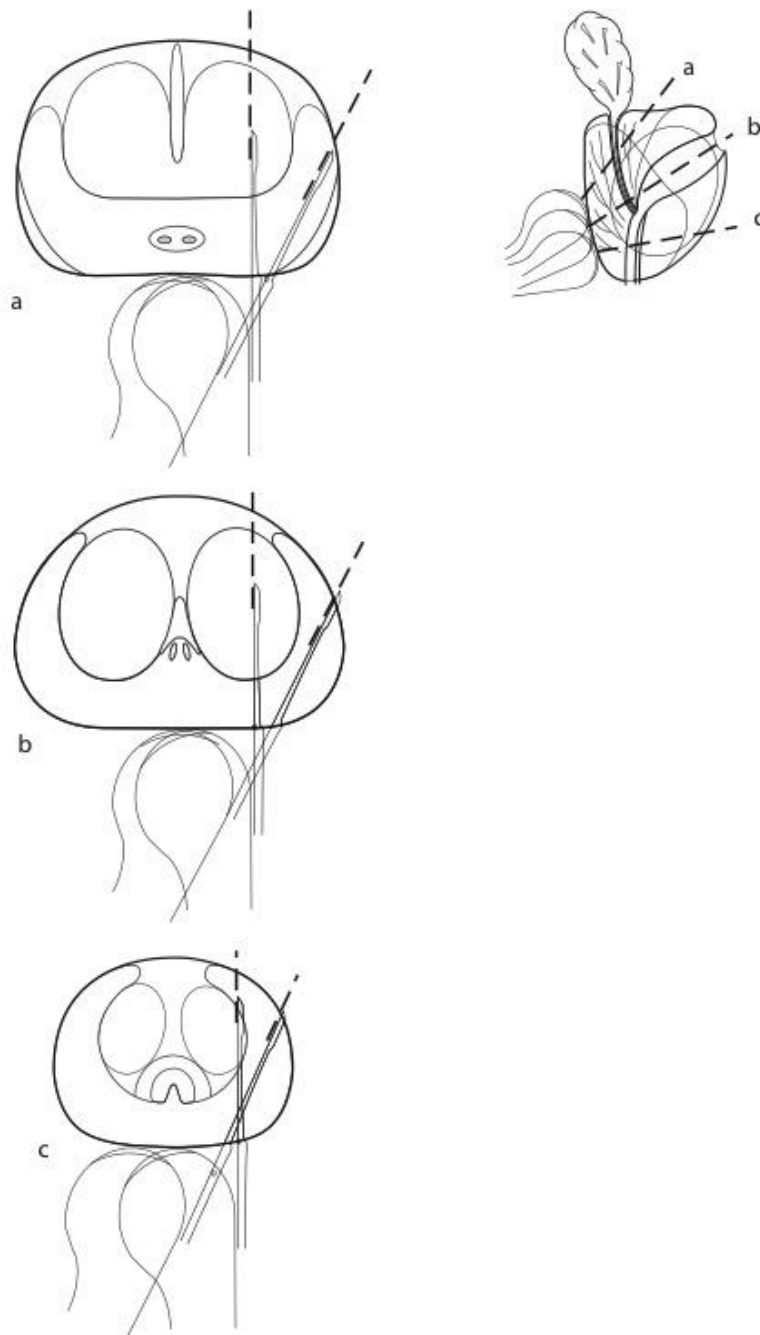
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Appendix 3: Example of systematic TRUS guided biopsyschema

5852

5853 Figure depicting 12-core systematic TRUS guided biopsyschema that sites are
5854 recommended to follow. Axial/coronal sections of a prostate gland (left) showing
5855 biopsy courses of the 12 biopsies performed under ultrasound guidance with an end
5856 fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,
5857 apex. From Haffner et al [37].



5858

5859 **Appendix 4: 2-page EQ-5D-5L Questionnaire**

5860 Under each heading, please tick the ONE box that best describes your health TODAY

5861

5862 **MOBILITY**

5863 I have no problems in walking about

5864 I have slight problems in walking about

5865 I have moderate problems in walking about

5866 I have severe problems in walking about

5867 I am unable to walk about

5868

5869 **SELF-CARE**

5870 I have no problems washing or dressing myself

5871 I have slight problems washing or dressing myself

5872 I have moderate problems washing or dressing myself

5873 I have severe problems washing or dressing myself

5874 I am unable to wash or dress myself

5875

5876 **USUAL ACTIVITIES** (*e.g. work, study, housework,*

5877 *family or leisure activities*)

5878 I have no problems doing my usual activities

5879 I have slight problems doing my usual activities

5880 I have moderate problems doing my usual activities

5881 I have severe problems doing my usual activities

5882 I am unable to do my usual activities

5883

5884 **PAIN / DISCOMFORT**

5885 I have no pain or discomfort

5886 I have slight pain or discomfort

5887 I have moderate pain or discomfort

5888 I have severe pain or discomfort

5889 I have extreme pain or discomfort

5890

5891 **ANXIETY / DEPRESSION**

5892 I am not anxious or depressed

5893 I am slightly anxious or depressed

5894 I am moderately anxious or depressed

5895 I am severely anxious or depressed

5896 I am extremely anxious or depressed

5897

5898 © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

5899 • We would like to know how good or bad your health
5900 is TODAY.

The best health
you can imagine

5901 • This scale is numbered from 0 to 100.

5902 • 100 means the best health you can imagine.

5903 0 means the worst health you can imagine.

5904 • Mark an X on the scale to indicate how your health is
5905 TODAY.

5906 • Now, please write the number you marked on the
5907 scale in the box below.

5908

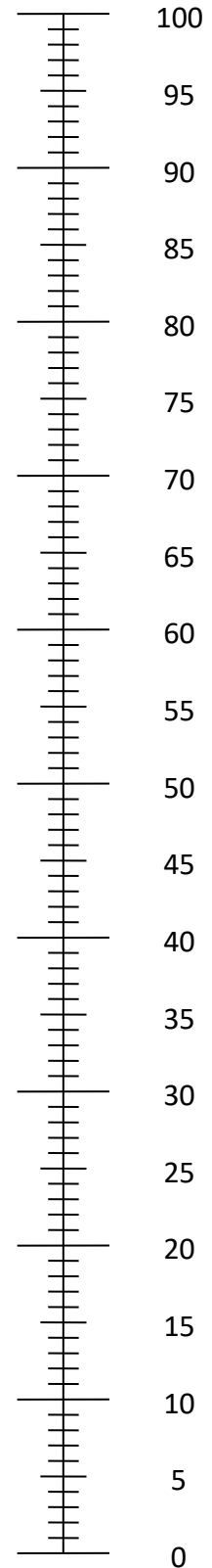
5909

5910

5911

YOUR HEALTH TODAY=

5913



The worst health
you can imagine

Did you experience any of the following in the month **before** your biopsy procedure.
For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

11. Pain at the site where the biopsies were taken from

Yes

1

No

2

Thank you for completing the questionnaire. Please hand this to a member of staff before you leave. Please ensure you are given the 30-day questionnaire for completion at 30 days following the biopsy.

5917

Appendix 6: 30-day post biopsy questionnaire

30-day post biopsy questionnaire

30-days after the biopsy procedure, the patient should complete this questionnaire:

Did you experience the following problem in the 30-days after the biopsy procedure:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the biopsy did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

5920

Did you experience the following problem in the 30-days after the biopsy procedure:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the biopsy did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

25. Pain at the site where the biopsies were taken from

Yes No
1 2

26. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

5921

28. Please list any **new** medications that you have taken **since the biopsy**. Do not list your regular medications but do list any **new** medications started related to the biopsy. Think especially about any painkillers or antibiotics that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. ciprofloxacin</i>	<i>500mg</i>	<i>2</i>	<i>3</i>

29. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

1

No

2

30. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over fevers*)

(iii) manner of contact (*e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency*)

(iv) any treatment you received (please be as specific as possible *e.g. "I was admitted to the ward and treated for an infection of the blood stream for 5 days of intravenous antibiotics with 1.2g co-amoxiclav three times a day and I had 2 days of painkillers with intravenous paracetamol 1g four times a day"*):

5922

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the biopsy, have you had contact with the community healthcare team for reasons related to the biopsy?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at GP surgery/home visit)

(iv) any treatment you received (please be as specific as possible e.g. "I received 5 days of oral antibiotics for a urinary tract infection- 625mg co-amoxiclav three times a day and I had 2 days of painkillers with paracetamol 1g four times a day"):

5923
5924

37. Have you felt unwell in any other way that we have not asked that you feel is due to the biopsy?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days:	0-2	3-5	6-10	11-15	16-20	21-30
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another biopsy** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

?

Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

?

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PRECISE Trial: Amendment 2

Summary of Changes

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- Minor administrative changes were made to the current protocol to avoid discrepancy. Minor errors were corrected.
- The following changes were made:
- Methodology - page 5, correction in language
 - Abbreviations - page 9, correction in text
 - Section 9.3 Table 3, omission in Vitals, DRE indication in columns, added.
 - Section 10.1, second bullet removed.
 - Section 9.3 Table 3 – clarification of footnotes at the end of the table on page 28
 - Section 10.1 – language added to reflect Arm A who do not require a biopsy will complete an EQ-5D-5L at visit 4
 - Section 11.3 – removal of the last sentence (In addition, subject needs to.....) in the paragraph that starts Men with a positive MRI.....
 - Sections 11.7, 11.8, 11.9, 11.10, - 'Vitals, DRE' added to these sections
 - Section 13, deletion of parentheses referring to maximum cancer core length
 - Section 13.0 Data, first bullet, EQ-5D-5L -amended verbage
 - Section 14.5.10 Health related Quality of Life – Removal of '24-48 hours post intervention' added 'at 2 years'
 - Appendix 1 – Visit 5 added 'vitals'
 - Appendix 1 – Visit 6 added 'vitals, DRE'
 - Appendix 1 – Visit 7 added 'vitals'
 - Appendix 1 – Visit 8 added 'vitals, DRE'

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1. Title Page

Full title:

A phase III multi-centre open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.

2. Short title: Prostate Evaluation for Clinically Important disease: MRI vs Standard Evaluation procedures. (PRECISE)

Date: 13 March 2017

Version 3.0

Sponsor:

Canadian Urology Research Consortium (CURC)

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Dr. Craig Earle

5999 Sunnybrook Health Sciences Centre
6000 2075 Bayview Avenue
6001 Toronto Ontario M4N 3M5 Canada

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6006 solely for the guidance of the clinical investigation. Reproduction or disclosure of this
6007 document - whether in part or in full - to parties not associated with the clinical
6008 investigation, or its use for any other purpose, without the prior written consent of
6009 the PI is not permitted.

6010
6011

6012 **2. Signature of Investigators**

6013

6014 **A phase III multi-centre open-label randomized controlled trial of**
6015 **multi-parametric magnetic resonance imaging (MRI)-targeted biopsy**
6016 **compared to systematic trans-rectal ultrasound (TRUS) guided biopsy**
6017 **for the diagnosis of prostate cancer in men without prior biopsy.**

6018

6019 **Date: 13 March 2017**

6020 **Version 3.0**

6021

6022

6023

6024 The signatory agrees to the content of the final clinical study protocol as presented.

6025

6026

6027 Signature: _____

6028

6029 Name: _____

6030

6031 Title: _____

6032

6033 Date: _____

6034

6035 Site name: _____

6036

6037

6038

3. Synopsis

Title	A phase III multi-centre, open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.
Short Title	<u>P</u> rostate <u>E</u> valuation for <u>C</u> linically <u>I</u> mportant disease: MRI vs <u>S</u> tandard <u>E</u> valuation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	<p>Primary Objective</p> <p>To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.</p> <p>Secondary Objectives</p> <p>27. To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy.</p> <p>28. Proportion of men in each arm with clinically insignificant cancer detected.</p> <p>29. Proportion of men in each arm with Gleason $\geq 4+3$ detected.</p> <p>30. Proportion of men in MRI arm who avoid biopsy.</p> <p>31. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected.</p> <p>32. Proportion of men in each arm who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy).</p> <p>33. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer by 2 years.</p> <p>34. Proportion of men with post-biopsy adverse events</p> <p>35. Health-related quality of life scores.</p> <p>36. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.</p> <p>37. To determine the cost per diagnosis of cancer.</p> <p>38. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield</p> <p>39. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone</p>
Test procedures	Subjects will be randomized to either ARM A: multi-parametric magnetic resonance imaging (MRI)

	<p>which, depending on outcome, may be followed by (MRI)-targeted biopsy.</p> <p>ARM B: systematic trans-rectal ultrasound (TRUS) guided biopsy.</p> <p>Subjects in both arms will complete a number of different questionnaires and will have PSA measurements taken. If subjects consent to participate in correlative studies, they will also need to provide blood, urine, semen and tissue samples at pre-specified time points.</p>
Indication	Clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy.
Diagnosis and main criteria for inclusion	<p>In order to be eligible, <u>all</u> inclusion criteria must be met.</p> <p>11. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;</p> <p>12. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk assessment of prostate cancer calculator, PCPTRC 2.0, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp; For men under age 55, the default age of 55 should be entered on the risk calculator.</p> <p>13. Serum PSA ≤ 20ng/ml;</p> <p>14. Fit to undergo all procedures listed in protocol;</p> <p>15. Able to provide written informed consent.</p>
Exclusion Criteria	<p>Men who meet the following criteria at the time of screening will be excluded:</p> <p>13. Prior prostate biopsy;</p> <p>14. Prior treatment for prostate cancer;</p> <p>15. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min);</p> <p>16. Contraindication to prostate biopsy;</p> <p>17. Men in whom artifact would reduce the quality of the MRI; i.e, previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work;</p> <p>18. Unfit to undergo any procedures listed in protocol.</p>
Study Design	This is a multi-centre open-label, randomized two arm study. Men are either randomized to receive MRI or a systematic trans-rectal ultrasound (TRUS) guided biopsy.
Methodology	<p>Eligible subjects will be randomized in a 1:1 ratio to receive either (ARM A) multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy, or (ARM B) systematic trans-rectal ultrasound (TRUS) guided biopsy. The time frame for data collection is shown in Appendix 1.</p> <p><u>All subjects</u> will have a PSA test prior to, or at Visit 1, and will complete a baseline EQ-5D-5L questionnaire. In addition, they will contribute optional blood, urine, semen and tissue samples if they consent to correlative studies.</p>

	<p><u>All subjects in ARM A</u> will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI.</p> <p><u>Subjects in ARM A who do not receive a subsequent biopsy</u> will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (\pm 1 week) after the procedure. They will have another MRI and PSA test 2 years after the initial MRI. When they complete the study after 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>Subjects in ARM A who do receive a MRI-targeted biopsy</u> will complete an immediate post-biopsy questionnaire at the time of the biopsy, another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>All subjects in ARM B</u> will complete an immediate post-biopsy questionnaire following the standardized TRUS-guided biopsy. They will complete another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p>
Type of control	This is an open-label randomized study.
Number of subjects	This study requires 422 subjects (211 in each arm). To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size will be inflated by 5%, and a target of 450 men will be recruited.
Primary endpoint	The proportion of men in each arm with clinically significant cancer (Gleason \geq 7) will be calculated based on histology results from biopsy procedures. Analysis will be on the per protocol study population.
Secondary endpoints	See section 7.4
Plan for statistical analysis	See section 14.0.
Funding	The total budget for this trial is \$3,000,000. (see attached).Ontario Institute for Cancer Research (OICR) has committed to \$1,500,000 in support of this study (letter appended).We hope to obtain the additional \$1,500,000 from the Movember Accelerated Translational Research Grant Competition

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4. Abbreviations and definitions

6171		
6172	Abbreviations:	
6173		
6174	ADC	Apparent diffusion coefficient
6175	CI	Confidence interval
6176	CRF	Case report form
6177	DSMC	Data Safety and Monitoring Committee
6178	DRE	Digital rectal examination
6179	DWI	Diffusion weighted imaging
6180	DCE	Dynamic contrast enhancement
6181	EDC	Electronic Data Capture
6182	ITT	Intention to treat
6183	MCCL	Maximum cancer core length
6184	MPMRI	Multi-parametric MRI, used interchangeably with MRI
6185		in this protocol.
6186	MPMRI-TB	Multi-parametric magnetic resonance image-targeted
6187		biopsy of the prostate
6188	MRI	Magnetic resonance imaging, used interchangeably
6189		with MPMRI in this protocol
6190	MRI-TB	Magnetic resonance imaging targeted biopsy
6191	MRS	Magnetic resonance spectroscopy
6192	PI	Principal Investigator
6193	PI-RADS	Prostate Imaging Reporting and Data System
6194	PTC	Permission to Contact
6195	PSA	Prostate specific antigen
6196	REB	Research Ethics Board
6197	STARD	Standards for the reporting of diagnostic studies
6198	TRUS	Trans-rectal ultrasound
6199	TSC	Trial Steering Committee
6200	T2W	T2-weighted imaging
6201		
6202		
6203	Definitions:	
6204		
6205	MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is
6206		used to determine the location of a suspicious
6207		target prior to biopsy.
6208		
6209	Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure
6210		is not influenced by findings on MRI imaging.
6211		Currently this is the standard of care for
6212		prostate cancer in the province of Ontario.
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5. Trial summary

5.1 Aim and Rationale

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6220 The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided
6221 (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is
6222 performed primarily for anatomic guidance as the ultrasound poorly discriminates
6223 between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are
6224 concentrated in areas of the peripheral zone, thought to harbor the majority of
6225 cancer.

6226

6227 An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to
6228 perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer.
6229 This information is used to direct a subsequent biopsy, known as an MRI-targeted
6230 biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a
6231 similar or greater amount of clinically significant cancer than systematic TRUS guided
6232 biopsy and has several other potential advantages including: the ability to
6233 differentiate between clinically significant and insignificant cancer, reducing
6234 unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related
6235 side-effects.

6236

6237 A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an
6238 individual's life expectancy and therefore does not warrant treatment. However
6239 when diagnosed with low grade cancer that is likely to be insignificant, a large
6240 proportion of subjects request treatment in case a more significant cancer is
6241 present[1]. A challenge in this area is that subjects are typically not aware that their
6242 cancer is clinically insignificant, and often view the early diagnosis and aggressive
6243 treatment they have been subjected to as life-saving.

6244 A prostate cancer detection procedure that differentiates clinically significant cancer
6245 from clinically insignificant cancer is therefore a major unmet need.

6246

6247 The potential implications of this trial include:

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- A redefinition of the prostate cancer diagnostic pathway;
- A reduction in the number of subjects undergoing prostate biopsy;
- A reduction in the number of biopsy cores taken per subject;
- A reduction in biopsy-related adverse events including sepsis and pain;
- A reduction in the over-diagnosis of clinically insignificant prostate cancer;
- A reduction in the economic burden of diagnosing and treating prostate cancer.

5.2 Methods

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Men referred with clinical suspicion of prostate cancer who have had no prior biopsy are randomized to either systematic TRUS guided biopsy(standard of care) or to a multi-parametric MRI (MPMRI) arm (the investigational arm). In the MRI arm, areas of the prostate are scored on a 5-point scale of suspicion for clinically significant cancer based on the Prostate Imaging Reporting and Data System

(PI-RADS) v2[2]:

PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be present)

PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

PI-RADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)

PI-RADS 4 – High (clinically significant cancer is likely to be present)

PI-RADS 5 – Very high (clinically significant cancer is highly likely to be present)

Each suspicious area will be given a separate score as described by consensus meeting recommendations [2, 3]. Lesions scoring 3, 4 or 5 will undergo targeted biopsy; up to three suspicious areas will be targeted.

In the control arm, subjects will undergo a standard 12 core systematic TRUS guided biopsy as per standard recommendations[4]. Suspicious sono graphic lesions will be targeted (12 cores *in toto*).

Pathologic findings from all biopsies will be recorded and will undergo statistical analysis (see statistics section, 14.0).

In both arms, self-reported questionnaires to capture biopsy-specific side effects will be administered immediately post-procedure, and at the post-procedure appointment which will take place 3 weeks (\pm 1 week) after the procedure. Euro QOL group 5 domain EQ-5D-5L questionnaires or a comparable QOL instrument will also be completed at baseline (prior to MRI or TRUS biopsy), 24 hours post MRI and 24 hours post-biopsy. Men will be followed up for 30-days post intervention and until a treatment decision is made and recorded. Pathology results from men requiring a radical prostatectomy will be recorded.

Men will complete the trial after they complete treatment for prostate cancer (radical prostatectomy) or the required follow-up procedures for each arm are met (see study timelines, section 9.3). Once men complete the trial, they revert to standard of care.

Annual questionnaires will be administered for all men with negative biopsy in both arms during a two-year follow-up period to determine cancer and treatment status.

No diagnostic test is perfect, and even with the best test some cancers may be missed. To minimize the risk of false negatives, men with negative biopsy results will

6306 be followed with serial PSA testing; PSA levels will increase if cancer is present. In
6307 addition to serial PSA testing, in this study men who had a negative MRI (defined as
6308 no cancer detected) and do not have a biopsy will have a follow up MRI at 24
6309 months.

6310
6311 As recruitment is expected to take up to 24 months (see section 7.6) and each
6312 subject will be followed up for two years, the estimated maximal duration of this
6313 study is four years in total. The primary endpoint will be reached at approximately 2
6314 years after study initiation.

6315 **5.3 Participating Sites**

6316 This is a multi-centre study. Institutions participating in the study must be able to
6317 perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able
6318 to randomize men to one of these two diagnostic tests.

6319
6320 We expect to recruit 3-6 subjects per month per site, based on recruitment rates
6321 from previous diagnostic trials performed by the centers involved. A typical centre
6322 sees 15-30 eligible men per month. We expect 5 recruitment sites, with 100 men to
6323 be recruited at each site over an 18-24 month period (see section 7.6).

6324 **5.4 Study outcomes**

6325 **5.4.1 Primary outcome**

6326 To determine whether the proportion of men with clinically significant cancer
6327 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
6328 guided biopsy.

6329 **5.4.2 Secondary outcomes**

6330 27. To determine whether the proportion of men with clinically significant cancer
6331 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
6332 guided biopsy.

6333 28. Proportion of men in each arm with clinically insignificant cancer detected.

6334 29. Proportion of men in each arm with Gleason $\geq 4+3$ detected.

6335 30. Proportion of men in MRI arm who avoid biopsy.

6336 31. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
6337 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
6338 detected.

6339 32. Proportion of men in each arm who go on to definitive local treatment (e.g.
6340 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
6341 hormone therapy, chemotherapy).

6342 33. Proportion of men with a negative MRI who develop a positive MRI and/ or
6343 Gleason ≥ 7 cancer by 2 years.

6344 34. Proportion of men with post-biopsy adverse events

6345 35. Health-related quality of life scores.

6346 36. Proportion with Gleason grade upgrading in men undergoing radical
6347 prostatectomy.

6348 37. To determine the cost per diagnosis of cancer.

-
- 6349 38. To determine the impact of the addition of Gd based contrast compared to a non
6350 contrast abbreviated MRI protocol on target yield
6351 39. To determine if a radiologist Likert score not based on Pi-Rads has a better target
6352 yield than Pi_Rads alone
6353
6354

6355 **6. Background**

6356 **6.1 Prostate cancer diagnosis**

6357 Prostate cancer is the most common male cancer in the Western world with an
6358 incidence of 24,000 new cases in Canada and 233,000 in the USA[5, 6]. It is the
6359 second most common cause of cancer death in European and North American men,
6360 with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe[5, 6].
6361 The incidence of the disease has increased by 22% over the last decade due to the
6362 widespread use of the prostate specific antigen (PSA) blood test; by 2030 the
6363 Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.As
6364 prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal
6365 digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one
6366 million prostate biopsies are performed in North America and Europe every year[7].
6367

6368 **6.2 Clinically significant versus clinically insignificant prostate cancer**

6369
6370 Clinically significant prostate cancer is cancer that is likely to progress and affect a
6371 man's life expectancy if left untreated. Though there is no universally agreed upon
6372 definition on what histological parameters define clinically significant cancer, most
6373 agree that larger volume cancers with a higher Gleason grade are more likely to be
6374 clinically significant; an historically accepted threshold is a tumour volume above
6375 0.5milliliters or any Gleason pattern 4 or 5 cancer[8-11].
6376

6377 This definition is likely overly stringent. An increasing consensus views all Gleason
6378 pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of
6379 pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate
6380 cancers fall into this category, and are unlikely to progress and affect a man's life
6381 expectancy if left untreated. The widespread use of PSA testing has led to more men
6382 being diagnosed with insignificant cancer that does not warrant any treatment [13];
6383 however they are typically monitored closely with active surveillance. This is
6384 associated with anxiety about harbouring untreated cancer, and the negative
6385 psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate
6386 cancer are also subjected to serial biopsies and other tests, requiring long term
6387 follow up. Further, many men with low risk disease receive radical treatment, either
6388 because their physicians are not advocates of surveillance or because of anxiety
6389 [15].These treatments may expose them to morbidity including urinary incontinence
6390 and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate
6391 clinically significant cancer from clinically insignificant cancer will help reduce patient
6392 anxiety, alleviate further testing, and avoid radical treatment and associated
6393 morbidities.

6395 **6.3 Current standard of care: systematic TRUS guided biopsy**

6396 The European association of Urology and NICE guidelines recommend systematic
6397 TRUS guided biopsy as the current standard of care for the diagnosis of prostate
6398 cancer [4, 17]. This procedure has several advantages: it can be delivered quickly in
6399 an outpatient clinic under local anesthetic, it can be offered at most Urology centres,
6400 and the expertise is widely distributed.

6401
6402 Limitations of systematic TRUS guided biopsy are as follows: the procedure requires
6403 the operator to take 10-12 samples in the peripheral zone, where it is thought that
6404 the majority of prostate cancer can be found (See Appendix 2)[18]. The ultrasound
6405 guidance used during the procedure is useful for visualizing the prostate and
6406 assessing the location of the needle within the prostate but has a poor ability to
6407 discriminate tumour from normal tissue [19], which means that the systematic TRUS
6408 guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has
6409 been shown to have a high false negative rate of 30-45% [20, 21]. As a systematic
6410 TRUS guided biopsy is not specifically targeted to the location of a suspected
6411 significant cancer, there is also a greater chance that a significant cancer may be
6412 missed.

6413 **6.4 The emerging role of MRI in prostate cancer diagnosis and** 6414 **treatment**

6415 **6.4.1 The role of imaging in prostate cancer diagnosis**

6416 Although used to diagnose many other solid organ cancers such as breast, renal and
6417 colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic
6418 pathway. Imaging in prostate cancer, is typically limited to stage the disease
6419 following histological diagnosis. Magnetic resonance imaging (MRI) is used in many
6420 centres to assess for extra-capsular extension during prostate cancer staging. In the
6421 past five years however, the possibility of using multi-parametric MRI (MPMRI) for
6422 diagnosing prostate cancer prior to biopsy, has generated tremendous interest[22].

6423 **6.4.2 Limitations of early MRI studies in prostate cancer**

6424 Early literature reported conflicting results on the ability of MRI to detect prostate
6425 cancer. A recent systematic review of the literature showed that the quality of
6426 studies evaluating MRI was disappointing [22]. Limitations of reported studies
6427 include:

- 6428 • **Poor reporting standards.** Many early studies failed to closely follow
6429 published guidelines for the standards of reporting of diagnostic studies
6430 (STARD) [23].
- 6431 • **Biopsy artifact.** The majority of early studies evaluated MRI after biopsy.
6432 Evidence has shown that post-biopsy hemorrhage can remain for several
6433 months and affect interpretation of the image [24].
- 6434 • **Poor reference standards.** Many early studies use systematic TRUS guided
6435 biopsy as a reference standard, which due to its limitations, can influence the
6436 validity of the index test of MRI. Using radical prostatectomy specimens as

6437 reference standards can lead to a selection bias, as MRI is only validated in
6438 men with disease characteristics that require radical prostatectomy. Further,
6439 correlation of radical prostatectomy specimen with an MRI image is not
6440 without difficulty given the shrinkage (10-20%), distortion, absent perfusion,
6441 orientation and tissue loss as a result of specimen trimming.

- 6442 • **Incomplete analysis of the prostate.** Many early studies only evaluate the
6443 validity of MRI in the peripheral zone, even though studies have shown that
6444 around 25% of prostate cancers may be located in the transition zone [18].
- 6445 • **Segmentation.** Many early studies artificially divide the prostate into a
6446 number of segments in order to increase the amount of data obtained and
6447 the power of the analysis. Segments should not be treated as independent
6448 regions of interest, and this should be factored into the analysis.

6449

6450 **6.4.3 Emerging role of MRI in the diagnosis of prostate cancer**

6451 Since the publication of these early reports, improvements in diagnostic technology
6452 have changed the field and more evidence supporting the role of pre-biopsy MRI has
6453 been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla
6454 and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image
6455 acquisition and the addition of functional sequences including magnetic resonance
6456 spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast
6457 enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for
6458 biopsy artifacts.

6459
6460 The combination of anatomical sequences (T2-weighted imaging) and functional
6461 sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI.
6462 Combining the sequences improves the validity of the test [25, 26].

6463
6464 A systematic review determined that 60% of men with a clinical suspicion of prostate
6465 cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI
6466 with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity,
6467 positive predictive value and negative predictive value of 90%, 88%, 77% and 95%
6468 respectively for the identification of prostate tumours greater than 0.5ml [28].
6469 Systematic reviews and meta-analysis of recent studies have demonstrated
6470 sensitivity and specificity consistently between 70-90% for the detection of clinically
6471 significant prostate cancer[26, 29-31].

6472
6473 As a result of this accumulating evidence, MRI is increasingly used in clinical practice
6474 in the diagnostic pathway for prostate cancer. The results of MRI can influence the
6475 decision to perform a prostate biopsy, as well as the technique and targeting used
6476 during the biopsy.

6477
6478 MRI has tremendous potential to enhance the outcome of men on active
6479 surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA <
6480 10) harbor higher-grade disease. This occult high-grade disease "*the wolf in sheep's*
6481 *clothing*", is responsible for the 3-5% of prostate cancer deaths that have been
6482 reported in long term surveillance series that did not incorporate MRI[32, 33]. The
6483 early use of MRI in men on surveillance has the potential both to reduce the need

6484 for confirmatory biopsies, and to identify the *wolf in sheep's clothing* earlier, prior to
6485 the development of metastasis.

6486

6487 This was the rationale for the very successful ASIST study, which recently successfully
6488 completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in*
6489 *toto* by the Ontario Institute of Cancer Research. The project was managed by the
6490 Canadian Urology Research Consortium (CURC). It randomized 273 men recently
6491 diagnosed with low risk prostate cancer, on surveillance, between systematic
6492 confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end
6493 point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or
6494 higher prostate cancer. The study had numerous secondary end points and
6495 correlative science components. We expect to report the initial results by 3Q
6496 2016. We believe that the success and potential impact of the ASIST trial has created
6497 strong momentum to proceed with the PRECISE trial, which has even greater
6498 potential to substantially influence prostate cancer screening and diagnosis.

6499 **6.4.3.1 MRI can influence the decision to perform a prostate biopsy**

6500 With reported negative predictive values of 95% [28, 34,35], MRI can help determine
6501 whether a prostate biopsy is necessary; if the MRI does not identify a suspicious area
6502 the biopsy can be avoided. Using MRI, 40-50% of men referred with clinical suspicion
6503 of prostate cancer might avoid a biopsy [27]. The recent National Institute for Health
6504 Research (NIHR) Health Technology Assessment (HTA) report [11] acknowledged the
6505 value of MRI in this context. The NIHR HTA report suggests that using MRI to reduce
6506 the number of men who undergo biopsy, can be cost effective despite the costs
6507 associated with MRI[11]. Cost savings for the publically funded health care system
6508 accrue as a result of reduced number of biopsies and costs of attendant
6509 complications, and reduced treatment of clinically insignificant cancer.

6510 **6.4.3.2 MRI can influence the biopsy technique**

6511 For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI
6512 information is used to influence the prostate biopsy technique. This is known as MRI-
6513 targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of
6514 ways.

6515

6516 The biopsy operator can use the MRI images or report to direct biopsies into the
6517 area of the prostate where the tumour is located. The location of the tumour on the
6518 MRI (carried out in advance) is registered to the real-time ultrasound images with
6519 the use of software (software assisted registration or image-fusion) or without the
6520 use of software (visual registration or cognitive registration), while the prostate is
6521 visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted
6522 directly "in-bore", where the biopsy is conducted within an MRI scanner where the
6523 target identified on MRI during a prior diagnostic scan is biopsied using guidance
6524 from serial MRI scans during the biopsy procedure, performed in an open magnet.

6525

6526 For the PRECISE study, the biopsy will be performed using an image fusion-targeting
6527 device. Two devices have been FDA approved: the Artemis, made by Eigen, and the
6528 Urostation, made by Koelis. These devices import the MR target into the TRUS
6529 image, and direct the biopsy needle into the target.

6530 **6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are**
6531 **similar to other methods**

6532 A systematic review determined that 60% of men with a clinical suspicion of prostate
6533 cancer will have a suspicious area identified on MRI [27]. One study found that a
6534 prostate biopsy strategy using only MPMRI-targeted cores resulted in the same
6535 detection rate of clinically significant cancer as 20-sector transperineal biopsies[36].
6536 Other studies also show that a targeted-alone approach would detect a similar
6537 amount of clinically significant cancer when compared to a 10-12 core systematic
6538 TRUS guided biopsy[37]. A targeted-alone approach detects 17% less clinically
6539 insignificant cancer compared to systematic TRUS guided biopsy[38].

6540
6541 The detection rates achieved with a targeted-alone biopsy strategy require fewer
6542 biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis,
6543 targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer
6544 detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores
6545 compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of
6546 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material
6547 for histopathological analysis as the maximum cancer core length obtained from
6548 targeted biopsies can be greater than that obtained from systematic biopsies[37].

6549
6550 Robust comparative evidence from randomized controlled trials is needed to
6551 determine if MRI scans can improve our ability over systematic TRUS guided biopsy
6552 to diagnose clinically significant cancer and our ability to avoid detecting clinically
6553 insignificant cancer.

6554

6555 **6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy**

6556 Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine
6557 clinical practice for prostate cancer diagnosis. Most existing studies have cohort
6558 study designs which make interpretation difficult as they do not conform well to
6559 STARD [23] recommendations [27]. Limitations of these studies include:

- 6560 • **Broad definition of the study population.** The cancer detection rates depend on
6561 the prevalence of the condition in the population being investigated. This varies
6562 amongst men with no prior biopsy, prior negative biopsy and prior positive
6563 biopsy. In many studies the detection rates are not attributable to a clearly
6564 defined population.
- 6565 • **MRI conduct and reporting.** The detail in which MRI is conducted and
6566 interpreted varies greatly amongst published studies.
- 6567 • **Reporting of cancer detection.** The cancer detection by systematic and targeted
6568 cores is not always presented separately and cancer detection is not always
6569 specified by clinical significance. These are both essential in order to evaluate the
6570 technique.

6571 There is a strong need for a randomized controlled trial comparing MRI-targeted
6572 biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical
6573 practice can be established.

6574 **6.5 Novelty of PRECISE**

6575 PRECISE is the first randomized study in biopsy-naïve men in which men are
6576 randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal
6577 areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic
6578 TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-
6579 targeted biopsy approach in the detection of clinically significant cancer. In order to
6580 evaluate a biopsy technique that could replace standard of care, the standard of care
6581 test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to
6582 allow a direct comparison.

6583

6584 Other constituencies with an interest in MRI in prostate cancer (University College,
6585 London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New
6586 York) have considered similar studies, however in these centres MRI has largely
6587 replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to
6588 date. As a result, these centres have acknowledged that randomization to a standard
6589 biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as
6590 equipoise has been lost.

6591

6592 In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not
6593 recommended for the indication of an elevated PSA in men who have not had a
6594 biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed
6595 to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a
6596 biopsy will make entry into this trial very appealing to potential candidates. Further,
6597 the barriers, both financial and physical, to obtaining a quality MRI outside of the
6598 health care system are substantial. Thus we believe men who are randomized to the
6599 systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant
6600 contamination (i.e. men randomized to the systematic biopsy arm seeking out an
6601 MRI instead).

6602

6603 **7. Trial objectives**

6604 **7.1 Overall aim**

6605 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
6606 standard of care systematic TRUS guided biopsy in the detection of clinically
6607 significant and clinically insignificant prostate cancer in men without prior biopsy.
6608 The implication of this trial is that MRI-targeted biopsy could replace systematic
6609 TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

6610 **7.2 Hypotheses**

6611 The proportion of men with clinically significant cancer detected by MRI-targeted
6612 biopsy will be no less than that detected by systematic TRUS guided biopsy.

6613 **7.3 Primary Objective**

6614 To determine whether the proportion of men with clinically significant cancer
6615 (Gleason \geq 7) detected by MRI-targeted biopsy is no less than systematic TRUS
6616 guided biopsy.

6617 **7.4 Secondary Objectives**

- 6618 40. To determine whether the proportion of men with clinically significant cancer
6619 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
6620 guided biopsy.
- 6621 41. Proportion of men in each arm with clinically insignificant cancer detected.
- 6622 42. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 6623 43. Proportion of men in MRI arm who avoid biopsy.
- 6624 44. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
6625 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
6626 detected.
- 6627 45. Proportion of men in each arm who go on to definitive local treatment (e.g.
6628 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
6629 hormone therapy, chemotherapy).
- 6630 46. Proportion of men with a negative MRI who develop a positive MRI and/ or
6631 Gleason ≥ 7 cancer by 2 years.
- 6632 47. Proportion of men with post-biopsy adverse events
- 6633 48. Health-related quality of life scores.
- 6634 49. Proportion with Gleason grade upgrading in men undergoing radical
6635 prostatectomy.
- 6636 50. To determine the cost per diagnosis of cancer.
- 6637 51. To determine the impact of the addition of Gd based contrast compared to a non
6638 contrast abbreviated MRI protocol on target yield
- 6639 52. To determine if a radiologist Likert score not based on Pi-Rads has a better target
6640 yield than Pi_Rads alone

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6643 **7.5 Explanation for non-inferiority hypothesis**

6644 Due to the putative advantages of MRI-TB in reducing the number of men who
6645 require a biopsy, reducing the number of cores required in each man who is
6646 biopsied, more accurate representation of disease burden, less insignificant disease
6647 detected and reducing the number of men at risk of complications of biopsy, the
6648 primary outcome of detection of clinically significant cancer in each arm will be
6649 compared using a non-inferiority hypothesis. Even if a similar amount of clinically
6650 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these
6651 advantages would support the use of MRI-TB instead of systematic TRUS guided
6652 biopsy in clinical practice.

6653

6654 **7.6 Anticipated timeline of study progression**

6655 The study will commence once sponsorship, ethical approval and local approvals
6656 have been obtained at a participating site and once site initiation training has
6657 occurred and a letter of site activation has been issued from the coordinating centre.
6658 Additional sites may join after the study has commenced. At this time, five sites will
6659 participate. Assuming a minimum recruitment rate of 3-6 men per site per month,
6660 recruitment will be complete by 24 months, if not sooner. If accrual is slower than
6661 expected, an additional 1-2 sites will be recruited for year 2.

6662

Month	Number of Sites	Total recruitment
0	2	0
3	4	18-36
6	5	54-108
9	5	99-198
12	5	144-288
15	5	189-378
18	5	234-468
21	5	279-558
24	5	324-648

6663

6664 **8.Study Population**

6665 **8.1 Number of Subjects**

6666 Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or
6667 results of digital rectal exam, with no prior biopsy will be eligible for participation.
6668 Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be
6669 enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

6670 **8.2 Subject inclusion criteria**

6671 In order to be eligible, all inclusion criteria must be met:

- 6672 13. Men at least 18 years of age referred with clinical suspicion of prostate cancer
6673 who have been advised to have a prostate biopsy;
- 6674 14. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk
6675 assessment of prostate cancer calculator, PCPTRC 2.0, found at
6676 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> For men under age 55,
6677 the default age of 55 should be entered on the risk calculator.
- 6678 15. Serum PSA ≤ 20 ng/ml within 3 months of randomization
- 6679 16. Fit to undergo all procedures listed in protocol;
- 6680 17. Able to provide written informed consent.

6681 **8.3 Subject exclusion criteria**

6682 Men who meet the following criteria at the time of screening will be excluded:

- 6683 13. Prior prostate biopsy
- 6684 14. Prior treatment for prostate cancer
- 6685 15. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR
6686 ≤ 50 mls/min)
- 6687 16. Contraindication to prostate biopsy
- 6688 17. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip
6689 replacement surgery, metallic hip replacement or extensive pelvic orthopaedic
6690 metal work
- 6691 18. Unfit to undergo any procedures listed in protocol.
- 6692

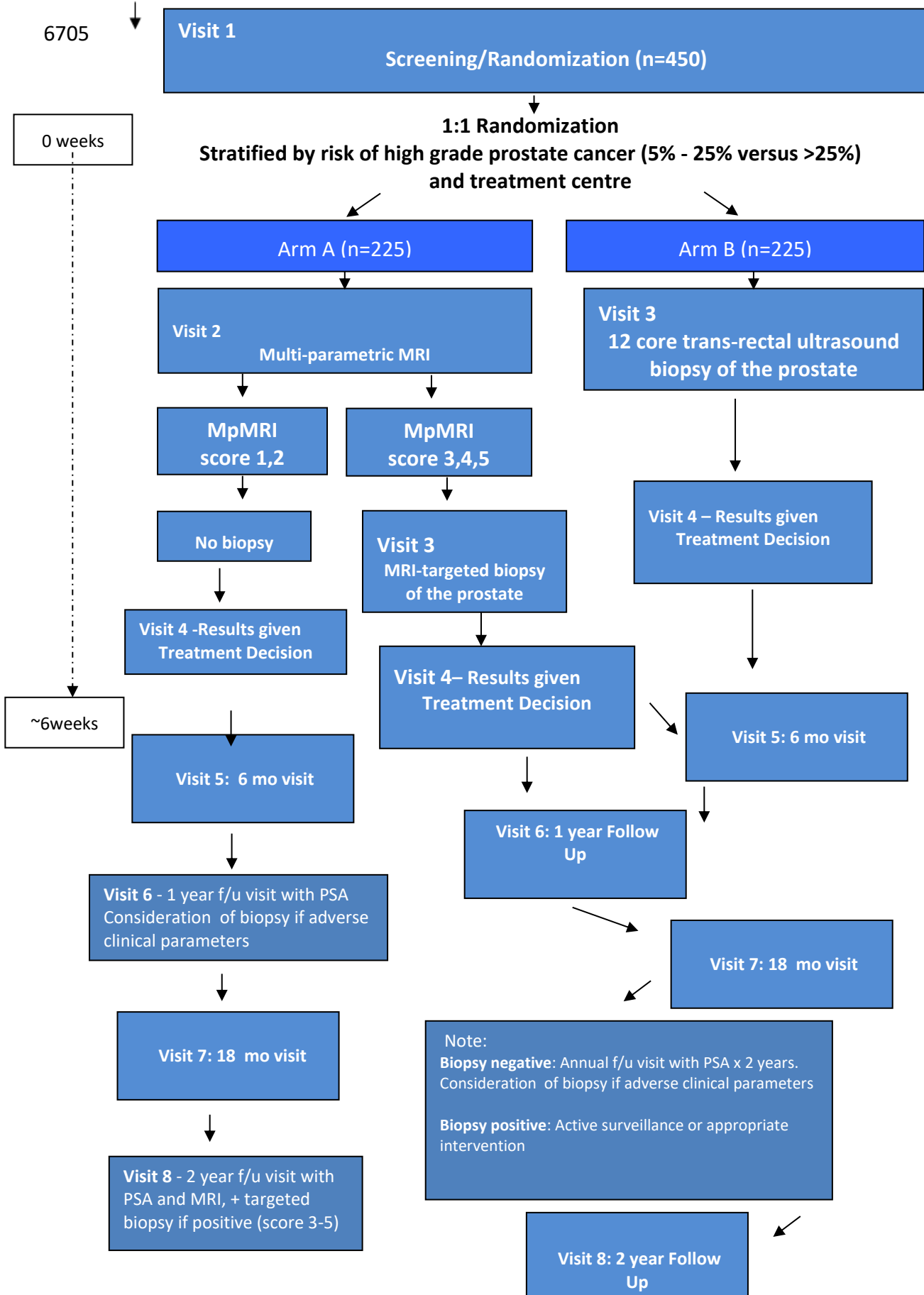
6693 **9. Study design**

6694 **9.1 Study design**

6695 The study is a multi-centre, open-label randomized controlled trial, with men
6696 randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in
6697 Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or
6698 will be followed for two years if there is no suspicious areas identified by MRI. The
6699 unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-
6700 core systematic TRUS guided biopsy. All men in the study will be followed for two
6701 years or until they have had radical treatment (whichever comes first).
6702

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9.2 Study Trial Schema



6706 **9.3 Timeline of subject contact**

6707 Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial.

6708 The individual pathway that each subject experiences is dependent on both the arm
6709 he is randomized to and results of the tests.

6710

6711 **Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require**
6712 **a biopsy**

	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3 N/A	Visit 4 Post- Test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	5	26	52	78	104
Consent	X							
Screening (eligibility review, med hx,	X							
Vitals, DRE ¹	X				X	X	X	X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue- NA								
Creatinine	X							
PSA ⁴	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI		X						X ⁵
MRI-Targeted Biopsy								X if target
Immediate post- biopsy questionnaire								
Follow up for results of tests				X				
Treatment decision ⁶				X				
30-day post- biopsy questionnaire								
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

6713 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
6714 Science component. See correlative manual for instruction.
6715 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
6716 catch' and post-DRE samples. See the Correlative Science Manual for further details on
6717 collection and processing.
6718 ³Collected at baseline, and annually.
6719 ⁴PSA will have been done prior to visit 1 as part of screening.
6720 ⁵ If MRI indicates a target, biopsy must be done
6721 ⁶After treatment decision men revert to standard of care.
6722

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Table 2: ARM A: Men randomized to MRI arm who have a lesion on MRI and require a biopsy

	Visit 1 Screening / Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post- test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follo w up
Weeks:	0	1	2	6	26	52	78	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals, DRE ¹	X				X	X	X	X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue ⁴			X					X
Creatinine	X							
PSA ⁵	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI		X						X ⁶
MRI-Targeted Biopsy			X					X ⁶
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁷				X				
30-day post- biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

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¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First catch' and post-DRE samples. See the Correlative Science Manual for further details on collection and processing.

³Collected at baseline, and annually.

⁴ tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

⁵PSA will have been done prior to visit 1 as part of screening.

⁶See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

⁷After treatment decision men revert to standard of care.

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Table 3: ARM B: Men randomized to systematic TRUS guided biopsy arm

	Visit 1 Screening/ Randomization	Visit 2	Visit 3 Biopsy	Visit 4 Post- test visit	Visit 5 6 mos	Visit 6 1 year follo w up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	6	26	52	52	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals, DRE ¹	X				X	X	X	X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X				X	X	X	X
• semen ³	X					X		X
• tissue			X					
Creatinine	X							
PSA ⁴	X				X	X	X	X
Systematic TRUS guided biopsy			X					
MRI								X ⁵
MRI-Targeted Biopsy								X ⁵
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁶				X				
30-day post- biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							

ConMeds Form	Complete as required at any time following registration				
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6779 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
6780 Science component. See correlative manual for instruction.

6781 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
6782 catch' and post-DRE samples. See the Correlative Science Manual for further details on
6783 collection and processing.

6784 ³Collected at baseline, and annually.

6785 ⁴PSA will have been done prior to visit 1 as part of screening.

6786 ⁵See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue
6787 must be obtained if subject has agreed to the Correlative Science component. See
6788 correlative manual for instruction.

6789 ⁶After treatment decision men revert to standard of care.

6790

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6792 **10. Trial Interventions and procedures**

6793

6794 The following procedures will be applied as necessary to subjects enrolled in both
6795 arm of the trial.

6796 **10.1 EQ-5D-5L Questionnaires**

6797

6798 **For all subjects enrolled in trial**

6799 Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L
6800 questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to
6801 evaluate health related quality of life. It takes approximately 2 minutes to complete.

- 6802 • All subjects should complete the baseline questionnaire at the screening visit
6803 before leaving the department.
- 6804 • Subjects who have a normal MRI and do not require a biopsy will complete an
6805 EQ-5D-5L questionnaire at Visit 4.
- 6806 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
6807 be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date
6808 that the subject should fill out the questionnaires should be written on top of the
6809 questionnaire. (This can also be done at Visit 4).
- 6810 • All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up
6811 visit.

6812

6813

6814 **10.2 Multiparametric MRI imaging procedure**

6815 **For subjects in Arm A only**

6816

6817 **10.2.1 MRI Protocol**

6818 A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic
6819 phased array coil and an automated injector system with the subject in the supine
6820 position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast

6821 enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS
6822 v2.
6823
6824 Within the specified PiRads-2 framework a common protocol will be formulated by a
6825 consensus of the radiologists involved in the trial at each site at a startup meeting.
6826 The highest agreed upon b-value image for DWI (at least 1400s/mm²) will be
6827 selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast
6828 media, injection rates and dynamic scanning temporal resolution will be matched for
6829 all sites. An optional multi b value DWI acquisition will be undertaken as well to
6830 allow for ancillary studies into non log linear apparent diffusion coefficient (ADC)
6831 models for tumor characterization. This is summarized in an MRI Operations Manual
6832
6833
6834 Subjects will be asked to follow their local standard of care MRI examination
6835 preparation instructions for the MRI procedure.

6836 **10.2.2 MRI reporting**

6837 The MRI will be reported by an experienced radiologist using the MRI Reporting
6838 Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored
6839 based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5
6840 pointLikert score for purposes of comparison. Biopsy decisions will be based on the
6841 PiRads scores.

6842

6843

6844 Lesions in the prostate will be scored on the following scale:

6845 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
6846 present)

6847 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

6848 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
6849 equivocal)

6850 PI-RADS 4 – High (clinically significant cancer is likely to be present)

6851 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
6852 present)

6853

6854 The location of the suspicious areas in the prostate should be marked on a diagram
6855 of the prostate (see Appendix2) and the sector numbers containing each suspicious
6856 area should be recorded in the case report form.

6857

6858 Radiologists will be blinded to the PSA.

6859

6860

6861 Imaging interpretation will be carried out at each site, however ensuring consistency
6862 and quality of imaging interpretation is crucial. A central imaging site will be
6863 designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site
6864 will perform the interpretation of all images for that site. The designated radiologist
6865 must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A
6866 startup meeting involving all radiologists will be held prior to start of accrual where
6867 each site will bring 5 MRI cases performed at their site for consensus review, scoring

6868 and discussion. This will provide a commonality of approach to interpretation among
6869 the radiologists before the study begins. After this startup meeting each site will
6870 send one set of MRI images and its interpretation for central review for site
6871 qualification.

6872
6873 A copy of all images will be sent on CD/DVD to the central site for archiving.

6874 **10.3 No target identified on MPMRI (PiRads 1 or 2)**

6875 **For subjects in Arm A only, who do not require a biopsy**

6876 Men who have MRIs that do not identify any suspicious lesion will not receive a
6877 biopsy. These subjects will benefit from being part of the trial as a result of not
6878 having to undergo an invasive biopsy procedure, avoiding the discomfort associated
6879 with the procedure, the risk of being diagnosed with clinically insignificant cancer
6880 and the risk of sepsis associated with the biopsy procedure. Studies suggest that if
6881 the MRI does not identify areas suspicious for cancer there is an 85-95% chance that
6882 clinically significant cancer is not present [28, 34, 35].

6883
6884 As soon as the results of the MRI are discussed with the subject, their treatment
6885 decision will be recorded and they will return to standard of care management. As
6886 part of standard of care these subjects can undergo further PSA surveillance and / or
6887 prostate biopsies if indicated.

6888 **10.4 MRI-Targeted biopsy**

6889 **For subjects in Arm A who do require a biopsy**

6890 **10.4.1 MRI choice of targets for targeted biopsy**

6891 Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will
6892 subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in
6893 MRI-targeted biopsy. Operator experience (number of targeted biopsies performed
6894 to date) will be recorded before each procedure. The number of biopsy operators
6895 should be kept to the minimum number possible.

6896
6897 Targets will be stratified by PI-RADS score and if the same score then by size and
6898 labeled T1, T2, T3...etc. If there are more than 3 lesions with a score of 3 or more
6899 only T1-T3 will be targeted. The radiologist should record the sectors involved with
6900 tumor in order of most to least involved using the PI-RADS v2 sector scheme.
6901 The number of biopsy operators should be kept to the minimum number possible.

6902
6903 Subjects in the MRI cohort will not have systematic biopsies, with one exception.
6904 Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small
6905 volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core
6906 biopsy will be conducted.

6907 **10.4.2 MRI Biopsy**

6908 The procedure will be performed in the outpatient departments of sites possessing
6909 the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An
6910 operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI

6911 fusion system at their institution before they are qualified to participate as an
6912 operator in the study.
6913
6914 Coumarin anticoagulant, clopidogrel treatment and other relevant
6915 anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and
6916 advice sought as to appropriate substitutes if indicated. Aspirin will be continued at
6917 the discretion of the physician doing the biopsy.
6918
6919 Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will
6920 be performed via the trans-rectal route or via the trans-perineal route depending
6921 upon local practice.
6922
6923 Targeted biopsies should be performed by software-assisted fusion devices
6924 (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This
6925 software is safe and poses no risks to the subject since the same CE-marked
6926 ultrasound probes that are designed to perform the biopsy when performed as
6927 standard of care biopsy are used during targeted biopsy. Should the operator wish to
6928 not use the information provided by the software registration system and use
6929 cognitive (visual) registration alone they can do so, but should indicate this on the
6930 subject's case report form.
6931
6932 The samples per target will be 4cores spread across the target region for a maximum
6933 total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be
6934 conducted in order meaning T1 then T2 then T3.
6935
6936 Biopsy cores from different suspicious areas will be aliquoted separately. The vials
6937 will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there
6938 are) which should match the assignment of suspicious areas by the radiologist on the
6939 MRI report. The order of lettering a-d should match the order in which the biopsies
6940 were performed in each region. The first biopsy should be at the center of the target
6941 and the remaining fanning out from the center. Each core from the same suspicious
6942 area must be submitted separately. Alternative methods of storing cores that allow
6943 identification of the order of score samples from each target are acceptable.
6944

6945 **10.5 Systematic TRUS guided biopsy**

6946 **For all subjects in Arm B**

6947 Systematic TRUS guided biopsy is the current standard of care for the diagnosis of
6948 prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local
6949 site of recruitment.
6950

6951 A clinician competent in systematic TRUS guided biopsy will perform the procedure.
6952 The experience of the operator (number of systematic TRUS guided biopsies
6953 performed to date) will be recorded prior to each procedure. Software that guides
6954 clinicians in placing biopsy cores should not be used.
6955

6956 Coumarin anticoagulant, clopidogrel treatment and other relevant
6957 anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy

6958 and advice sought as to appropriate substitutes if indicated. Aspirin will be continued
6959 at the discretion of the physician doing the biopsy.

6960

6961 The subject will be positioned in left lateral position. 10-12 core biopsies will be
6962 taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed
6963 to the peripheral zone (See Appendix 3 for standardized method for conducting 12-
6964 core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be
6965 given as per local guidelines.

6966 **10.6 Pathology**

6967 The 2005 International Society of Urological Pathology guidelines for Gleason
6968 Grading of Prostatic Carcinoma will be followed [43].

6969

6970 For men undergoing MRI-targeted biopsy it is required that pathology reported per
6971 suspicious area targeted and per targeted core. For systematic TRUS guided biopsy,
6972 each core will be reported and graded.

6973 **10.7 Post-procedural care**

6974 **For all subjects in ARMS A and B receiving a biopsy**

6975 After a biopsy procedure the subject can be discharged within 2-3 weeks for results
6976 of the histopathology and treatment options to be discussed.

6977 **10.8 Immediate post-biopsy questionnaire**

6978 **For all subjects in ARMS A and B receiving a biopsy**

6979 A modified version of a self-reported questionnaire validated previously [39] in the
6980 assessment of post-biopsy complications will be completed immediately post-biopsy
6981 after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject
6982 should complete the immediate post-biopsy questionnaire before they leave the
6983 department. It aims to assess intensity of discomfort and pain associated with the
6984 procedure.

6985 **10.9 30-day post-biopsy questionnaire**

6986 **For all subjects in ARMS A and B receiving a biopsy**

6987 A modified version of a self-reported questionnaire validated previously [39] in the
6988 assessment of post-biopsy complications at 30 days post-biopsy should be given to
6989 all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home
6990 (Appendix 8). The subject should fill this out on day 30 following the procedure. It
6991 should take 5 minutes to fill out. The date that the participant should complete the
6992 questionnaire should be written on top of the questionnaire. Data on specific biopsy-
6993 related complications including pain, fever, hematuria, hematochezia,
6994 hematospermia, urinary retention and urinary incontinence will be recorded. Any
6995 other adverse events will not be recorded. Contact with healthcare and resource
6996 used data following the biopsy will also be ascertained. The completed questionnaire
6997 can be returned to the investigator in a pre-addressed envelope.

6998

6999 Subjects should be reminded at 30 days to complete this questionnaire.

7000 **10.10 Results and treatment decision (Visit 4)**

7001 The results of the biopsies and/or MRI will be explained to the subject by the clinical
7002 care team during this visit, which is approximately 2-3 weeks after the biopsy.

7003 The research team should record the treatment decision in the subject file.

7004 Possibilities for treatment decision include but are not limited to:

- 7005 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 7006 • Active Surveillance
- 7007 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 7008 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 7009 • Hormone therapy

7010 **10.11 Follow up period**

7011 All study participants will be followed up for up to two years or until they have
7012 radical treatment. Each year, subjects will be surveyed to obtain the following
7013 information:

- 7014 • time to cancer diagnosis
- 7015 • Gleason score progression
- 7016 • time to intervention on active surveillance
- 7017 • time on active surveillance
- 7018 • PSA

7019

7020 **10.11.1 Indications for biopsies off protocol**

7021 For subjects who are not biopsied due to a negative MRI, have negative or non-
7022 significant systematic biopsies, or who have a positive MRI but no or non-significant
7023 cancer on targeted biopsy, the following are guidelines for subjects management
7024 during the 2 year follow up period.

7025 It is an accepted standard of care in Ontario for subjects on active surveillance or
7026 with a prior negative biopsy who have a worsening risk profile to undergo mpMRI
7027 followed by targeted biopsy. We propose the following guidelines for risk profile
7028 assessment and consideration of repeat biopsy

7029 Subjects should continue to be followed with semi-annual PSA and DRE. A biopsy
7030 should be considered under one or more of the following circumstances:

- 7031 1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.
- 7032 2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase
7033 in PSA in 1 year.
- 7034 3. Biopsy if a doubling of the risk of high grade cancer according to the NCI
7035 nomogram.
- 7036 4. Biopsy if development of a suspicious nodule on DRE.
- 7037

7038 5. For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy
7039 which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or
7040 more increase in PSA over 1 year or a PSA density > 0.15.

7041

7042 18. For men on the systematic biopsy arm which was negative or showed only
7043 Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or
7044 a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these
7045 subjects.

7046

7047

7048 These are guidelines and should be interpreted with clinical judgment.

7049

7050 Follow-up will cease once treatment beyond active surveillance is undertaken
7051 (prostatectomy, radiation therapy, focal therapy, etc.)

7052 PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI
7053 identifies a target.

7054 **10.12 Additional tests for biomarker discovery - Optional**

7055 Though not related to the primary outcome of this study, this cohort represents a
7056 unique opportunity to obtain human samples for future biomarker discovery studies.
7057 Participants will be consented to provide a blood, urine, semen, and tissue sample
7058 after the consent and screen visit, and subsequent visits for storage and use in future
7059 biomarker studies. In addition, men will be consented for use of the prostate biopsy
7060 tissue in the biomarker discovery studies.

7061

7062 We propose two initial biomarker analyses for men recruited to the PRECISE study.
7063 First we propose testing the utility of existing validated tests, these potentially
7064 include the Genomic Prostate Score (OncotypeDx) [44] and a recently developed
7065 multiple Kallikrein biomarker test[45]. We will test the hypothesis that alongside
7066 conventional PSA measurements, the multiple Kallikrein test or other serum
7067 biomarker test, may identify subjects whose MRI was initially negative for prostate
7068 cancer, but who are at high risk of harboring clinically significant disease as detected
7069 by the secondary MRI at 2 years. We will also test the association between serum
7070 biomarkers and clinically significant or clinically insignificant prostate cancer
7071 detected during the PRECISE study. We will also explore the potential for the
7072 Genomic Prostate Score to provide additional information over and above Gleason
7073 grade. These studies will be separately funded from PRECISE.

7074

7075 Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will
7076 be planned to assess markers which might identify men at higher risk of developing
7077 prostate cancer.

7078 **10.12.1 Samples to be collected for future biomarker discovery work** 7079 **(Optional)**

7080 Participants will be asked to consent to provide a blood, urine, semen, and tissue
7081 sample after the consent and screen visit and subsequent visits for storage and use
7082 in future biomarker studies. This will involve a separate consent form.

-
- 7083 Samples include:
- 7084 • Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
 - 7085 • Urine – 75 mls urine
 - 7086 • Semen-1-5 cc (single ejaculate)
 - 7087 • Tissue-unstained biopsy sections -15 unstained slides from cancer, and
 - 7088 -15 unstained slide from non-cancer cores
 - 7089 (if possible)

7090 **10.13 Long-term data linkage – Permission to Contact**

7091 The cohort of men who consent to participate in this study represent a uniquely
7092 characterized group. Their long-term outcomes will contribute to our understanding
7093 of the epidemiology of prostate cancer beyond the questions being addressed in this
7094 study.

7095
7096 Permission to Contact (PTC) is a feasible mechanism to engage subjects in research
7097 programs. This will allow researchers to contact study participants in the future to
7098 assess their willingness to respond to questionnaires. This potentially enables
7099 research that would complement the planned long-term follow up in terms of health
7100 status, for obtaining information about future biopsies not included in the study, and
7101 allow assessment of quality of life.

7102 **10.14 End of Study**

7103 The end of study assessment comprises an essential safety evaluation that should be
7104 completed prior to discharging any subject from the study.

- 7105 • Adverse events;
- 7106 • PSA measurement;
- 7107 • EQ-5D-5L questionnaire;
- 7108 • An MRI in those who did NOT have a biopsy;
- 7109 • Complete CRF.

7110 **10.15 Risks and Benefits to Participants**

7111 An important consideration of this study is that men are being randomized to one of
7112 two biopsy techniques when it is not known which will be more effective. Both
7113 diagnostic tests are currently used in clinical practice at the institutions involved in
7114 the trial. Though systematic TRUS guided biopsy could be considered standard of
7115 care, there is enough evidence to support the concept that MRI-targeted biopsy may
7116 be at least as effective as systematic TRUS guided biopsy[27].

7117 **10.15.1 Risks to subjects**

7118 The intervention proposed in this trial (MRI-biopsy) do not offer participants any
7119 more risk than if they underwent standard of care (systematic TRUS guided biopsy)
7120 for the diagnosis of prostate cancer.

7121 **10.15.1.1 Risk of Systematic TRUS guided biopsy**

7122 Systematic TRUS guided biopsy can be associated with discomfort, haematuria,
7123 haematospermia and dysuria in a large proportion of subjects, which is self-resolving
7124 (See Table 4). There is a 4% risk of systemic urosepsis[46].

7125 **10.15.1.2 Risks of MPMRI**

7126 MRI is associated with few risks. It is a safe procedure used in everyday clinical
 7127 practice (See Table 4). Small risks of allergic reactions are associated with the
 7128 intravenous administration of gadolinium, the contrast agent used in MRI scans. The
 7129 study uses a low molecular weight Gd chelate as a contrast agent (Gadovist, Bayer,
 7130 gadobutrol – generic). This contrast agent is used routinely for contrast enhanced
 7131 MRI and is approved by Health Canada. Subjects will be screened for any
 7132 contraindications to Gd injection or to MRI as per current clinical Dept of Medical
 7133 Imaging protocols at each institution. The commonest reported sides effects are of
 7134 limited duration and mild to moderate in intensity and include headache,
 7135 vasodilation, injection site pain, nausea, dizziness, rash, and dyspnea. The incidence
 7136 of these are <1%. Severe life threatening reactions such as severe anaphylaxis occur
 7137 very rarely, about 1:10,000-1: 100,000. These are treatable with epinephrine and
 7138 steroids. The risk of death is <1:100,000. There is a known risk of nephrogenic
 7139 systemic fibrosis, a potentially fatal condition in subjects with impaired renal
 7140 function, with an eGFR <30ml/min/1.73m². These subjects are ineligible for this
 7141 study.

7142 **10.15.1.3 Risks of MRI-targeted biopsy**

7143 MRI-targeted biopsy is associated with similar risks to the standard of care
 7144 systematic TRUS guided biopsy. As fewer biopsy cores are being taken with MRI-
 7145 targeted biopsy, the theoretical risk of adverse events associated may be less than
 7146 that of systematic TRUS guided biopsy. In addition, as a proportion of men may not
 7147 require a biopsy (approximately 30%) on a group level there will be reduced number
 7148 of men experiencing these complications, which is one of the major advantages of an
 7149 MRI-based approach.

7150

7151 **Table 4: Adverse events associated with procedures**

7152

Side Effect \ Procedure	Systematic TRUS guided biopsy (Standard of care)	MRI	MRI-targeted biopsy
Pain / discomfort	Some have discomfort Some have pain	Intravenous cannulation (to allow contrast administration) can cause minimal discomfort	Similar / reduced compared to systematic TRUS guided biopsy
Dysuria	Majority have dysuria (self-resolving in 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematuria	Majority (self-resolving, 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haemospermia	Majority (self-resolving, 1-2 weeks)	No	Similar / reduced compared to systematic TRUS guided biopsy
Erectile dysfunction	30% (self resolving after 1-2 months)	No	Similar / reduced compared to systematic TRUS guided biopsy

Urinary Tract infection	1-8 %	No	Similar / reduced compared to systematic TRUS guided biopsy
Systemic urosepsis	2-4%	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary retention	1%	No	Similar / reduced compared to systematic TRUS guided biopsy
Contrast allergy	N/A	Rare < 1 in 10000 – severe allergic reaction (breathing problems) < 1 in 2000 – moderate allergic reaction (nausea and vomiting) < 1 in 250 – mild allergic reaction (rash, itching)	N/A
Adverse effects of antibiotics	Rare <1%	N/A	Rare <1%

7153
7154
7155

7156 **10.15.2 Benefits to subjects**

7157 Subjects enrolled in this trial will benefit from the following:

- 7158 • Subjects in both arms may benefit from receiving a diagnostic test for suspected
7159 prostate cancer and will receive further treatment if required. The research team
7160 will also ensure streamlined diagnostic investigations to promptly conduct the
7161 diagnostic test and communicate the test outcome for the subject.
- 7162 • Subjects enrolled in the trial will benefit from the dedicated research team
7163 involved in their care in addition to the clinical team normally involved in their
7164 care.
- 7165 • Subjects will benefit from additional discussions regarding the trial, which could
7166 increase their understanding of prostate cancer and help them to make a more
7167 informed decision about their health.
- 7168 • Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will
7169 remove any risk of post-biopsy infection. MRI-randomized subjects may also
7170 benefit from a reduced probability of having a clinically insignificant prostate
7171 cancer diagnosed. Clinically insignificant prostate cancer is often treated
7172 definitively per subject preference despite the lack of evidence supporting the
7173 need. All definitive local therapies for prostate cancer carry the risk of peri-
7174 operative complications as well as long-term risk of incontinence and erectile
7175 dysfunction.

7176

7177 **10.16 Concomitant medications**

7178 **10.16.1 Permitted Medications**

7179 All concomitant medications taken during the study will be recorded in the CRF with
7180 indication, dose information and dates of administration. The definition of which
7181 medication would be considered outside the routine medical practice is up to the
7182 discretion of the investigator. All dietary and herbal supplement usage will be
7183 recorded in the CRF.

7184 **10.16.2 Non-Drug Therapies**

7185 Any occurrence of prostate-related surgical and/or non-surgical (or minimally
7186 invasive) intervention during the conduct of the study will be recorded in the CRF.
7187

7188 **11. Schedule of Study Visits**

7189 **11.1 Visit 1 (Screening/Randomization): Screening, Consent,**
7190 **Randomization**

7191 **For all subjects enrolled in trial**

7192 Screening will occur any time following the referral of the subject. Ideally, this will be
7193 performed as soon as possible following receipt of referral.

7194 Subjects will be consented only after they have had time to consider the study. This
7195 may happen on the same visit as the screening visit.

7196 Randomization can happen immediately after the consent form is signed and
7197 eligibility is confirmed.

7198

7199 Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L
7200 questionnaire (Appendix 4), which is a validated 2-page questionnaire representing
7201 health related quality of life. It takes approximately 2 minutes to complete. This
7202 questionnaires should be completed at the screening visit before the subject leaves
7203 the clinic.

7204

7205 If a subject agrees to the optional informed consent, from randomization until any
7206 point prior to a biopsy, optional blood, urine, semen and tissue samples will be
7207 collected for correlative studies.

7208

7209 Even if PSA testing was done prior to Visit 1, PSA should be obtained at Visit 1.

7210

7211 **11.2 Visit 2 (MRI): ARM A, for men randomized to MRI**

7212 This will occur approximately within one week of randomization. Men will receive an
7213 MRI (see Section 10.2.)

7214 **11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate**

7215 **For men randomized to ARM A, who have a lesion identified by MRI.** This
7216 appointment will follow approximately one-two weeks of MRI.

7217

7218 Depending on local Urology service structure, an appointment for a biopsy may need
7219 to be booked at the same time as the MRI is booked (i.e. immediately after
7220 randomization) in order for a biopsy to occur in timely fashion. If the results of the
7221 MRI show that a biopsy is not required, then the biopsy appointment can be used
7222 instead of Visit 4 for follow up of results and treatment decision.

7223

7224 Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy
7225 of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy
7226 Questionnaire (Appendix 7) ideally completed and returned immediately after a
7227 biopsy, before the subject leaves the department.

7228

7229 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
7230 and complete as instructed on day 30 post-biopsy. This is to be returned by post or
7231 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
7232 biopsy then this questionnaire can be given to the research team when 30 days is
7233 finally complete. If Visit 4 is on or later than 30 days then this can be returned at the
7234 Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-
7235 biopsy, it will be acceptable, however, the questionnaire should be completed as
7236 close as possible to 30 days post-biopsy.

7237

7238 At 30-days post biopsy interval, a member of the research team will call the subject
7239 to remind them to complete and return the 30-day questionnaires.

7240 **11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic** 7241 **TRUS-biopsy**

7242 **For men randomized to ARM B only.**

7243

7244 Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will
7245 complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed
7246 and returned immediately after the biopsy.

7247 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
7248 and completed as instructed on day 30 post-biopsy. This is to be returned by post or
7249 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
7250 biopsy then this questionnaire can be given to the research team when 30 days is
7251 reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
7252 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it
7253 will be acceptable, however the questionnaire should be completed as close as
7254 possible to 30 days post-biopsy.

7255

7256 At 30-days post biopsy a member of the research team will call the subject to remind
7257 them to complete and return the 30-day questionnaires.

7258 **11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a** 7259 **biopsy**

7260 This appointment will include a follow up meeting with the investigator to discuss
7261 the results of the MRI as well as treatment decisions. This follow up should occur

7262 after the availability of the MRI report. At this visit the subject will also complete a
7263 30-day post intervention EQ-5D-5L Questionnaire.

7264

7265 Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8), which has been
7266 posted to them by the research team. If Visit 4 is earlier than 30 days post MRI then
7267 this questionnaire can be given to the research team when 30-days is finally
7268 complete. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
7269 appointment. As long as questionnaire is completed at 30-60 days post-MRI, it will
7270 be acceptable, however the questionnaire should be completed as close as possible
7271 to 30 days post-MRI.

7272

7273 At 30-days post MRI, a member of the research team will call the subject to remind
7274 them to complete the 30-day questionnaires.

7275 **11.6 Visit 4 (Post-test follow up): For all men who received a biopsy**

7276 This appointment will include a follow up meeting with the investigator to discuss
7277 the results of the biopsy as well as treatment decisions. This should be completed as
7278 soon as possible following the availability of any pathology results. The follow up
7279 appointment should be within 1 month of the biopsy. Depending on local Urology
7280 service structure, these results may need to be discussed at an MDT meeting to
7281 inform treatment decision.

7282

7283 The research team should record the treatment decision in the subject file.

7284

7285 Possibilities for treatment decision include but are not limited to:

- 7286 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 7287 • Active Surveillance
- 7288 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 7289 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 7290 • Hormone therapy

7291

7292 At this visit the subject will also receive a 30-day post intervention EQ-5D-5L
7293 Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy
7294 questionnaire (Appendix 8), which has been posted to them by the research team.
7295 The questionnaire needs to be completed on the 30th day post-intervention (i.e. post
7296 biopsy). However it will be accepted if completed up to 72 hours prior to or after the
7297 30th day. A telephone reminder from the research team to the subject can take
7298 place.

7299

7300 **11.7 Visit 5 (6 month follow up):26 week follow up**

7301 All subjects will have a 26 week visit

7302 Subjects will have the following:

- 7303 • Vitals, DRE
- 7304 • PSA
- 7305 • Optional sample collection (blood, urine)

7306 **11.8 Visit 6(1 year follow up): 52 week follow up**

7307 All subjects are planned to have a 52 week follow up visit.

7308 Subjects will be followed to obtain the following information on an annual basis:

- 7309 • Vitals, DRE
- 7310 • time to cancer diagnosis;
- 7311 • Gleason score progression;
- 7312 • time to intervention on active surveillance;
- 7313 • time on active surveillance;
- 7314 • results of PSA tests.
- 7315 • Time to follow up biopsy and/or mpMRI if performed (see follow up
- 7316 guidelines)
- 7317 • Indication for follow up biopsy
- 7318 • Was MRI performed prior to follow up biopsy
- 7319 • Was the biopsy systematic, targeted only or both systematic + targets, not
- 7320 done because of negative MRI
- 7321 • Optional sample collection (blood, urine)
- 7322

7323 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
7324 will have an additional MRI at Visit 6 (year 2).

7325 **11.9 Visit 7 (18 month follow up): 78 week follow up**

7326 All subjects will have a 78 week visit

7327 Subjects will have the following:

- 7328 • Vitals, DRE
- 7329 • PSA
- 7330 • Optional sample collection (blood, urine)

7331

7332 **11.10 Visit 8 (2 year follow up): End of study**

7333 All study participants will be followed for up to two years or until they undergo
7334 radical treatment

7335 Subjects will be followed to obtain the following information on an annual basis:

- 7336 • Vitals, DRE
- 7337 • time to cancer diagnosis;
- 7338 • Gleason score progression;
- 7339 • time to intervention on active surveillance;
- 7340 • time on active surveillance;
- 7341 • results of PSA tests.
- 7342 • Optional sample collection (blood, urine)
- 7343
- 7344 • Time to follow up biopsy and/or mpMRI if performed (see follow up
- 7345 guidelines)
- 7346 ○ Indication for follow up biopsy
- 7347 ○ Was MRI performed prior to follow up biopsy

7348 ○ Was the biopsy systematic, targets only or both systematic + targets,
7349 not done because of negative mpMRI

7350

7351

7352 Follow-up will cease once treatment beyond active surveillance is undertaken
7353 (prostatectomy, radiation therapy, focal therapy, etc.).

7354

7355 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
7356 will have an additional MRI at Visit 8.

7357

7358 **12. Randomization**

7359 **12.1 Randomization Procedure**

7360 Written informed consent will be obtained from all eligible subjects prior to
7361 commencing any study related procedures. The Ontario Clinical Oncology Group
7362 (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre,
7363 Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate
7364 subject randomization. Subjects will be allocated to the two treatment arms in an
7365 approximate 1:1 ratio by use of a dynamic allocation scheme[47].

7366

7367 After documentation of written informed consent and confirmation of subject
7368 eligibility, clinical centres will randomize the subject by accessing the CMC's web-
7369 based Interactive Registration/Randomization System (IRIS). Prior to randomization
7370 and treatment allocation, the subjects' individualized risk of high-grade prostate
7371 cancer, obtained using the PCPTRC 2.0 calculator found at
7372 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> must be determined.

7373 **12.2 Stratification**

7374 Eligible, consenting subjects will be stratified by: (1) individualized risk of high-grade
7375 prostate cancer (5% to 25%, >25%); and (2) clinical centre

7376 **12.3 Blinding and measures taken to avoid bias**

7377 This study is unblinded, and all subjects will be aware of the treatment that they are
7378 receiving. As the MRI scan is unique to one of the arms it will not be possible to blind
7379 the participants or investigators as to what intervention is being received. Therefore,
7380 participants will be informed which arm they have been allocated to. Where
7381 possible, the data will be coded so as to blind individuals analyzing the data from
7382 which of the groups the data was from. Summary details of randomized allocation
7383 and outcomes will not be made available (unless specifically authorized by the Trial
7384 Steering Committee and/or Data Monitoring Committee) in order to maintain the
7385 overall blind of the trial.

7386

7387 Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be
7388 aware that the subject is part of the trial.

7389 Pathologists will be blinded to the cohort allocation. Concealment may be
7390 challenging due to the different number of cores in the two groups, but this is
7391 unavoidable. This is unlikely to represent a significant source of bias.

7392

7393

7394 **13. Data**

7395

7396 Type of data to be collected:

- 7397 • EQ-5D–5L questionnaires. These will measure quality of life and will be measured
7398 at specific times throughout the trial.
- 7399 • Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and
7400 continuous data
- 7401 • MRI – diagram representing MRI; categorical data for areas and scores of
7402 suspicion (e.g. Sector 1p, score of suspicion 4/5)
- 7403 • MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and
7404 continuous data
- 7405 • Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers
7406 yes/no)
- 7407 • Treatment decisions – categorical data (e.g. radical treatment)
- 7408 • PSA – continuous data (e.g. value of PSA in ng/ml)

7409

7410 Please see **Appendix1** for the time window for data collection.

7411

7412 **14. Statistical Considerations**

7413 **14.1 Sample Size Calculation**

7414 **STATISTICAL methods**

7415 **Primary Analysis**

7416 Absolute differences in the proportion of clinically significant cancer detected
7417 between arms will be calculated and compared using the Clopper-Pearson method.
7418 If the lower boundary of an one-sided, 97.5% confidence interval for the difference
7419 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less
7420 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower
7421 bound is greater than zero, superiority can be claimed.

7422

7423 A supportive analysis will be performed by using a logistic regression model,
7424 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification
7425 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of
7426 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower
7427 bound was calculated to approximate an absolute 5% difference of interest (NOTE:
7428 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

7429

7430 **Secondary Analyses**

7431 For each secondary outcome, where appropriate, a difference in proportions with
7432 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.
7433 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for
7434 time-to-event outcomes.

7435

7436 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
7437 differences between allocation arms in secondary outcomes. Logistic regression and
7438 Cox proportional hazards regression will be used to examine the effect of allocation
7439 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
7440 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
7441 adjustments will be made due to multiple testing, however, results for secondary
7442 outcomes will be interpreted cautiously, acknowledging that tests were performed
7443 on secondary outcomes and numerous secondary tests were performed. Figures and
7444 tables will be used to illustrate results of interest.

7445

7446 **Treatment Allocation and Stratification**

7447 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
7448 use of a dynamic allocation scheme. Specifically, the first 20 subjects will be
7449 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a
7450 biased coin method will be used, whereby the number of subjects within each
7451 stratum will be calculated, and the next eligible subject will be allocated (with
7452 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
7453 allocation to each arm will occur with probability $p=0.5$.

7454

7455 Stratification

7456 For treatment allocation, the subjects' individualized risk of high-grade prostate
7457 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
7458 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
7459 subjects will be stratified by:

7460 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);

7461 (2) clinical centre.

7462

7463 **Sample Size**

7464 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
7465 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
7466 50% from another study [36].

7467

7468 Rates of clinically significant cancer detection from one the largest studies of
7469 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
7470 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will
7471 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
7472 systematic TRUS guided biopsy.

7473

7474 For this study, it will be conservatively hypothesized that systematic TRUS guided
7475 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
7476 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
7477 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
7478 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
7479 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
7480 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
7481 choice of 5% as the margin of non-inferiority represents a difference that would be
7482 considered clinically important.

7483

7484 Thus total men required in study = **422**.

7485

7486 To account potential withdrawal / loss to follow up and the effect of stratification,
7487 the sample size will be inflated by 5%, and a target of **450 men** will be recruited.

7488

7489 Note that the rate of clinically significant cancers is very dependent on the
7490 population registered for this study. It is possible that fewer (or more) subjects will
7491 have clinically significant cancers than what is initially hypothesized. However, if the
7492 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
7493 biopsy detection rate is <30%) and other statistical assumptions remain as stated
7494 previously, the statistical power will increase. The minimum statistical power would
7495 be obtained if the clinically significant cancer detection rate was 45% for systematic
7496 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
7497 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
7498 rate of clinically significant cancer in the population is miss-specified, assuming an
7499 absolute difference of 10% between targeted and systematic TRUS guided
7500 biopsydetection rates, and a 5% margin of non-inferiority.

7501

7502 **Statistical Conventions**

7503 For categorical data, tables will be presented showing the n and percentage
7504 (n/N*100%) of subjects. Analyses will be presented by study allocation arm
7505 separately.

7506

7507 Duration of time will be described in either years, months or weeks, and calculated
7508 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or
7509 X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date –
7510 date of birth + 1)/365.25.

7511

7512 Transformations of the data in order to meet statistical assumptions may be
7513 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
7514 assess any of the model fittings. All the statistical analysis will be carried out using
7515 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-
7516 project.org) or higher.

7517

7518 **Missing Data**

7519 Missing values for the primary endpoint will be examined closely. Sources and
7520 reasons for the absence of data incurred as a result of subjects lost-to-follow up,
7521 dropouts, and intermittent missing values will be described and explored by various
7522 summary statistics as well as graphical displays between the two allocation arms.
7523 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
7524 those subjects will be described by allocation arm and tested using Fisher's exact
7525 tests or Wilcoxon rank sum tests.

7526

7527 Missing data for secondary endpoints will be described. The methods for evaluating
7528 missing data of the primary endpoint may be employed for endpoints of interest. For
7529 summarization of baseline data, the following conventions will be used for partial
7530 missing date information occurring prior to randomization (e.g. for medical history
7531 or prior treatment). If year is missing, the date will be set at missing. If year is

7532 available, but month and date is missing, the month and date will be set to July 1st of
7533 the respective year. If date is missing, but year and month available, the day will be
7534 set to the 15th of the respective month.

7535 **14.2 Interim Analyses**

7536
7537 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
7538 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
7539 conduct if there are concerns about subject safety or futility. Unless otherwise
7540 specified by one of these bodies, a futility analysis will be performed after
7541 approximately 200 subjects are enrolled and have their primary outcome
7542 ascertained. Simulation will be used to estimate the conditional probability of futility
7543 assuming the study was to continue to completion, and assuming the clinically
7544 significant cancer detection rate is 30% in both arms. If the conditional probability is
7545 0.95 or higher that continuation of the study will result in a negative result, the
7546 DSMC will recommend a suspension of recruitment to the trial, and initiation of a
7547 quality assurance review. A decision to permanently close the study or continue with
7548 accrual will be determined by the Steering Committee, based on the results of the
7549 quality assurance review, and the recommendation of the DSMC.

7550

7551 **Timing of Final Analysis**

7552 A single, final, analysis will occur after all subjects have undergone their initial biopsy
7553 and all data related to the initial biopsy is documented and validated. Follow-up
7554 analyses will be conducted after all subjects have completed two years of follow-up.

7555 **14.3 Populations:**

7556 The per protocol, study population will consist of all subjects who satisfy all eligibility
7557 criteria and are randomized to the study, who undergo MPMRI-TB or systematic
7558 TRUS guided biopsy and have their primary outcome measured. This population will
7559 be used for the primary analysis of non-inferiority.

7560 The intent-to-treat (ITT) population will consist of all subjects randomized to the
7561 study, regardless of any protocol violations or if they do not complete the study as
7562 defined in the protocol. The ITT population will be used as a supportive analysis of
7563 the primary analysis, for all safety analyses, and for any analysis investigating
7564 superiority.

7565 **14.4 Primary Outcome**

7566 **14.4.1 Detection rate of clinically significant cancer**

7567 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will
7568 be calculated based on histology results from biopsy procedures. Analysis will be on
7569 the intention to treat population.

7570

7571 Absolute differences in proportion of clinically significant cancer detected between
7572 arms will be calculated and compared. If the lower boundary of the 97.5%
7573 confidence interval for the difference in detection rates of MPMRI-TB compared to
7574 systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-

7575 inferior. In the event that the lower bound is greater than zero, superiority can be
7576 claimed.

7577

7578 The primary analysis will be conducted once all subjects have completed visit 4,
7579 when the results of the biopsy or MRI are given to the subject.

7580

7581 **14.5 Secondary Outcomes**

7582 For each secondary outcome, where appropriate, a difference in proportions with
7583 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

7584

7585 **14.5.1 Proportion of men in each arm with clinically insignificant 7586 cancer detected**

7587 The proportion of men in each arm with clinically insignificant cancer (Gleason <7)
7588 will be calculated based on histology results from biopsy procedures. In addition, the
7589 numbers with clinically insignificant cancer identified by MRI alone will also be
7590 included.

7591

7592 **14.5.2 Proportion of men in each arm with Gleason $\geq 4+3$ detected**

7593 The proportion of men in each arm with Gleason $\geq 4+3$ will be calculated based on
7594 histology results from biopsy procedures. In addition, the numbers with clinically
7595 insignificant cancer identified by MRI alone will also be included.

7596

7597 **14.5.3 Proportion of men in MPMRI arm who avoid biopsy.**

7598

7599 **14.5.4 Proportion of men in the MRI arm whom the PI-RADS score for 7600 suspicion of clinically significant cancer was 3, 4 or 5 but no clinically 7601 significant cancer was detected.**

7602 The proportion of men in each arm whom the PI-RADS score for suspicion of
7603 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
7604 detected, will be calculated based on histology results from biopsy procedures.

7605

7606 **14.5.5 Proportion of men in each arm who go on to definitive local 7607 treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or 7608 systemic treatment (e.g. hormone therapy, chemotherapy)**

7609

7610

7611

7612 **14.5.8 Proportion of men with a negative MRI who progress within 24 7613 months after their study MRI, or who are upgraded within 24 months**

7614 Men with a negative MRI who do not undergo a biopsy will have a follow-up MRI 2
7615 years after their study MRI. We will determine the proportion of men whose
7616 subsequent MRI shows a PI-RADS 3 or greater lesion. The results of targeted biopsy
7617 of those lesions will be recorded and analyzed. The number of men who are
7618 upgraded to Gleason ≥ 7 due to an off-protocol biopsy will also be recorded.

7619

7620 **14.5.9 Proportion of men with post-biopsy adverse events**

7621 Immediate post-biopsy discomfort and pain will be characterized by intensity using
7622 the numerical analogue score. Scores for each arm will be compared. 30-day biopsy
7623 specific complications and adverse events will be characterized according to their
7624 presence, absence, duration and how much of a problem the symptoms caused the
7625 subject. Whether the subject had contact with health care providers/system will also
7626 be recorded. The proportion of individuals experiencing each symptom, proportion
7627 in whom that symptom caused a problem and proportion who had contact with
7628 healthcare providers/system will be calculated and compared qualitatively between
7629 arms utilizing classification systems validated in previous studies [39]. The biopsy
7630 specific complications that will be compared include pain, urinary retention, fever,
7631 pain, erectile dysfunction, urinary incontinence, haematuria, haematochezia and
7632 haemotospermia.

7633

7634 Any post-biopsy complications up to 30-days post biopsy procedure will be tabulated
7635 and listed by duration and management.

7636

7637 **14.5.10 Health related quality of life**

7638 EQ-5D-5L descriptive domain summary indices and visual analogue scores will be
7639 assessed at baseline, at 2 years and changes will be compared between arms.

7640

7641 EQ-5D was selected as a simple, low burden quality of life instrument that will
7642 provide validated information on symptoms, particularly anxiety, that could be
7643 compared across disease states and studies. Other subject-reported outcomes
7644 directly linked to the interventions will be captured in the post-biopsy surveys. Since
7645 it provides utilities, these will be incorporated into a secondary economic analysis if
7646 the results permit.

7647

7648 **14.5.11 Proportion Gleason score upgrading in men undergoing radical 7649 prostatectomy**

7650 Of the men who undergo radical prostatectomy, the proportion who have cancer
7651 upgraded from the biopsy histopathology to the radical prostatectomy
7652 histopathology in each arm will be calculated and compared.

7653

7654 **14.5.12 Cost Outcomes**

7655 As the study design for clinical outcomes is one of non-inferiority, the primary
7656 economic analysis will be **cost minimization analysis**. The perspective of the
7657 economic analysis will be that of the public payer. The primary goal of the analysis
7658 will be to support arguments for public funding. Thus the costs of participant
7659 burden, logistical challenges, and expense of obtaining societal costs, will not be
7660 evaluated.

7661

7662 **14.5.12.1 Data collection:**

7663 As part of the informed consent process, participants in Ontario will also
7664 consent to having their Ontario Health Insurance Number recorded, to be
7665 later transferred to the Institute for Clinical Evaluative Sciences (ICES) where

7666 it will be linked to a number of administrative claims databases recording
7667 health system resource utilization such as physician billing [Ontario Health
7668 Insurance Plan (OHIP)]; laboratory and diagnostic tests (OHIP); hospitalization
7669 and surgery [Discharge Abstract Database (DAD)]; medications [Ontario Drug
7670 Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity
7671 Level Reporting (ALR)]; clinic and emergency department visits [National
7672 Ambulatory Care Reporting System (NACRS), Emergency Department visits];
7673 radiation (ALR); homecare (Home Care databases) and a few additional ones
7674 as determined necessary (e.g., Long-term care, Mental Health, Diabetes. The
7675 overall, number and proportion of health system resources will be
7676 determined. In this way we can capture comprehensive resource utilization
7677 related to on-trial management including any adverse events.

7678 **14.5.12.2 Health Insurance number handling and security**

7679 As the economic implications of this study are of prime importance to some
7680 of the funders, the request for data linkage will be part of the main consent
7681 form. If a participant indicates to the study team that they decline or
7682 withdraw consent, the OHIP number will be recorded as 9999-999-999-XX.
7683 The OHIP numbers will stay with the participating institution until after
7684 accrual is complete, and then they will all be transferred at one time under
7685 data sharing agreements between ICES and each institution. Data will be
7686 transferred using a secure electronic file transfer system established by ICES
7687 and managed by authorized ICES personnel responsible for receiving
7688 data. The file transfer system uses security safeguards including encryption
7689 and authentication.

7690
7691 ICES is a Prescribed Entity under the Personal Health Information Protection
7692 Act (PHIPA), and can receive and use personal health information for
7693 purposes of analysis and compiling statistical information and other research.
7694 Its policies and procedures for privacy protection and data security have been
7695 approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-
7696 monitored and requiring passkeys to access private offices and
7697 computers. ICES has extensive experience in the protection of confidentiality
7698 when using such data. It has a UNIX-based network that cannot be accessed
7699 externally. ICES data facilities are fully 'moated' (no connections to other
7700 computers). At ICES, routine procedures for data backup are instituted by a
7701 data management team. The data is burned onto a CD or placed on an
7702 external hard drive and placed in a locked vault. All ICES staff and scientific
7703 affiliates are required to sign agreements of confidentiality annually. Internal
7704 audits are conducted to monitor compliance with ICES policies, standards and
7705 procedures.

7706
7707 Study data with direct personal identifiers such as OHIP numbers will
7708 reside on a dedicated and secure server at ICES and will only be
7709 accessible by a named Data Covenantor. The Covenantor will encode
7710 the OHIP number, replacing it with an ICES key number (IKN) (a code)
7711 and transferring it to a "moated" server for the study project. (The
7712 Data Covenantor is an ICES person named in our data sharing

7713 agreements and identified to the Office of the Information and
7714 Privacy Commissioner, who can access personal health information at
7715 ICES for the purposes of receiving, coding, transferring or destroying
7716 personal health information.) The coded study data will only be made
7717 available to the Principal Investigator and project staff directly
7718 responsible for data analysis (under the supervision of the
7719 investigator). No subject, physician or institution will be identified in
7720 the reporting of results
7721

7722 **14.5.12.3 Cost calculation**

7723 Once the utilization of health services is determined from those cases linked
7724 to administrative databases, publicly available costs (2016\$CAN) will be
7725 applied to health services. Costs for physician and laboratory services will be
7726 determined by applying that year's fee code. Costs for hospital care will be
7727 estimated using the Canadian Institute for Health Information (CIHI) Resource
7728 Intensity Weight method for the most recently available year. Outpatient
7729 prescription drug costs for participants not covered by ODB (those under age
7730 65 and not on social assistance) will be considered to be the same as the trial
7731 arm-specific average for those with coverage. Costs will then be inflated
7732 using the healthcare-specific Consumer Price Index reported by Statistics
7733 Canada into constant Canadian dollars for the year the study ends. Due to the
7734 short time horizon, discounting will not be applied.

7735 **14.5.12.4 Primary Analysis**

7736 A within-trial analysis will be conducted to calculate the total cost for each
7737 arm and mean cost per subject for each arm. Frequency distributions and
7738 measures of central tendency (e.g. means and medians) will be determined
7739 for each resource category (e.g. hospitalizations) for each arm of the study.
7740 Confidence intervals for the difference in costs and resource utilization
7741 between the strategies overall and for each resource category will also be
7742 calculated. Univariate comparisons between the groups will be made
7743 primarily using nonparametric tests, such as Wilcoxon rank-sum test. In the
7744 primary analysis, assuming equivalence in the primary outcome, an arm with
7745 significantly lower mean costs will be considered the economically most
7746 attractive approach.

7747
7748 Should the clinical trial find a difference between the two arms on the
7749 primary endpoint, an incremental cost-benefit analysis will be calculated by
7750 deriving the additional cost per case of clinically significant cancer diagnosed,
7751 according to the following equation:

7752

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\text{Diagnoses}_{(\text{Arm A})} - \text{Diagnoses}_{(\text{Arm B})}}$$

7753 The cost of avoiding each additional case of clinically insignificant cancer
7754 diagnosed may also be similarly calculated. Consideration will be given to

7755 extending this analysis using economic modeling with incorporation of utility
7756 values from the EQ-5D to allow a lifetime perspective to be taken and the
7757 estimation of quality adjusted life years (QALYs).

7758 **14.5.12.5 Secondary Cost Analyses**

7759 One and multi-way sensitivity analyses will be carried out around major cost
7760 drivers by varying the costs over their observed ranges and conducting
7761 threshold analyses where appropriate. Sensitivity analyses will also be
7762 performed to evaluate potential limitations in the data, such as ODB costs as
7763 described above (though the proportion without ODB coverage should be
7764 similar in the two arms, and it is not expected to be a major cost-driver).

7765

7766

7767

7768 **14.5.13 Missing Data**

7769 The impact of missing data will be explored in all analyses; sensitivity
7770 analyses/multiple imputation will be performed as appropriate.

7771

7772 **15. Participant compliance and withdrawal**

7773

7774 The study will be completed when at least 422 subjects have been randomized, have
7775 undergone a diagnostic test and completed follow up. Compliance to randomized
7776 treatment will be assessed by monitoring the completed forms, e.g. the systematic
7777 TRUS guided biopsy form or the MRI-targeted biopsy form.

7778

7779 In consenting to the study, subjects are consenting to study monitoring, imaging and
7780 biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to
7781 withdraw consent at any stage and their care will not be affected in any way. All
7782 communication surrounding the withdrawal and its reasons should be noted in the
7783 subject's record. Such cases should be reported to the PRECISE Study Operations
7784 Office. Data up to the time of withdrawal can be included in the study.

7785

7786 As the study diagnostic tests are for suspected cancer it is not anticipated that there
7787 will be significant loss to follow up.

7788

7789 **15.1 Subject Withdrawal from Study**

7790 A subject may discontinue participation in this study at any time at the investigator's
7791 discretion or at the request of the subject.

7792

7793 If a subject discontinues at or before Visit 1 (randomization), he is not required to
7794 complete end of study assessments.

7795

7796 If a subject discontinues after Visit 1 (randomization) for any reason, the investigator
7797 should make every effort to complete the activities bulleted below.

7798

- 7799
- End of study assessments as outlined in **Section 10.17.**

-
- 7800 • Any occurrence of death, prostatic surgical intervention, non-surgical treatment
7801 for prostate cancer after study withdrawal should be documented in the CRF and
7802 source documents.

7803

7804 Subjects who are discontinued from the study after randomization will not be
7805 replaced. Subjects withdrawn from the study retain their subject number if already
7806 given. New subjects will be allocated a new subject number.

7807

7808 In the event that a subject is prematurely discontinued from the study at any time
7809 due to an AE, the procedures describe in **Section 16.3** must be followed.

7810

7811 Subjects should be withdrawn from the study for any of the following criteria:

7812

- Non-compliance with the requirements of the study.

7813

- Request to discontinue treatment. This request can be made by either the
7814 subject or the investigator.

7815

- Develops progressive disease.

7816

7817 **15.2 Study completion**

7818 The primary end point will be reached when the last subject entered has their
7819 systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be
7820 followed for up to 2 years following study entry or until they have radical treatment.
7821 Subjects who are found to have significant prostate cancer and are treated will not
7822 be included in follow up for this period. This includes subjects diagnosed as part of
7823 study protocol, and subjects diagnosed during the follow up period by standard-of-
7824 care procedures. However, post MRI/biopsy questionnaires will not be required
7825 following non-protocol based procedures.

7826

7827 **16. Data Monitoring, Quality Control and Safety**

7828 **16.1 Stopping / discontinuation rules**

7829 The study will be completed when 450 participants have been randomized,
7830 undergone a diagnostic test and completed follow up.

7831

7832 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
7833 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
7834 conduct if there are concerns about subject safety or futility. See Section 14.2.1 for
7835 further details on the interim analysis. Appropriate documentation as per the PI's
7836 requirement will be completed if stopping the trial is necessary and the ethics
7837 committee will be informed.

7838

7839 As the study is unblinded there will be no need for randomization code breaks.

7840

7841 **16.2 Monitoring, quality control and assurance**

7842

7843 Members of the trial team will be Good Clinical Practice (or equivalent) trained.

7844

7845 An independent DSMC will be appointed to monitor subject safety and the rate of
7846 recruitment of subjects in the study. They will meet at least once a year whilst the
7847 trial is ongoing for routine review of safety data and trial progression. They have the
7848 power to call additional meetings and review data at any point in the trial should
7849 they wish to do so.

7850

7851 The PI may also arrange an independent trial monitor to review the study data.

7852 **16.3 Assessment of safety**

7853 The investigator is responsible for the detection and documentation of events
7854 meeting the criteria and definition of an AE or SAE as provided in this protocol.
7855 During this study, when there is a safety evaluation, the investigator or site staff will
7856 be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

7857 **16.3.1 Definition of an Adverse Event (AE)**

7858 Adverse events (AE) will be defined as “any untoward medical occurrence in a
7859 clinical trial subject undergoing any intervention in the trial, which does not
7860 necessarily have a causal relationship with this treatment”.

7861

7862 Only adverse events specific to biopsy-related complications including pain, fever,
7863 hematuria, hematochezia, hematospermia, urinary retention and urinary
7864 incontinence will be recorded. Any other adverse events will not be recorded. Please
7865 refer to section 16.3.6 of the protocol.

7866 **16.3.2 Definition of a Serious Adverse Event (SAE)**

7867 Serious adverse events (SAE) will be defined as “any untoward medical occurrence as
7868 a result of any intervention in the trial that:

7869 **(a) results in death**

7870 **(b) is life-threatening**

7871 The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which
7872 the subject was at risk of death at the time of the event. It does not refer to an
7873 event, which hypothetically might have caused death, if it were more severe.

7874 **(c) requires hospitalisation or prolongation of existing hospitalisation**

7875 In general, hospitalization signifies that the subject has been detained (usually
7876 involving at least an overnight stay) at a hospital or emergency ward for observation
7877 and/or treatment that would not have been appropriate in the physicians’ office or
7878 outpatient setting. Complications that occur during hospitalization are AEs. If a
7879 complication prolongs hospitalization or fulfils any other serious criteria, the event is
7880 serious. When in doubt as to whether ‘hospitalization’; occurred or was necessary,
7881 the AE should be considered serious. Hospitalization for elective treatment of a pre-
7882 existing condition that did not worsen from baseline is not considered an AE.

7883 **(d) results in disability / incapacity**

7884 The term disability means substantial disruption of a person’s ability to conduct
7885 normal life functions. This definition is not intended to include experiences of
7886 relatively minor medical significance such as uncomplicated headache, nausea,
7887 vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may

7888 interfere or prevent everyday life functions but do not constitute a substantial
7889 disruption.
7890 **(e) is a congenital abnormality/birth defect.**
7891 Medical or scientific judgement should be exercised in deciding whether reporting is
7892 appropriate in other situations, such as important medical events that may not be
7893 immediately life threatening or result in death or hospitalization but may jeopardise
7894 the subject or may require medical or surgical intervention to prevent one of the
7895 outcomes listed in the above definition. These should also be considered serious.
7896 Examples of such events are invasive or malignant cancers, intensive treatment in an
7897 emergency room or at home for allergic bronchospasm, blood dyscrasias or
7898 convulsions that do not result in hospitalization, or development of drug
7899 dependence or drug abuse.

7900 **16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs**

7901 An event which is part of the natural course of the disease under study (i.e., disease
7902 progression) does not need to be reported as a serious adverse event. Progression of
7903 the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death
7904 due to progressive disease is to be recorded on 'Record of Death' CRF page and not
7905 as an SAE. However, if the progression of the underlying disease is greater than that
7906 which would normally be expected for the subject, or if the investigator considers
7907 that there was a causal relationship between treatment with study medication or
7908 protocol design/procedures and the disease progression, then this must be reported
7909 as an SAE. Any new primary cancer must be reported as an SAE.

7910 **16.3.4 Lack of Efficacy**

7911 "Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical
7912 sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE
7913 definition (including clarifications).

7914 **16.3.5 Clinical Laboratory Abnormalities and Other Abnormal 7915 Assessments as AEs and SAEs**

7916 Abnormal laboratory findings or other abnormal assessments that are judged by the
7917 investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet
7918 the definition of an AE or SAE. Clinically significant abnormal laboratory findings or
7919 other abnormal assessments that are detected during the study or are present at
7920 baseline and significantly worsen following the start of the study will be reported as
7921 AEs or SAEs. However, clinically significant abnormal findings or other abnormal
7922 assessments that are associated with the disease being studied, unless judged by the
7923 investigator as more severe than expected for the subject's condition or that are
7924 present or detected at the start of the study and do not worsen, will not be reported
7925 as AEs or SAEs.

7926
7927 The trial interventions are routinely carried out in clinical practice for investigation of
7928 suspected cancer and the risks of the interventions are therefore not any greater
7929 than if a man was not part of the trial. The risks of the procedures are relatively low,
7930 as detailed in Section 11.
7931

7932 The investigator will exercise his or her medical and scientific judgment in deciding
7933 whether an abnormal laboratory finding or other abnormal assessment is clinically
7934 significant.

7935 **16.3.6 Recording/Reporting AEs and SAEs**

7936 The first AE reporting period for this study begins at randomization and
7937 will be recorded until 30-days post-biopsy. In the event that the subject does not
7938 undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

7939
7940 Only adverse events specific to biopsy-related complications including pain, fever,
7941 hematuria, hematochezia, hematospermia, urinary retention and urinary
7942 incontinence will be recorded. Any other adverse events will not be recorded.

7943
7944 AEs will be recorded by a member of the research team or clinical team on an AE
7945 report form. All SAEs must be recorded on a SAE report form. Completed AEs and
7946 SAE report forms should be sent to the CTG who will keep a log of AEs and SAEs. AE
7947 and SAE logs will be reviewed by the DSMC.

7948
7949 For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or
7950 DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria
7951 as a SAE, will be collected and reported.

7952
7953 Expected AEs includes the following:

- 7954 • Pain
- 7955 • Blood in the urine
- 7956 • Blood in the semen
- 7957 • Blood in the stool or back passage
- 7958 • Erectile dysfunction
- 7959 • Urinary incontinence
- 7960 • Urinary tract infection
- 7961 • Fevers

7962
7963 In addition, small risks of allergic reactions are associated with the intravenous
7964 administration of gadolinium, the contrast agent used in MRI scans, as described in
7965 section 10.18.1.2. This contrast agent is used consistently in MRI scanning and is not
7966 limited to this trial.

7967
7968 If any of these symptoms are accompanied by events consistent with the definition
7969 of an SAE as specified above, then the event will be considered an SAE.

7970
7971 The Trial Coordinator, Principle Investigator or Chief Investigator should be informed
7972 of any SAE within 24 hours.

7973 All SAE report forms must be completed and the SAE logs updated. All SAEs must be
7974 followed up until a resolution is reached (i.e. recovered, recovering, recovered with
7975 sequelae, fatal, not recovered or unknown).

7976

7977 Local sites may have specific institutional protocols for reporting SAEs, which should
7978 be followed in addition.

7979

7980 When an AE/SAE occurs, it is the responsibility of the investigator to review all
7981 documentation relative to the event. The investigator will then record all relevant
7982 information regarding an AE/SAE on the CRF.

7983

7984 The investigator will attempt to establish a diagnosis of the event based on signs,
7985 symptoms and/or other clinical information. In such cases, the diagnosis should be
7986 documented as the AE/SAE and not the individual signs/symptoms.

7987 **16.3.7 Evaluating AEs and SAEs**

7988 **16.3.7.1 Assessment of Intensity**

7989

7990 The investigator will make an assessment of intensity for each AE and SAE reported
7991 during the study. Degree of severity and change in severity will be recorded by
7992 means of National Cancer Institute, Common Terminology Criteria for Adverse
7993 Events (NCI CTCAE), version 4.03.

7994

7995 If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on
7996 the investigator's clinical judgment. The intensity of each AE and SAE recorded in the
7997 CRF should be assigned to one of the following categories:

7998

7999 **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort
8000 and not interfering with everyday activities.

8001 **Moderate:** An event that is sufficiently discomforting to interfere with normal
8002 everyday activities.

8003 **Severe:** An event that prevents normal everyday activities.

8004

8005 An event that is classified as severe should not be confused with a SAE. Severity is a
8006 category utilized for rating the intensity of an event; both AEs and SAEs can be
8007 assessed as severe.

8008 **16.3.7.2 Assessment of Causality**

8009 The investigator is obligated to assess the relationship between investigational
8010 product and the occurrence of each AE/SAE. The investigator will use clinical
8011 judgment to determine the relationship. Alternative causes and the temporal
8012 relationship of the event to the investigational product will be considered and
8013 investigated. The investigator will also consult the CIB and or Product Information,
8014 for marketed products, in the determination of his/her assessment.

8015 **16.3.8 Follow-up of AEs and SAEs**

8016 After the initial AE/SAE report, the investigator is required to proactively follow each
8017 subject and provide further information to the PI of the study, on the subject's
8018 condition.

8019

8020 All AEs and SAEs documented at a previous visit/contact and are ongoing, will be
8021 reviewed at subsequent visits/contacts.

8022

8023 All AEs and SAEs will be followed until resolution, until the condition stabilizes, until
8024 the event is otherwise explained or until the subject is lost to follow-up. Once
8025 resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will
8026 ensure that follow-up includes any supplemental investigations as may be indicated
8027 to elucidate the nature and/or causality of the AE or SAE.

8028

8029 The PI may request that the investigator perform or arrange for the conduct of
8030 supplemental measurements and/or evaluations to elucidate as fully as possible the
8031 nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a
8032 subject dies during participation in the study or during a recognized follow-up
8033 period, the PI will be provided with any post-mortem findings.

8034

8035 New or updated information will be recorded on the originally completed SAE CRF,
8036 with all changes signed and dated by the investigator or designate. The updated SAE
8037 CRF should be resent to the PI.

8038 **16.3.9 Prompt Reporting of SAEs**

8039 Once the investigator determines that an event meets the protocol definition of an
8040 SAE, the SAE will be reported to the PI (CURC) within 24 hours.

8041

8042 **16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI**

8043 The Site Investigator must immediately inform the PI (CURC) of all SAE (within 24
8044 hours) at the following fax number: 1-416-480-6121.

8045

8046 The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing
8047 addresses is as follows:

8048 Dr. Laurence Klotz

8049 c/o Marlene Keabadjian

8050 Sunnybrook Health Sciences Centre

8051 2075 Bayview Avenue A304

8052 Toronto, Ontario M4N 3M5 Canada

8053 Phone: (416) 480-6100 ext 2890

8054 E-mail: Laurence.Klotz@sunnybrook.ca

8055 Marlene.keabadjian@sunnybrook.ca

8056 **16.3.9.2 Completion and Transmission of the SAE Reports**

8057 Once an investigator becomes aware that an SAE has occurred in a study subject,
8058 she/he will report the information to the PI within 24 hours. The SAE CRF will always
8059 be completed as thoroughly as possible with all available details of the event, signed
8060 by the investigator (or designee), and forwarded to the PI within the designated time
8061 frames. If the investigator does not have all information regarding as SAE, he/she will
8062 not wait to receive additional information before notifying the PI of the event and
8063 completing the form. The form will be updated when additional information is
8064 received.

8065

8066 The investigator will always provide an assessment of causality at the time of the
8067 initial report as described in Section 16.3.6.2.

8068 **16.3.10 Post-study AEs and SAEs**

8069 If the investigator learns of any SAE at any time after a subject has been discharged
8070 from the study, and such event(s) is (are) reasonably related to the study
8071 intervention, the investigator should promptly notify the PI (CURC).

8072

8073 **17. Study Administration**

8074 **17.1 Regulatory and Ethical Considerations**

8075 An important consideration is that men are being randomized to one of two biopsy
8076 techniques when it is not known which will be more effective in diagnosing clinically
8077 significant prostate cancer. Both diagnostic tests are currently used in everyday
8078 clinical practice at the institutions involved in the trial. Though systematic TRUS
8079 guided biopsy could be considered standard of care, there is enough evidence to
8080 support the concept that MPMRI-targeted biopsy may be as effective, if not more so,
8081 than systematic TRUS guided biopsy[27]. This study aims to confirm this.

8082 **17.1.1 Ethical Conduct of the Study and Ethics Approval**

8083 The PI and each participating site will obtain approval to conduct the study from the
8084 Research Ethics Board (REB) prior to initiating the study.

8085

8086 Participating sites from Ontario will use the Ontario Cancer Research Ethics Board
8087 (OCREB) as their Board of Record.

8088 This study will be conducted in accordance with 'good clinical practice' (GCP) and all
8089 applicable regulatory requirements, including where applicable, the 2013 version of
8090 the Declaration of Helsinki.

8091

8092 The investigator is responsible for ensuring that this protocol, the site's informed
8093 consent form and any other information that will be present to potential subjects
8094 are reviewed and approved by the appropriate REB. The investigator agrees to allow
8095 the REB direct access to all relevant regulatory documents. The PI will provide the
8096 site investigator(s) with relevant document(s)/data that are needed for REB review
8097 and approval of the study. Before CRFs can be shipped to the site, the PI must
8098 receive copies of the REB approval, the approved informed consent form and any
8099 other information that the REB has approved for presentation to potential subjects.

8100

8101 If the protocol, the informed consent form or any other information that the REB has
8102 approved for presentation to potential subjects is amended during the study, the
8103 site investigator(s) is responsible for ensuring the REB reviews and approves, where
8104 applicable, these amended documents. The site investigator(s) must follow all
8105 applicable regulatory requirements pertaining to the use of an amended informed
8106 consent form including obtaining the REB approval of the amended form before new
8107 subjects consent to take part in the study using this version of the form. Copies of
8108 the REB approval of the amended informed consent form/other information and the

8109 approved amended informed consent form/other information must be forwarded to
8110 the PI promptly.

8111 **17.1.2 Informed Consent**

8112 Informed consent will be obtained before the subject can participate in the study.
8113 The contents and process of obtaining informed consent will be in accordance with
8114 all applicable regulatory requirements.

8115
8116 The subject's consent to participate in the study should be obtained after a full
8117 explanation has been provided of the procedures to be given. Subjects should be
8118 given sufficient time (at least 24 hours) after being given the study subject
8119 information sheet to consider and discuss participation in the study with family and
8120 friends.

8121
8122 A contact number will be given to the subject should he wish to discuss any aspect of
8123 the study. Following this, the clinician will determine that the subject is fully
8124 informed of the study and their participation, in accordance with Good Clinical
8125 Practice Guidelines. Subjects will always be asked to sign a consent form. One copy
8126 will be given to the subject, one copy will be kept with subject's hospital notes and
8127 one copy should be kept in the local investigator's file.

8128 **17.1.3 Investigator Reporting Requirements**

8129 The investigator is responsible for reporting SAEs to the REB in accordance with all
8130 applicable regulations. Furthermore, the investigator may be required to provide
8131 periodic safety updates on the conduct of the study at his or her site and notification
8132 of study closure to the REB.

8133 **17.2 Study Monitoring**

8134 This study will be monitored by a CRA. The CRA will contact the sites by telephone
8135 on a predetermined basis and would conduct a monitoring visits based on the data
8136 entered in the EDC and queries.

8137

8138 During these contacts, the monitor will:

- 8139 • Check the progress of the study
- 8140 • Review study data collected
- 8141 • Conduct source document verification
- 8142 • Identify any issues and address their resolution

8143

8144 This will be done in order to verify that the:

- 8145 • Data are authentic, accurate and complete
- 8146 • Safety and rights of subjects are being protected
- 8147 • Study is conducted in accordance with the currently approved protocol (and
8148 any amendments), GCP and all applicable regulatory requirements

8149

8150 The investigator agrees to allow CRA personnel direct access to all relevant
8151 documents and to allocate his/her time and the time of his/her staff to CRA
8152 personnel to discuss findings and any relevant issues.

8153 **17.3 Quality Assurance**

8154 To ensure compliance with GCP and all applicable regulatory requirements,
8155 regulatory agencies may conduct a regulatory inspection of the study. Such
8156 audits/inspections can occur at any time during or after completion of the study. If
8157 an audit or inspection occurs, the investigator and institution agree to allow the
8158 auditor/inspector direct access to all relevant documents and to allocate his/her
8159 time and the time of his/her staff to the auditor/inspector to discuss findings and
8160 any relevant issues.

8161 **17.4 Study and Site Closure**

8162 Upon completion of the study, the site investigator(s) will conduct the following
8163 activities:

- 8164 • Return of all study data to the Sponsor (CURC)
- 8165 • Submission of all study data and data queries to OCOG
- 8166 • Review of site study records for completeness

8167
8168 In addition, the Principal Investigator has the right to temporarily suspend or
8169 prematurely discontinue this study either at a single site or at all sites at any time for
8170 reasons including but not limited to, safety or ethical issues or severe non-
8171 compliance. If the PI determines such action is needed, the PI will discuss this with
8172 the site investigator (including the reasons for taking such action) at that time. When
8173 feasible, the PI will provide advance notification to the site investigator of the
8174 impending action prior to it taking effect.

8175
8176 Individual site Investigators may also terminate their participation in the study at any
8177 time. If the investigator determines such action is needed, the investigator will
8178 discuss this with the PI(including the reasons for taking such action) at that time.
8179 When feasible, the investigator will provide advance notification to the PI of the
8180 impending action prior to it taking effect.

8181
8182 The PI will promptly inform all other investigators and/or institutions conducting the
8183 study if the study is suspended or terminated for safety reasons and will also inform
8184 the regulatory authorities of the suspension or termination of the study and the
8185 reason(s) for the action. If required by applicable regulations, the investigator must
8186 inform the REB promptly and provide the reason for the suspension or termination.

8187
8188 If the study is prematurely discontinued, all study data must be returned to the PI. In
8189 addition, the investigator has the responsibility to return any used/unused clinical
8190 supplies.

8191
8192 Financial compensation to investigators and/or institutions will be in accordance
8193 with the agreement established between the investigator and the PI.

8194 **17.5 Records Retention**

8195 Following closure of the study, the site investigator(s) must maintain all site study
8196 records in a safe and secure location. The records must be maintained to allow easy
8197 and timely retrieval when needed and whenever feasible, to allow any subsequent

8198 review of data in conjunction with assessment of the facility, supporting systems and
8199 staff.

8200

8201 The site investigator(s) will retain study records to comply with all applicable
8202 regulatory requirements. The minimum retention time will meet the strictest
8203 standard applicable to that site for the study as dictated by any institutional
8204 requirements or local laws or regulations of Health Canada standards/procedures;
8205 otherwise, the retention period will default to 25 years.

8206

8207 The site investigator(s) must inform the PI of any changes in the archival
8208 arrangements, including but not limited to the following: archival at an off-site
8209 facility, transfer of ownership of the records in the event the investigator leaves the
8210 site. The PI should be informed of this change if it affects their access to the
8211 information in case of an audit.

8212 **17.6 Data Management**

8213 Subject data are collected by the investigator or designee using the CRF within an
8214 Electronic Data Capture (EDC) system. Subject data necessary for analysis and
8215 reporting will be entered/transmitted into a validated database. Clinical data
8216 management will be performed in accordance with applicable standards and data
8217 cleaning procedures. Database lock will occur when data management quality
8218 control procedures are completed.

8219 **17.7 Publication**

8220 The results from the study will be analyzed and published as soon as possible and is
8221 appropriate. All study-related communications can only be presented or published
8222 after approval from all relevant members involved in the trial.

8223

8224 All publications shall include appropriate indication named authors as agreed on by
8225 the members involved in the trial. For the main study reports, senior and first
8226 authorship will be determined by agreement of the Chief Investigator, the Principle
8227 Investigator at time of manuscript drafting. Authorship will be based on
8228 recommendations of the International Committee of Medical Journal Editors
8229 (www.ICMJE.org) where all authors meet the following for criteria:

8230

- 8231 9. Substantial contributions to the conception or design of the work; or the
8232 acquisition, analysis, or interpretation of data for the work; AND
8233 10. Drafting the work or revising it critically for important intellectual content;
8234 AND
8235 11. Final approval of the version to be published; AND
8236 12. Agreement to be accountable for all aspects of the work in ensuring that
8237 questions related to the accuracy or integrity of any part of the work are
8238 appropriately investigated and resolved.

8239

8240 If there are no named authors (i.e. group authorship) then a writing committee will
8241 be identified that would usually include these people. The clinical trials.gov

8242 registration number that will be allocated to this trial will be attached to any
8243 publications resulting from this trial.
8244
8245 Trial funding agencies (OICR, PCC and collaborators as appropriate) will be
8246 acknowledged in all publications.
8247
8248 The members of the trial steering committee will be listed with their affiliations in
8249 the acknowledgements/appendix of the main publication.
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8457
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8459 **Appendices**

8460 **Appendix 1: Time windows for data collection**

8461

8462 For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3

8463 For details on time windows permitted for each trial intervention to be completed
8464 please see Table 5 below.

8465

8466 Table 5: Details of time windows permitted for all trial interventions.

8467

Contact and Purpose if not clear	Time window permitted +/-30 days of scheduled visit
Visit 1 Screening (eligibility review, med hx,)	Any time following referral of subject. Ideally perform as soon as possible following receipt of referral.
Visit 1 Consent Vitals, DRE Randomization EQ-5D-5L Questionnaire (baseline) Optional blood, urine, semen and tissue sample	Complete only once subject has had 24 hours after receiving the patient information to fully consider the study. Ideally on same visit as screening. Complete at screening Immediately after consent form signed and eligibility is confirmed. Complete immediately after consent form is signed Complete after additional informed consent signed, after randomization and up until any point prior to a biopsy.
Visit 2 MRI	Only for men randomized to this arm. Any time following randomization. Ideally within 1 week of randomization.

<p>Visit 3</p> <p>MRI-Targeted Biopsy of Prostate</p>	<p>Only for men randomized to this arm who have a lesion on MRI that needs a biopsy.</p> <p>Any time following the MRI being reported, ideally within 1 week of MRI.</p> <p>Depending on local Urology service structure, an appointment for a biopsy may need to be booked at the same time as the MRI is booked (i.e. immediately after randomization) in order for a slot to be secured for a biopsy to occur in timely fashion.</p> <p>If it is determined from the MRI that a biopsy is not required then the biopsy appointment can be used instead of Visit 4 for follow up of results and treatment decision.</p>
<p>Visit 3</p> <p>Systematic TRUS guided biopsy</p>	<p>Only for men randomized to this arm.</p> <p>Any time following randomization. Ideally within 4 weeks of randomization.</p>
<p>Visit 3</p> <p>Immediate post-biopsy questionnaire</p> <p>30-day post-biopsy questionnaire</p>	<p>Should be completed and returned immediately after a biopsy, before the subject leaves the department. As long as questionnaire completed within 24 hours it will be acceptable.</p> <p>To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy.</p> <p>To be returned by post or at follow up appointment (Visit 4).</p> <p>If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as</p>

Telephone reminder	<p>possible to 30 days post-biopsy.</p> <p>At 30-days post biopsy a member of the research team will phone the subject to remind them to fill out the 30-day questionnaires</p>
<p>Visit 4</p> <p>Follow up for results And treatment Decision</p> <p>EQ-5D-5L Questionnaire</p>	<p>Should be completed as soon as possible following the availability of any pathology results. Alternatively, if a man is in the MRI arm and the MRI is negative, this follow up should occur after the availability of the MRI report. Ideally the follow up appointment should be within 6 weeks of randomization.</p> <p>Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.</p> <p>To be completed</p>
<p>Visit 5 26 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood, urine
<p>Visit 6 1 year follow up 52 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • Vitals, DRE • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
<p>Visit 7 78 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood, urine

Visit 8

104 week follow up visit

The following information will be obtained on an annual basis:

- Vitals, DRE
- time to cancer diagnosis;
- Gleason score progression;
- time to intervention on active surveillance;
- time on active surveillance;
- results of PSA tests.
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MPMRI-targeted biopsy will have an additional MPMRI at Visit 8. This will be followed by a targeted-biopsy if results of MRI are positive (PI-RADS 3-5).

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

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Appendix 2: MPMRI Reporting Proforma

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Date of MRI scan:

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Date of Report:

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day			month			year		

Reporting Radiologist:

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8476

8477 Radiologists should annotate this diagram with up to 3 suspicious areas
 8478 scoring 3 or greater on the PI-RADS v2 scale of suspicion. The three most
 8479 suspicious areas should be annotated, each with the score clearly marked.
 8480 "T1" should be the area with the greatest degree of suspicion. If
 8481 applicable, "T2" should be the area with the next greatest degree of
 8482 suspicion and finally if applicable, "T3" should be the area with the next
 8483 greatest degree of suspicion. For each suspicious area, triaxial
 8484 measurements should be recorded with all 3 measurements in orthogonal
 8485 planes provided whenever possible. In the PZ, lesions should be measured
 8486 on ADC. In the TZ, lesions should be measured on T2W. If lesion
 8487 measurement is difficult or compromised on ADC (for PZ) or T2W (for TZ),
 8488 measurement should be made on the sequence that show the lesion best.
 8489 For example, coronal measurements may be best performed in the
 8490 peripheral zone on T2 images.

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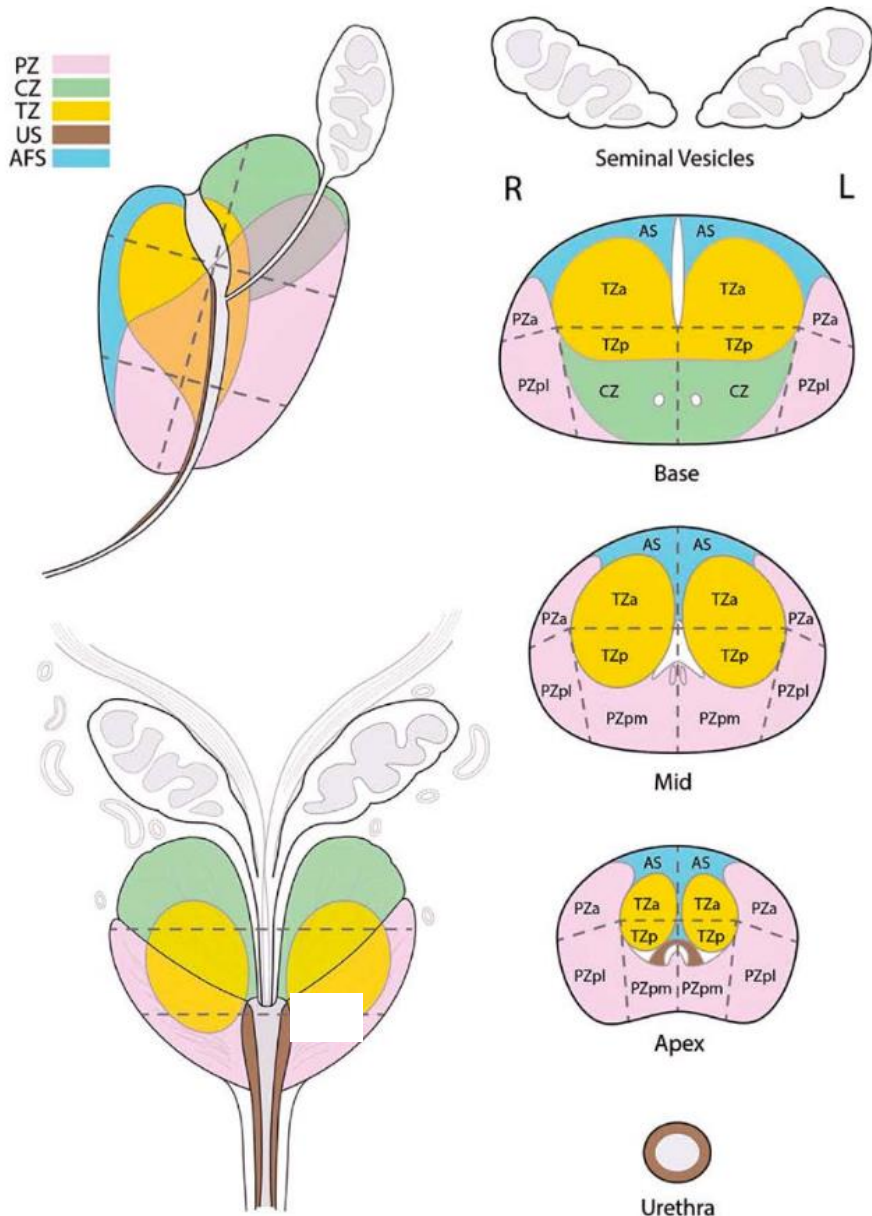
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NO DCE (Part 1 or 2) – T2/DWI/ADC
DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE PSA

Draw lesions on diagram below annotating each with the T index (i.e T1; T2...)



8555
8556
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8558
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NO DCE (Part 1 or 2) – T2/DWI/ADC
**DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE
PSA**

- Image quality:** **Good**
 Minor image quality issues
 Acceptable for diagnosis
 Unacceptable

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If image quality is not good please comment:

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8571

How to record locations

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

8572
8573
8574

Number of candidate tumor sites: _____

8575
8576

Target 1 (Highest Pi-Rads score and then largest):

Present (Y/N): _____

8577

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

8578

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

8579

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

8580

x10⁻⁶

8581

Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

8582

Location(s) (largest to smallest area involved):

8583

_____, _____, _____, _____

8584

_____, _____, _____, _____ (as per location code

8585

format above)

8586

Extraprostatic extension (Y/N/E-equivocal): _____

8587

8588

Target 2:

8589

Present (Y/N): _____

8590

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

8591

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

8592

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

8593

x10⁻⁶

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Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

8595

Location(s) (largest to smallest area involved):

8596

_____, _____, _____, _____

8597

_____, _____, _____, _____ (as per location code

8598

format above)

8599

Extraprostatic extension (Y/N/E-equivocal): _____

8600

8601

8602

8603 Target 3:

8604 Present (Y/N): _____

8605 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

8606 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

8607 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
8608 x10⁻⁶

8609 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

8610 Location(s) (largest to smallest area involved):

8611 _____, _____, _____, _____

8612 _____, _____, _____, _____ (as per location code
8613 format above)

8614 Extraprostatic extension (Y/N/E-equivocal): _____

8615

8616 There are more than 3 targets seen (Y/N): _____

8617 If yes give describe:

8618 _____

8619 _____

8620 _____

8621 _____

8622

8623 LSV invasion (Y/N/E): _____ RSV invasion (Y/N/E): _____

8624

8625 Adenopathy (Y/N): _____

8626

8627 Worst Pi-Rads Score: _____

8628

8629 Other Findings:

8630 _____

8631 _____

8632 _____

8633 _____

8634

_____	(SI)	_____	(AP)	_____	(LR)	Volume:	_____	cc
cm	x	cm	x	cm				

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DCE (Part 2 or 2) – T2/DWI/ADC/DCE
VIEW DCE – YOU SHOULD NOT KNOW THE PSA

- Image quality (including DCE):**
- Good**
 - Minor image quality issues (still acceptable)**
 - Acceptable for diagnosis**
 - Unacceptable**

If image quality is not good please comment:

Number of candidate tumor sites: _____

There was a change in lesions number or rank when adding DCE sequence
(Y/N): _____

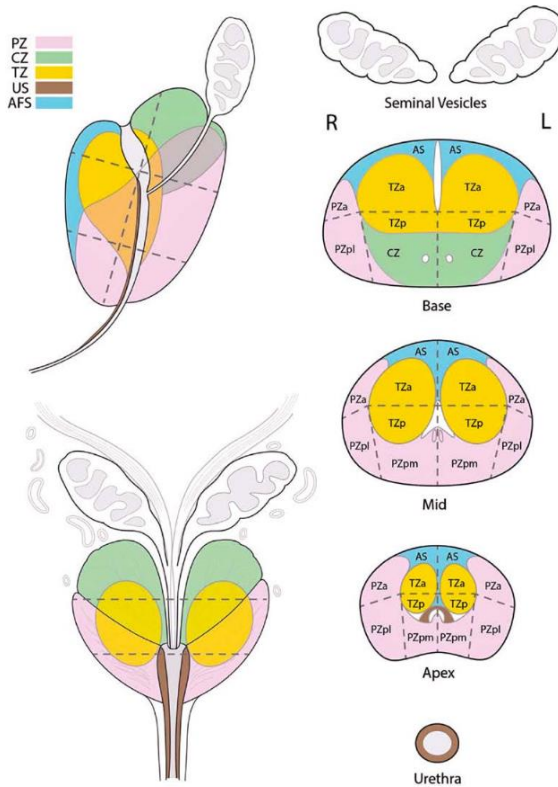
If Yes, please give the correspondence between Target numbers with and without DCE (i.e. Target 1 without DCE = Target x with DCE) and **fill in all fields below to avoid confusion. Also draw lesions on diagram below again**

Correspondence:

Old T1 = New T____ Old T2 = New T____ Old T3 = New
T____

8693
8694
8695
8696

If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2...)



8697

8698 Target 1:

8699 Present (Y/N): _____

8700 Change from Part 1 (Y/N): _____,

8701 **If YES, complete ALL sections below**

8702 **If NO change in scores, ONLY complete DCE PiRads score below.**

8703 **All other entries are assumed = to Part 1**

8704 Overall Pi-Rads Score: _____ Your Likert Score: _____

8705 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE, 0,1): _____**

8706
8707
8708 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
8709 x10⁻⁶

8710 Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

8711 Location(s) (largest to smallest area involved):

8712 _____ / _____ / _____ / _____

8713 _____ / _____ / _____ / _____

8714 Extraprostatic extension (Y/N/E-equivocal): _____

8715

8716 Target 2:

8717 Present (Y/N): _____

8718 Change from Part 1 (Y/N): _____

8719 **If YES, complete ALL sections below**

8720 **If NO change in scores, ONLY complete DCE PiRads score below.**

8721 **All other entries are assumed = to Part 1**

8722

8723

8724 Overall Pi-Rads Score: _____ Your Likert Score: _____

8725 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE,**

8726 **0,1):** _____

8727 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

8728 x10⁻⁶

8729 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

8730 Location(s) (largest to smallest area involved):

8731 _____/_____/_____/_____

8732 _____/_____/_____/_____

8733 Extraprostatic extension (Y/N/E-equivocal): _____

8734

8735 Target 3:

8736 Present (Y/N): _____

8737 Change from Part 1 (Y/N): _____

8738 **If YES, complete ALL sections below**

8739 **If NO change in scores, ONLY complete DCE PiRads score below.**

8740 **All other entries are assumed = to Part 1**

8741 Overall Pi-Rads Score: _____ Your Likert Score: _____

8742 Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____ **Pi-Rads Score (DCE,**

8743 **0,1):** _____

8744 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

8745 x10⁻⁶

8746 Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

8747 Location(s) (largest to smallest area involved):

8748 _____/_____/_____/_____

8749 _____/_____/_____/_____

8750 Extraprostatic extension (Y/N/E-equivocal): _____

8751

8752 There are more than 3 targets seen (Y/N): _____

8753 If yes give describe:

8754 _____

8755 _____

8756 _____

8757 _____

8758

8759 LSV invasion (Y/N/E): _____ RSV invasion (Y/N/E): _____

8760

8761 Adenopathy (Y/N): _____

8762

8763 Worst Pi-Rads Score: _____

8764

8765 Other Findings:

8766 _____

8767 _____

8768 _____

8769 _____

8770

8771 **Safety:**

8772 Was there an immediate reaction to Gd contrast injection (Y/N): _____

8773

8774 If yes, please give details:

8775

8776

8777

**Will subject require an TRUS/MRI-fused No Yes
biopsy (Pi-Rads ≥ 3)?**

8778

8779 Please send this form and a DVD with the images AND completed MRI

8780 Report to:

8781

8782 Marlene Kebabdjian

8783 Sunnybrook Health Sciences Center

8784 *Urology Research, A304*

8785 2075 Bayview Avenue

8786 Toronto, Ontario M4N 3M5

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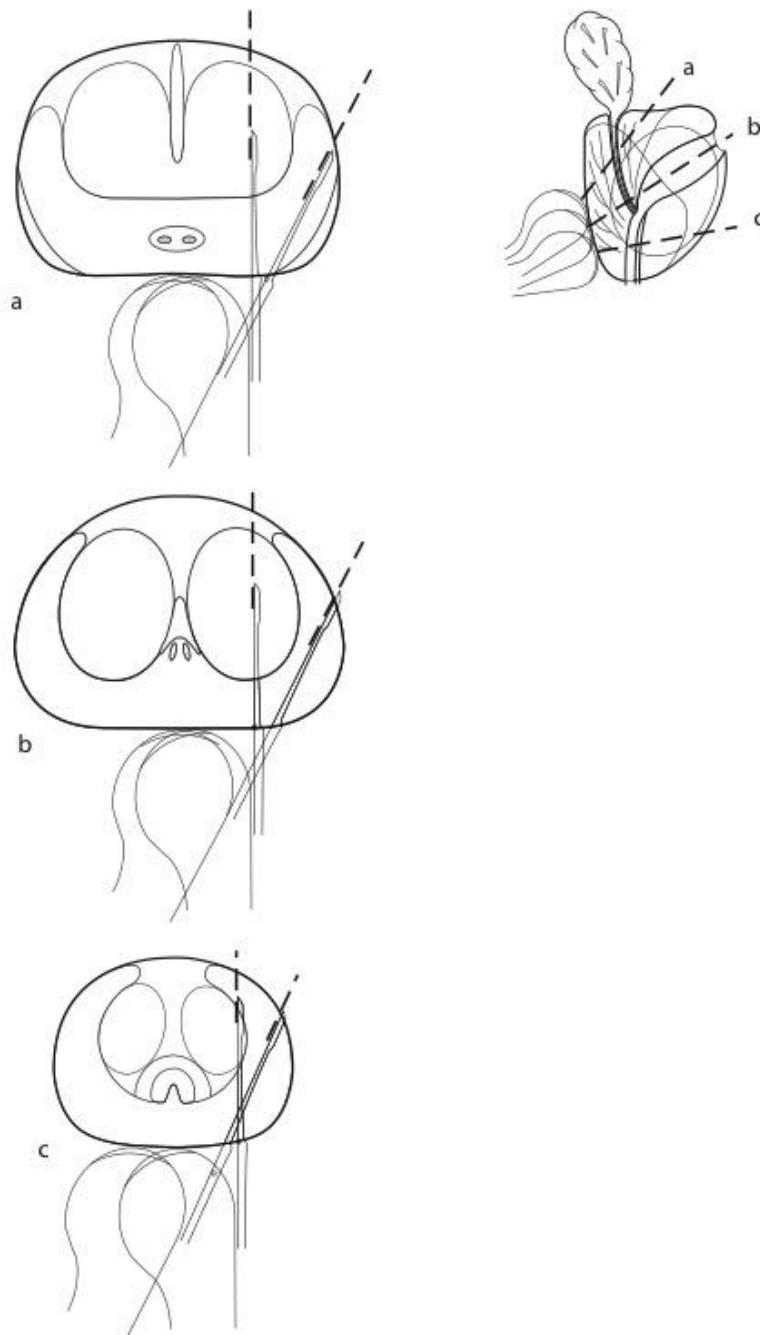
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Appendix 3: Example of systematic TRUS guided biopsy schema

8828

8829 Figure depicting 12-core systematic TRUS guided biopsyschema that sites are
8830 recommended to follow. Axial/coronal sections of a prostate gland (left) showing
8831 biopsy courses of the 12 biopsies performed under ultrasound guidance with an end
8832 fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,
8833 apex.F romHaffneret al[37].



8834

8835 **Appendix 4: 2-page EQ-5D-5L Questionnaire**

8836 Under each heading, please tick the ONE box that best describes your health TODAY

8837

8838 **MOBILITY**

8839 I have no problems in walking about

8840 I have slight problems in walking about

8841 I have moderate problems in walking about

8842 I have severe problems in walking about

8843 I am unable to walk about

8844

8845 **SELF-CARE**

8846 I have no problems washing or dressing myself

8847 I have slight problems washing or dressing myself

8848 I have moderate problems washing or dressing myself

8849 I have severe problems washing or dressing myself

8850 I am unable to wash or dress myself

8851

8852 **USUAL ACTIVITIES** (*e.g. work, study, housework,*

8853 *family or leisure activities*)

8854 I have no problems doing my usual activities

8855 I have slight problems doing my usual activities

8856 I have moderate problems doing my usual activities

8857 I have severe problems doing my usual activities

8858 I am unable to do my usual activities

8859

8860 **PAIN / DISCOMFORT**

8861 I have no pain or discomfort

8862 I have slight pain or discomfort

8863 I have moderate pain or discomfort

8864 I have severe pain or discomfort

8865 I have extreme pain or discomfort

8866

8867 **ANXIETY / DEPRESSION**

8868 I am not anxious or depressed

8869 I am slightly anxious or depressed

8870 I am moderately anxious or depressed

8871 I am severely anxious or depressed

8872 I am extremely anxious or depressed

8873

8874 © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

8875 • We would like to know how good or bad your health
8876 is TODAY.

The best health
you can imagine

8877 • This scale is numbered from 0 to 100.

8878 • 100 means the best health you can imagine.

8879 0 means the worst health you can imagine.

8880 • Mark an X on the scale to indicate how your health is
8881 TODAY.

8882 • Now, please write the number you marked on the
8883 scale in the box below.

8884

8885

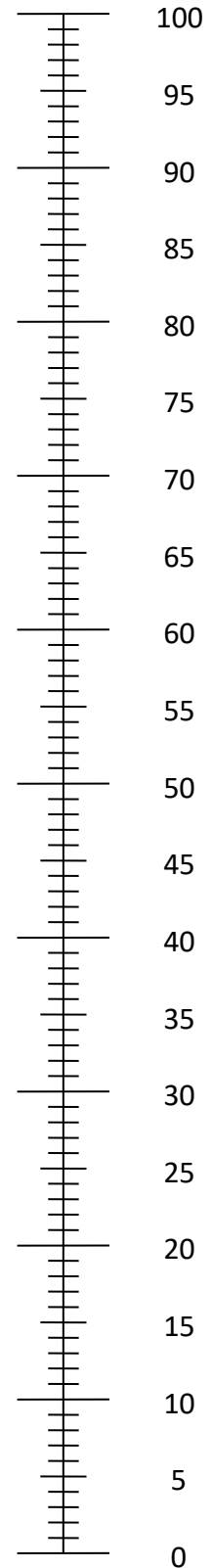
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8889

YOUR HEALTH TODAY=



The worst health
you can imagine

Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

Please ask the patient to fill this out after the biopsy, before they leave the department.

Please tick the box corresponding to the number, which describes how you felt immediately after the biopsy procedure:

1. Overall, how much discomfort did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Discomfort		Moderate Discomfort						Worst Discomfort Possible		

2. Overall, how much pain did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Pain		Moderate Pain						Worst pain Possible		

- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?

Please complete the next page of questions

Did you experience any of the following in the month **before** your biopsy procedure.
For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

11. Pain at the site where the biopsies were taken from

Yes

1

No

2

Thank you for completing the questionnaire. Please hand this to a member of staff before you leave. Please ensure you are given the 30-day questionnaire for completion at 30 days following the biopsy.

8893

Appendix 6: 30-day post biopsy questionnaire

30-day post biopsy questionnaire

30-days after the biopsy procedure, the patient should complete this questionnaire:

Did you experience the following problem in the 30-days after the biopsy procedure:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the biopsy did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

8896

Did you experience the following problem in the 30-days after the biopsy procedure:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the biopsy did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

25. Pain at the site where the biopsies were taken from

Yes No
1 2

26. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

8897

28. Please list any **new** medications that you have taken **since the biopsy**. Do not list your regular medications but do list any **new** medications started related to the biopsy. Think especially about any painkillers or antibiotics that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. ciprofloxacin</i>	<i>500mg</i>	<i>2</i>	<i>3</i>

29. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

 1

No

 2

30. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency)

(iv) any treatment you received (please be as specific as possible e.g. "I was admitted to the ward and treated for an infection of the blood stream for 5 days of intravenous antibiotics with 1.2g co-amoxiclav three times a day and I had 2 days of painkillers with intravenous paracetamol 1g four times a day"):

8898

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the biopsy, have you had contact with the community healthcare team for reasons related to the biopsy?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at GP surgery/home visit)

(iv) any treatment you received (please be as specific as possible e.g. "I received 5 days of oral antibiotics for a urinary tract infection- 625mg co-amoxiclav three times a day and I had 2 days of painkillers with paracetamol 1g four times a day"):

8899

8900

37. Have you felt unwell in any other way that we have not asked that you feel is due to the biopsy?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days:	0-2	3-5	6-10	11-15	16-20	21-30
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
	1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another biopsy** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

?

Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

?

8901
8902

8903

8904 June 30, 2017

8905

PRECISE Trial: Amendment 3

8906

Summary of Changes

8907 The purpose of this Amendment is to provide comprehensive explanation regarding
8908 the correlative sample collection, it's custodianship and it's intended use.

8909 The Amendment also identifies the collaborators involved in the PRECISE Trial.

8910 In addition, minor administrative changes were made to the current protocol to
8911 avoid discrepancy. Minor errors were corrected.

8912 The following changes were made:

- 8913 • Version date to reflect Amendment 3: 30 June 2017
- 8914 • Study Objectives: Page 3, Secondary Objectives: #7 has been rephrased, to
8915 be more explanatory.
- 8916 • Section 5.2 Methods: additional paragraph identifying the plan for MRI
8917 follow up.
- 8918 • Section 9.2 Study Trial Schema: The trial schema has been revised to
8919 reflect the MRI follow-up schedule.
- 8920 • Section 9.3 Table 1: DRE has been given it's own line item, no longer being
8921 done at 6 and 18 months.
- 8922 • Section 9.3 Table 1: Urine will no longer be collected at 6 and 18 months.
- 8923 • Section 9.3 Table 2: DRE has been given it's own line item, no longer being
8924 done at 6 and 18 months.
- 8925 • Section 9.3 Table 2: Urine will no longer be collected at 6 and 18 months.
- 8926 • Section 9.3 Table 3: DRE has been given it's own line item, no longer being
8927 done at 6 and 18 months.
- 8928 • Section 9.3 Table 3: Urine will no longer be collected at 6 and 18 months.
- 8929 • Section 10.11: All patients in both Arm A and B who have remained
8930 undiagnosed or untreated (on active surveillance) will have a follow up
8931 MRI 2 years after study entry.
- 8932 • Section 10.12 Additional tests for biomarker discovery-Optional: the
8933 addition of general information regarding the assays being collected.
- 8934 • Addition of Section 10.12.2 Correlative Science Component: The addition
8935 of comprehensive information regarding Correlative Science Component
8936 -inclusion of biomarker, urine, semen, tissue testing; information has
8937 been added to this section to reflect the biomaterial testing that will take
8938 place during the study by each collaborator.
- 8939 • Addition of collaborators and banking address in newly added Section
8940 10.12.2
- 8941 • Deletion of 'completed AEs' from page 54
- 8942 • Deletion of 'The first' in Section 16.3.6 Recording/Reporting AEs and SAEs
- 8943 • Appendix 2: MPMRI Reporting Proforma: revised, for clarity.

8944

8945

8946 **1. Title Page**

8947 *Full title:*

8948 **A phase III multi-centre open-label randomized controlled trial of**
8949 **multi-parametric magnetic resonance imaging (MRI)-targeted biopsy**
8950 **compared to systematic trans-rectal ultrasound (TRUS) guided biopsy**
8951 **for the diagnosis of prostate cancer in men without prior biopsy.**

8952

8953 **3. Short title: Prostate Evaluation for Clinically Important disease:**
8954 **MRI vs Standard Evaluation procedures. (PRECISE)**

8955

8956 **Date: 30 June 2017**

8957 **Version 4.0**

8958

8959 **Sponsor:**

8960 Canadian Urology Research Consortium (CURC)

8961

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2. Signature of Investigators

A phase III multi-centre open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.

Date: 30 June 2017

Version 4.0

The signatory agrees to the content of the final clinical study protocol as presented.

Signature: _____

Name: _____

Title: _____

Date: _____

Site name: _____

3. Synopsis

Title	A phase III multi-centre, open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.
Short Title	<u>P</u> rostate <u>E</u> valuation for <u>C</u> linically <u>I</u> mportant disease: MRI vs <u>S</u> tandard <u>E</u> valuation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	<p>Primary Objective</p> <p>To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.</p> <p>Secondary Objectives</p> <ol style="list-style-type: none"> 40. To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy. 41. Proportion of men in each arm with clinically insignificant cancer detected. 42. Proportion of men in each arm with Gleason $\geq 4+3$ detected. 43. Proportion of men in MRI arm who avoid biopsy. 44. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected. 45. Proportion of men in each arm who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy). 46. Proportion of men in each arm who do not have significant cancer found at baseline who develop a positive MRI and/or have a progressive lesion found on MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or targeted) by 2 years 47. Proportion of men with post-biopsy adverse events 48. Health-related quality of life scores. 49. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy. 50. To determine the cost per diagnosis of cancer. 51. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield 52. To determine if a radiologist Likert score not based on PI-

	RADS has a better target yield than PI-RADS_Rads alone
Test procedures	Subjects will be randomized to either ARM A: multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy. ARM B: systematic trans-rectal ultrasound (TRUS) guided biopsy. Subjects in both arms will complete a number of different questionnaires and will have PSA measurements taken. If subjects consent to participate in correlative studies, they will also need to provide blood, urine, semen and tissue samples at pre-specified time points.
Indication	Clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy.
Diagnosis and main criteria for inclusion	In order to be eligible, <u>all</u> inclusion criteria must be met. 16. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy; 17. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk assessment of prostate cancer calculator, PCPTRC 2.0, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp ; For men under age 55, the default age of 55 should be entered on the risk calculator. 18. Serum PSA ≤ 20 ng/ml; 19. Fit to undergo all procedures listed in protocol; 20. Able to provide written informed consent.
Exclusion Criteria	Men who meet the following criteria at the time of screening will be excluded: 19. Prior prostate biopsy; 20. Prior treatment for prostate cancer; 21. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50 mls/min); 22. Contraindication to prostate biopsy; 23. Men in whom artifact would reduce the quality of the MRI; i.e, previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work; 24. Unfit to undergo any procedures listed in protocol.
Study Design	This is a multi-centre open-label, randomized two arm study. Men are either randomized to receive MRI or a systematic trans-rectal ultrasound (TRUS) guided biopsy.
Methodology	Eligible subjects will be randomized in a 1:1 ratio to receive either (ARM A) multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy, or (ARM B) systematic trans-rectal ultrasound (TRUS) guided biopsy. The time frame for data collection is shown in Appendix 1. <u>All subjects</u> will have a PSA test prior to, or at Visit 1, and will

	<p>complete a baseline EQ-5D-5L questionnaire. In addition, they will contribute optional blood, urine, semen and tissue samples if they consent to correlative studies.</p> <p><u>All subjects in ARM A</u> will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI.</p> <p><u>Subjects in ARM A who do not receive a subsequent biopsy</u> will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (\pm 1 week) after the procedure. They will have another MRI and PSA test 2 years after the initial MRI. When they complete the study after 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>Subjects in ARM A who do receive a MRI-targeted biopsy</u> will complete an immediate post-biopsy questionnaire at the time of the biopsy, another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>All subjects in ARM B</u> will complete an immediate post-biopsy questionnaire following the standardized TRUS-guided biopsy. They will complete another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p>
Type of control	This is an open-label randomized study.
Number of subjects	This study requires 422 subjects (211 in each arm). To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size will be inflated by 5%, and a target of 450 men will be recruited.
Primary endpoint	The proportion of men in each arm with clinically significant cancer (Gleason \geq 7) will be calculated based on histology results from biopsy procedures. Analysis will be on the per protocol study population.
Secondary endpoints	See section 7.4
Plan for statistical analysis	See section 14.0.
Funding	The total budget for this trial is \$3,000,000. (see attached).Ontario Institute for Cancer Research (OICR) has committed to \$1,500,000 in support of this study (letter appended).We hope to obtain the additional \$1,500,000 from the Movember Accelerated Translational Research Grant Competition

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9032

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9161 4. Abbreviations and definitions

9162 Abbreviations:

9163		
9164	ADC	Apparent diffusion coefficient
9165	CI	Confidence interval
9166	CRF	Case report form
9167	DSMC	Data Safety and Monitoring Committee
9168	DRE	Digital rectal examination
9169	DWI	Diffusion weighted imaging
9170	DCE	Dynamic contrast enhancement
9171	EDC	Electronic Data Capture
9172	ITT	Intention to treat
9173	MCCL	Maximum cancer core length
9174	MPMRI	Multi-parametric MRI, used interchangeably with MRI
9175		in this protocol.
9176	MPMRI-TB	Multi-parametric magnetic resonance image-targeted
9177		biopsy of the prostate
9178	MRI	Magnetic resonance imaging, used interchangeably
9179		with MPMRI in this protocol
9180	MRI-TB	Magnetic resonance imaging targeted biopsy
9181	MRS	Magnetic resonance spectroscopy
9182	PI	Principal Investigator
9183	PI-RADS	Prostate Imaging Reporting and Data System
9184	PTC	Permission to Contact
9185	PSA	Prostate specific antigen
9186	REB	Research Ethics Board
9187	STARD	Standards for the reporting of diagnostic studies
9188	TRUS	Trans-rectal ultrasound
9189	TSC	Trial Steering Committee
9190	T2W	T2-weighted imaging

9191

9192

9193 Definitions:

9194

9195	MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is
9196		used to determine the location of a suspicious
9197		target prior to biopsy.
9198		
9199	Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure
9200		is not influenced by findings on MRI imaging.
9201		Currently this is the standard of care for
9202		prostate cancer in the province of Ontario.

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5. Trial summary

5.1 Aim and Rationale

9209

9210 The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided
9211 (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is
9212 performed primarily for anatomic guidance as the ultrasound poorly discriminates
9213 between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are
9214 concentrated in areas of the peripheral zone, thought to harbor the majority of
9215 cancer.

9216

9217 An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to
9218 perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer.
9219 This information is used to direct a subsequent biopsy, known as an MRI-targeted
9220 biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a
9221 similar or greater amount of clinically significant cancer than systematic TRUS guided
9222 biopsy and has several other potential advantages including: the ability to
9223 differentiate between clinically significant and insignificant cancer, reducing
9224 unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related
9225 side-effects.

9226

9227 A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an
9228 individual's life expectancy and therefore does not warrant treatment. However
9229 when diagnosed with low grade cancer that is likely to be insignificant, a large
9230 proportion of subjects request treatment in case a more significant cancer is
9231 present[1]. A challenge in this area is that subjects are typically not aware that their
9232 cancer is clinically insignificant, and often view the early diagnosis and aggressive
9233 treatment they have been subjected to as life-saving.

9234 A prostate cancer detection procedure that differentiates clinically significant cancer
9235 from clinically insignificant cancer is therefore a major unmet need.

9236

9237 The potential implications of this trial include:

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- A redefinition of the prostate cancer diagnostic pathway;
- A reduction in the number of subjects undergoing prostate biopsy;
- A reduction in the number of biopsy cores taken per subject;
- A reduction in biopsy-related adverse events including sepsis and pain;
- A reduction in the over-diagnosis of clinically insignificant prostate cancer;
- A reduction in the economic burden of diagnosing and treating prostate cancer.

9249 **5.2 Methods**

9250

9251 Men referred with clinical suspicion of prostate cancer who have had no prior biopsy
9252 are randomized to either systematic TRUS guided biopsy(standard of care) or to a
9253 multi-parametric MRI (MPMRI) arm (the investigational arm). In the MRI arm, areas
9254 of the prostate are scored on a 5-point scale of suspicion for clinically significant
9255 cancer based on the Prostate Imaging Reporting and Data System

9256 (PI-RADS) v2[2]:

9257 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
9258 present)

9259 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

9260 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
9261 equivocal)

9262 PI-RADS 4 – High (clinically significant cancer is likely to be present)

9263 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
9264 present)

9265

9266 Each suspicious area will be given a separate score as described by consensus
9267 meeting recommendations [2, 3]. Lesions scoring 3, 4 or 5 will undergo targeted
9268 biopsy; up to three suspicious areas will be targeted.

9269

9270 In the control arm, subjects will undergo a standard 12 core systematic TRUS guided
9271 biopsy as per standard recommendations[4]. Suspicious sonographic lesions will be
9272 targeted (12 cores *in toto*).

9273

9274 Pathologic findings from all biopsies will be recorded and will undergo statistical
9275 analysis (see statistics section, 14.0).

9276

9277 In both arms, self-reported questionnaires to capture biopsy-specific side effects will
9278 be administered immediately post-procedure, and at the post-procedure
9279 appointment which will take place 3 weeks (\pm 1 week) after the procedure. Euro QOL
9280 group 5 domain EQ-5D-5L questionnaires or a comparable QOL instrument will also
9281 be completed at baseline (prior to MRI or TRUS biopsy), 24 hours post MRI and 24
9282 hours post-biopsy. Men will be followed up for 30-days post intervention and until a
9283 treatment decision is made and recorded. Pathology results from men requiring a
9284 radical prostatectomy will be recorded.

9285

9286 Men will complete the trial after they complete treatment for prostate cancer
9287 (radical prostatectomy) or the required follow-up procedures for each arm are met
9288 (see study timelines, section 9.3). Once men complete the trial, they revert to
9289 standard of care.

9290

9291 Annual questionnaires will be administered for all men with negative biopsy in both
9292 arms during a two-year follow-up period to determine cancer and treatment status.

9293

9294 No diagnostic test is perfect, and even with the best test some cancers may be
9295 missed. To minimize the risk of false negatives, men with negative biopsy results will
9296 be followed with serial PSA testing; PSA levels will increase if cancer is present.
9297 In both arms in addition to serial PSA testing all men who have no cancer found at
9298 systematic biopsy or targeted biopsy, have a negative MRI or enter active
9299 surveillance will have a followup MRI at 24. If a new Pi-Rads ≥ 3 lesion is found on
9300 the followup MRI or there is progression of an existing lesion this lesion will undergo
9301 targeted biopsy as part of standard of care.

9302
9303 As recruitment is expected to take up to 24 months (see section 7.6) and each
9304 subject will be followed up for two years, the estimated maximal duration of this
9305 study is four years in total. The primary endpoint will be reached at approximately 2
9306 years after study initiation.

9307 **5.3 Participating Sites**

9308 This is a multi-centre study. Institutions participating in the study must be able to
9309 perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able
9310 to randomize men to one of these two diagnostic tests.

9311
9312 We expect to recruit 3-6 subjects per month per site, based on recruitment rates
9313 from previous diagnostic trials performed by the centers involved. A typical centre
9314 sees 15-30 eligible men per month. We expect 5 recruitment sites, with 100 men to
9315 be recruited at each site over an 18-24 month period (see section 7.6).

9316 **5.4 Study outcomes**

9317 **5.4.1 Primary outcome**

9318 To determine whether the proportion of men with clinically significant cancer
9319 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
9320 guided biopsy.

9321 **5.4.2 Secondary outcomes**

- 9322 40. To determine whether the proportion of men with clinically significant cancer
9323 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
9324 guided biopsy.
- 9325 41. Proportion of men in each arm with clinically insignificant cancer detected.
- 9326 42. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 9327 43. Proportion of men in MRI arm who avoid biopsy.
- 9328 44. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
9329 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
9330 detected.
- 9331 45. Proportion of men in each arm who go on to definitive local treatment (e.g.
9332 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
9333 hormone therapy, chemotherapy).
- 9334 46. Proportion of men in each arm who do not have significant cancer found at
9335 baseline who develop a positive MRI and/or have a progressive lesion found on
9336 MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or

-
- 9337 targeted) by 2 years.
- 9338 47. Proportion of men with post-biopsy adverse events
- 9339 48. Health-related quality of life scores.
- 9340 49. Proportion with Gleason grade upgrading in men undergoing radical
- 9341 prostatectomy.
- 9342 50. To determine the cost per diagnosis of cancer.
- 9343 51. To determine the impact of the addition of Gd based contrast compared to a non
- 9344 contrast abbreviated MRI protocol on target yield
- 9345 52. To determine if a radiologist Likert score not based on PI-RADS has a better
- 9346 target yield than PI-RADS alone
- 9347
- 9348

9349 **6. Background**

9350 **6.1 Prostate cancer diagnosis**

9351 Prostate cancer is the most common male cancer in the Western world with an

9352 incidence of 24,000 new cases in Canada and 233,000 in the USA[5, 6]. It is the

9353 second most common cause of cancer death in European and North American men,

9354 with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe[5, 6].

9355 The incidence of the disease has increased by 22% over the last decade due to the

9356 widespread use of the prostate specific antigen (PSA) blood test; by 2030 the

9357 Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.As

9358 prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal

9359 digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one

9360 million prostate biopsies are performed in North America and Europe every year[7].

9361

9362 **6.2 Clinically significant versus clinically insignificant prostate cancer**

9363

9364 Clinically significant prostate cancer is cancer that is likely to progress and affect a

9365 man's life expectancy if left untreated. Though there is no universally agreed upon

9366 definition on what histological parameters define clinically significant cancer, most

9367 agree that larger volume cancers with a higher Gleason grade are more likely to be

9368 clinically significant; an historically accepted threshold is a tumour volume above

9369 0.5milliliters or any Gleason pattern 4 or 5 cancer[8-11].

9370

9371 This definition is likely overly stringent. An increasing consensus views all Gleason

9372 pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of

9373 pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate

9374 cancers fall into this category, and are unlikely to progress and affect a man's life

9375 expectancy if left untreated. The widespread use of PSA testing has led to more men

9376 being diagnosed with insignificant cancer that does not warrant any treatment [13];

9377 however they are typically monitored closely with active surveillance. This is

9378 associated with anxiety about harbouring untreated cancer, and the negative

9379 psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate

9380 cancer are also subjected to serial biopsies and other tests, requiring long term

9381 follow up. Further, many men with low risk disease receive radical treatment, either

9382 because their physicians are not advocates of surveillance or because of anxiety
9383 [15].These treatments may expose them to morbidity including urinary incontinence
9384 and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate
9385 clinically significant cancer from clinically insignificant cancer will help reduce patient
9386 anxiety, alleviate further testing, and avoid radical treatment and associated
9387 morbidities.
9388

9389 **6.3 Current standard of care: systematic TRUS guided biopsy**

9390 The European association of Urology and NICE guidelines recommend systematic
9391 TRUS guided biopsy as the current standard of care for the diagnosis of prostate
9392 cancer [4, 17].This procedure has several advantages: it can be delivered quickly in
9393 an outpatient clinic under local anesthetic, it can be offered at most Urology centres,
9394 and the expertise is widely distributed.
9395

9396 Limitations of systematic TRUS guided biopsy are as follows: the procedure requires
9397 the operator to take 10-12 samples in the peripheral zone, where it is thought that
9398 the majority of prostate cancer can be found (See Appendix 2)[18]. The ultrasound
9399 guidance used during the procedure is useful for visualizing the prostate and
9400 assessing the location of the needle within the prostate but has a poor ability to
9401 discriminate tumour from normal tissue [19], which means that the systematic TRUS
9402 guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has
9403 been shown to have a high false negative rate of 30-45% [20, 21].As a systematic
9404 TRUS guided biopsy is not specifically targeted to the location of a suspected
9405 significant cancer, there is also a greater chance that a significant cancer may be
9406 missed.

9407 **6.4 The emerging role of MRI in prostate cancer diagnosis and** 9408 **treatment**

9409 **6.4.1 The role of imaging in prostate cancer diagnosis**

9410 Although used to diagnose many other solid organ cancers such as breast, renal and
9411 colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic
9412 pathway. Imaging in prostate cancer, is typically limited to stage the disease
9413 following histological diagnosis. Magnetic resonance imaging (MRI) is used in many
9414 centres to assess for extra-capsular extension during prostate cancer staging. In the
9415 past five years however, the possibility of using multi-parametric MRI (MPMRI)for
9416 diagnosing prostate cancer prior to biopsy, has generated tremendous interest[22].

9417 **6.4.2 Limitations of early MRI studies in prostate cancer**

9418 Early literature reported conflicting results on the ability of MRI to detect prostate
9419 cancer. A recent systematic review of the literature showed that the quality of
9420 studies evaluating MRI was disappointing [22]. Limitations of reported studies
9421 include:

- 9422 • **Poor reporting standards.** Many early studies failed to closely follow
9423 published guidelines for the standards of reporting of diagnostic studies
9424 (STARD) [23].

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- 9443
- **Biopsy artifact.** The majority of early studies evaluated MRI after biopsy. Evidence has shown that post-biopsy hemorrhage can remain for several months and affect interpretation of the image [24].
 - **Poor reference standards.** Many early studies use systematic TRUS guided biopsy as a reference standard, which due to its limitations, can influence the validity of the index test of MRI. Using radical prostatectomy specimens as reference standards can lead to a selection bias, as MRI is only validated in men with disease characteristics that require radical prostatectomy. Further, correlation of radical prostatectomy specimen with an MRI image is not without difficulty given the shrinkage (10-20%), distortion, absent perfusion, orientation and tissue loss as a result of specimen trimming.
 - **Incomplete analysis of the prostate.** Many early studies only evaluate the validity of MRI in the peripheral zone, even though studies have shown that around 25% of prostate cancers may be located in the transition zone [18].
 - **Segmentation.** Many early studies artificially divide the prostate into a number of segments in order to increase the amount of data obtained and the power of the analysis. Segments should not be treated as independent regions of interest, and this should be factored into the analysis.

9444 **6.4.3 Emerging role of MRI in the diagnosis of prostate cancer**

9445 Since the publication of these early reports, improvements in diagnostic technology
9446 have changed the field and more evidence supporting the role of pre-biopsy MRI has
9447 been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla
9448 and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image
9449 acquisition and the addition of functional sequences including magnetic resonance
9450 spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast
9451 enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for
9452 biopsy artifacts.

9453

9454 The combination of anatomical sequences (T2-weighted imaging) and functional
9455 sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI.
9456 Combining the sequences improves the validity of the test [25, 26].

9457

9458 A systematic review determined that 60% of men with a clinical suspicion of prostate
9459 cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI
9460 with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity,
9461 positive predictive value and negative predictive value of 90%, 88%, 77% and 95%
9462 respectively for the identification of prostate tumours greater than 0.5ml [28].
9463 Systematic reviews and meta-analysis of recent studies have demonstrated
9464 sensitivity and specificity consistently between 70-90% for the detection of clinically
9465 significant prostate cancer[26, 29-31].

9466

9467 As a result of this accumulating evidence, MRI is increasingly used in clinical practice
9468 in the diagnostic pathway for prostate cancer. The results of MRI can influence the
9469 decision to perform a prostate biopsy, as well as the technique and targeting used
9470 during the biopsy.

9471

9472 MRI has tremendous potential to enhance the outcome of men on active
9473 surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA <
9474 10) harbor higher-grade disease. This occult high-grade disease “*the wolf in sheep’s*
9475 *clothing*”, is responsible for the 3-5% of prostate cancer deaths that have been
9476 reported in long term surveillance series that did not incorporate MRI[32, 33]. The
9477 early use of MRI in men on surveillance has the potential both to reduce the need
9478 for confirmatory biopsies, and to identify the *wolf in sheep’s clothing* earlier, prior to
9479 the development of metastasis.

9480

9481 This was the rationale for the very successful ASIST study, which recently successfully
9482 completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in*
9483 *toto* by the Ontario Institute of Cancer Research. The project was managed by the
9484 Canadian Urology Research Consortium (CURC). It randomized 273 men recently
9485 diagnosed with low risk prostate cancer, on surveillance, between systematic
9486 confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end
9487 point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or
9488 higher prostate cancer. The study had numerous secondary end points and
9489 correlative science components. We expect to report the initial results by 3Q
9490 2016. We believe that the success and potential impact of the ASIST trial has created
9491 strong momentum to proceed with the PRECISE trial, which has even greater
9492 potential to substantially influence prostate cancer screening and diagnosis.

9493 **6.4.3.1 MRI can influence the decision to perform a prostate biopsy**

9494 With reported negative predictive values of 95% [28, 34,35], MRI can help determine
9495 whether a prostate biopsy is necessary; if the MRI does not identify a suspicious area
9496 the biopsy can be avoided. Using MRI, 40-50% of men referred with clinical suspicion
9497 of prostate cancer might avoid a biopsy [27]. The recent National Institute for Health
9498 Research (NIHR) Health Technology Assessment (HTA) report [11] acknowledged the
9499 value of MRI in this context. The NIHR HTA report suggests that using MRI to reduce
9500 the number of men who undergo biopsy, can be cost effective despite the costs
9501 associated with MRI[11]. Cost savings for the publically funded health care system
9502 accrue as a result of reduced number of biopsies and costs of attendant
9503 complications, and reduced treatment of clinically insignificant cancer.

9504 **6.4.3.2 MRI can influence the biopsy technique**

9505 For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI
9506 information is used to influence the prostate biopsy technique. This is known as MRI-
9507 targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of
9508 ways.

9509

9510 The biopsy operator can use the MRI images or report to direct biopsies into the
9511 area of the prostate where the tumour is located. The location of the tumour on the
9512 MRI (carried out in advance) is registered to the real-time ultrasound images with
9513 the use of software (software assisted registration or image-fusion) or without the
9514 use of software (visual registration or cognitive registration), while the prostate is
9515 visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted
9516 directly “in-bore”, where the biopsy is conducted within an MRI scanner where the

9517 target identified on MRI during a prior diagnostic scan is biopsied using guidance
9518 from serial MRI scans during the biopsy procedure, performed in an open magnet.
9519

9520 For the PRECISE study, the biopsy will be performed using an image fusion-targeting
9521 device. Two devices have been FDA approved: the Artemis, made by Eigen, and the
9522 Urostation, made by Koelis. These devices import the MR target into the TRUS
9523 image, and direct the biopsy needle into the target.

9524 **6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are** 9525 **similar to other methods**

9526 A systematic review determined that 60% of men with a clinical suspicion of prostate
9527 cancer will have a suspicious area identified on MRI [27]. One study found that a
9528 prostate biopsy strategy using only MPMRI-targeted cores resulted in the same
9529 detection rate of clinically significant cancer as 20-sector transperineal biopsies[36].
9530 Other studies also show that a targeted-alone approach would detect a similar
9531 amount of clinically significant cancer when compared to a 10-12 core systematic
9532 TRUS guided biopsy[37]. A targeted-alone approach detects 17% less clinically
9533 insignificant cancer compared to systematic TRUS guided biopsy[38].
9534

9535 The detection rates achieved with a targeted-alone biopsy strategy require fewer
9536 biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis,
9537 targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer
9538 detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores
9539 compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of
9540 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material
9541 for histopathological analysis as the maximum cancer core length obtained from
9542 targeted biopsies can be greater than that obtained from systematic biopsies[37].
9543

9544 Robust comparative evidence from randomized controlled trials is needed to
9545 determine if MRI scans can improve our ability over systematic TRUS guided biopsy
9546 to diagnose clinically significant cancer and our ability to avoid detecting clinically
9547 insignificant cancer.
9548

9549 **6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy**

9550 Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine
9551 clinical practice for prostate cancer diagnosis. Most existing studies have cohort
9552 study designs which make interpretation difficult as they do not conform well to
9553 STARD [23] recommendations [27]. Limitations of these studies include:

- 9554 • **Broad definition of the study population.** The cancer detection rates depend on
9555 the prevalence of the condition in the population being investigated. This varies
9556 amongst men with no prior biopsy, prior negative biopsy and prior positive
9557 biopsy. In many studies the detection rates are not attributable to a clearly
9558 defined population.
- 9559 • **MRI conduct and reporting.** The detail in which MRI is conducted and
9560 interpreted varies greatly amongst published studies.

9561 • **Reporting of cancer detection.** The cancer detection by systematic and targeted
9562 cores is not always presented separately and cancer detection is not always
9563 specified by clinical significance. These are both essential in order to evaluate the
9564 technique.
9565 There is a strong need for a randomized controlled trial comparing MRI-targeted
9566 biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical
9567 practice can be established.

9568 **6.5 Novelty of PRECISE**

9569 PRECISE is the first randomized study in biopsy-naïve men in which men are
9570 randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal
9571 areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic
9572 TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-
9573 targeted biopsy approach in the detection of clinically significant cancer. In order to
9574 evaluate a biopsy technique that could replace standard of care, the standard of care
9575 test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to
9576 allow a direct comparison.

9577
9578 Other constituencies with an interest in MRI in prostate cancer (University College,
9579 London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New
9580 York) have considered similar studies, however in these centres MRI has largely
9581 replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to
9582 date. As a result, these centres have acknowledged that randomization to a standard
9583 biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as
9584 equipoise has been lost.

9585
9586 In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not
9587 recommended for the indication of an elevated PSA in men who have not had a
9588 biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed
9589 to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a
9590 biopsy will make entry into this trial very appealing to potential candidates. Further,
9591 the barriers, both financial and physical, to obtaining a quality MRI outside of the
9592 health care system are substantial. Thus we believe men who are randomized to the
9593 systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant
9594 contamination (i.e. men randomized to the systematic biopsy arm seeking out an
9595 MRI instead).

9596 **7. Trial objectives**

9598 **7.1 Overall aim**

9599 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
9600 standard of care systematic TRUS guided biopsy in the detection of clinically
9601 significant and clinically insignificant prostate cancer in men without prior biopsy.
9602 The implication of this trial is that MRI-targeted biopsy could replace systematic
9603 TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

9604 **7.2 Hypotheses**

9605 The proportion of men with clinically significant cancer detected by MRI-targeted
9606 biopsy will be no less than that detected by systematic TRUS guided biopsy.

9607 **7.3 Primary Objective**

9608 To determine whether the proportion of men with clinically significant cancer
9609 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
9610 guided biopsy.

9611 **7.4 Secondary Objectives**

9612 53. To determine whether the proportion of men with clinically significant cancer
9613 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
9614 guided biopsy.

9615 54. Proportion of men in each arm with clinically insignificant cancer detected.

9616 55. Proportion of men in each arm with Gleason $\geq 4+3$ detected.

9617 56. Proportion of men in MRI arm who avoid biopsy.

9618 57. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
9619 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
9620 detected.

9621 58. Proportion of men in each arm who go on to definitive local treatment (e.g.
9622 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
9623 hormone therapy, chemotherapy).

9624 59. Proportion of men in each arm who do not have significant cancer found at
9625 baseline who develop a positive MRI and/or have a progressive lesion found on
9626 MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or
9627 targeted) by 2 years.

9628 60. Proportion of men with post-biopsy adverse events

9629 61. Health-related quality of life scores.

9630 62. Proportion with Gleason grade upgrading in men undergoing radical
9631 prostatectomy.

9632 63. To determine the cost per diagnosis of cancer.

9633 64. To determine the impact of the addition of Gd based contrast compared to a non
9634 contrast abbreviated MRI protocol on target yield

9635 65. To determine if a radiologist Likert score not based on Pi-Rads has a better target
9636 yield than Pi_Rads alone

9637

9638

9639 **7.5 Explanation for non-inferiority hypothesis**

9640 Due to the putative advantages of MRI-TB in reducing the number of men who
9641 require a biopsy, reducing the number of cores required in each man who is
9642 biopsied, more accurate representation of disease burden, less insignificant disease
9643 detected and reducing the number of men at risk of complications of biopsy, the
9644 primary outcome of detection of clinically significant cancer in each arm will be
9645 compared using a non-inferiority hypothesis. Even if a similar amount of clinically
9646 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these

9647 advantages would support the use of MRI-TB instead of systematic TRUS guided
9648 biopsy in clinical practice.
9649

9650 **7.6 Anticipated timeline of study progression**

9651 The study will commence once sponsorship, ethical approval and local approvals
9652 have been obtained at a participating site and once site initiation training has
9653 occurred and a letter of site activation has been issued from the coordinating centre.
9654 Additional sites may join after the study has commenced. At this time, five sites will
9655 participate. Assuming a minimum recruitment rate of 3-6 men per site per month,
9656 recruitment will be complete by 24 months, if not sooner. If accrual is slower than
9657 expected, an additional 1-2 sites will be recruited for year 2.
9658

Month	Number of Sites	Total recruitment
0	2	0
3	4	18-36
6	5	54-108
9	5	99-198
12	5	144-288
15	5	189-378
18	5	234-468
21	5	279-558
24	5	324-648

9659

9660 **8. Study Population**

9661 **8.1 Number of Subjects**

9662 Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or
9663 results of digital rectal exam, with no prior biopsy will be eligible for participation.
9664 Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be
9665 enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

9666 **8.2 Subject inclusion criteria**

9667 In order to be eligible, all inclusion criteria must be met:

- 9668 19. Men at least 18 years of age referred with clinical suspicion of prostate cancer
9669 who have been advised to have a prostate biopsy;
- 9670 20. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk
9671 assessment of prostate cancer calculator, PCPTRC 2.0, found at
9672 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> For men under age 55,
9673 the default age of 55 should be entered on the risk calculator.
- 9674 21. Serum PSA ≤ 20 ng/ml within 3 months of randomization
- 9675 22. Fit to undergo all procedures listed in protocol;
- 9676 23. Able to provide written informed consent.

9677 **8.3 Subject exclusion criteria**

9678 Men who meet the following criteria at the time of screening will be excluded:

- 9679 19. Prior prostate biopsy

-
- 9680 20. Prior treatment for prostate cancer
9681 21. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR
9682 ≤50mls/min)
9683 22. Contraindication to prostate biopsy
9684 23. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip
9685 replacement surgery, metallic hip replacement or extensive pelvic orthopaedic
9686 metal work
9687 24. Unfit to undergo any procedures listed in protocol.
9688

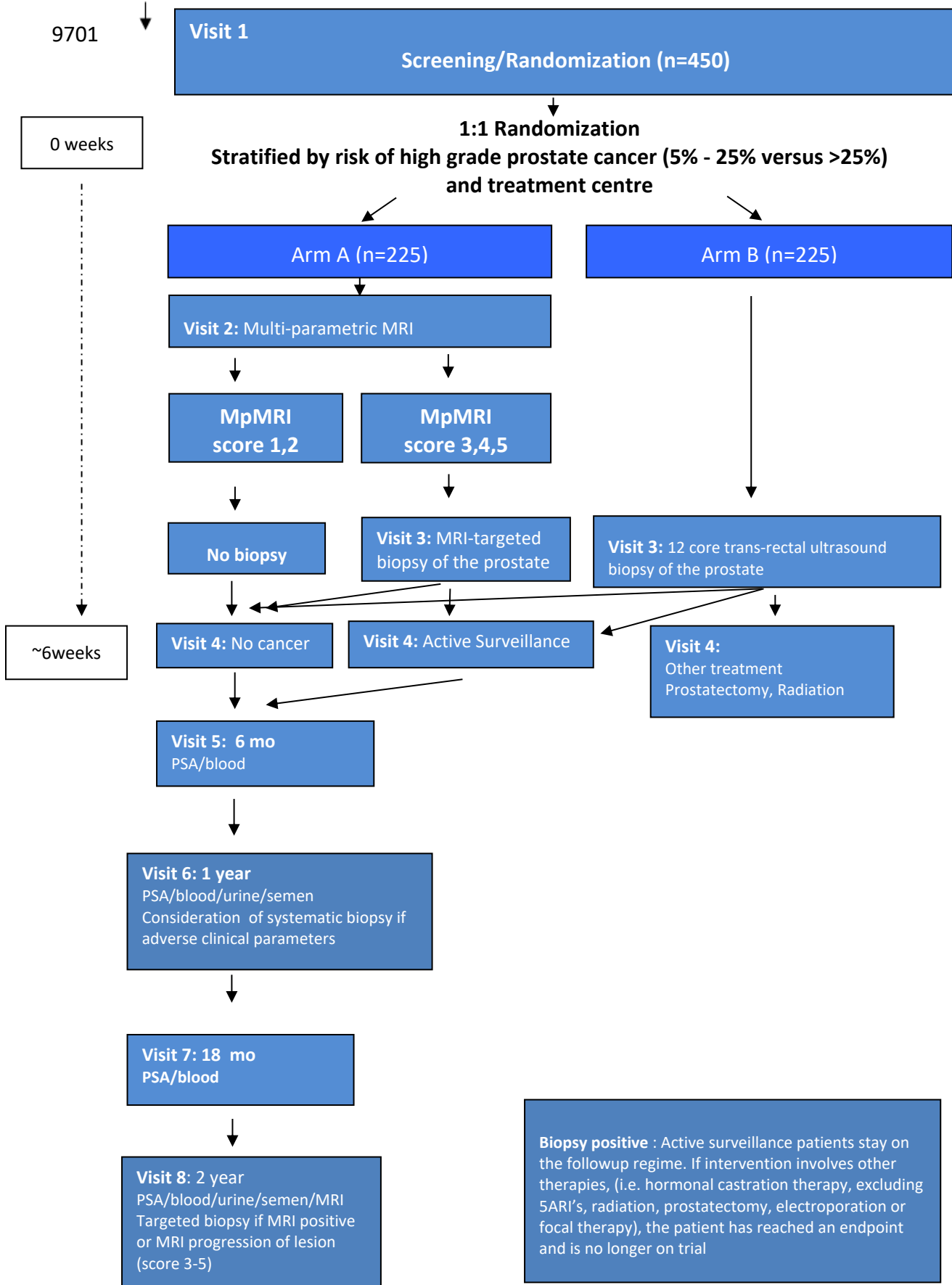
9689 **9. Study design**

9690 **9.1 Study design**

9691 The study is a multi-centre, open-label randomized controlled trial, with men
9692 randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in
9693 Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or
9694 will be followed for two years if there is no suspicious areas identified by MRI. The
9695 unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-
9696 core systematic TRUS guided biopsy. All men in the study will be followed for two
9697 years or until they have had radical treatment (whichever comes first).
9698

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9.2 Study Trial Schema



9702 **9.3 Timeline of subject contact**

9703 Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial.

9704 The individual pathway that each subject experiences is dependent on both the arm he is randomized to and results of the tests.

9706

9707 **Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require**
 9708 **a biopsy**

	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3 N/A	Visit 4 Post- Test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	5	26	52	78	104
Consent	X							
Screening (eligibility review, med hx,	X							
Vitals,	X					X		X
DRE ¹	X					X		X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection:								
• blood	X				X	X	X	X
• urine ²	X					X		X
• semen ³	X					X		X
• tissue-NA								
Creatinine	X							
PSA ⁴	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI		X						X ⁵
MRI-Targeted Biopsy								X if target
Immediate post- biopsy questionnaire								
Follow up for results of tests				X				
Treatment decision ⁶				X				
30-day post-biopsy questionnaire								
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

9709

9710 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
9711 Science component. See correlative manual for instruction.
9712 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
9713 catch' and post-DRE samples. See the Correlative Science Manual for further details on
9714 collection and processing.
9715 ³Collected at baseline, and annually.
9716 ⁴PSA will have been done prior to visit 1 as part of screening.
9717 ⁵ If MRI indicates a target, biopsy must be done
9718 ⁶After treatment decision men revert to standard of care.
9719

9720
9721

Table 2: ARM A: Men randomized to MRI arm who have a lesion on MRI and require a biopsy

	Visit 1 Screening / Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post- test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follo w up
Weeks:	0	1	2	6	26	52	78	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals,	X					X		X
DRE ¹	X					X		X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X					X		X
• semen ³	X					X		X
• tissue ⁴			X					X
Creatinine	X							
PSA ⁵	X				X	X	X	X
Systematic TRUS guided biopsy								
MRI		X						X ⁶
MRI-Targeted Biopsy			X					X ⁶
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁷				X				
30-day post- biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

9722
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9724 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
9725 Science component. See correlative manual for instruction.
9726 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
9727 catch' and post-DRE samples. See the Correlative Science Manual for further details on
9728 collection and processing.
9729 ³Collected at baseline, and annually.
9730 ⁴ tissue should be obtained if subject has agreed to the Correlative Science component. See
9731 correlative manual for instruction.
9732 ⁵PSA will have been done prior to visit 1 as part of screening.
9733 ⁶See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue
9734 obtained for correlative science studies if subject has agreed to the Correlative Science
9735 component. See correlative manual for instruction.
9736 ⁷After treatment decision men revert to standard of care.
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Table 3: ARM B: Men randomized to systematic TRUS guided biopsy arm

	Visit 1 Screening/ Randomization	Visit 2	Visit 3 Biopsy	Visit 4 Post- test visit	Visit 5 6 mos	Visit 6 1 year follo w up	Visit 7 18 mos	Visit 8 2 year follow up
Weeks:	0	1	2	6	26	52	52	104
Consent	X							
Screening (eligibility review, med hx)	X							
Vitals,	X					X		X
DRE ¹	X					X		X
Randomization	X							
EQ-5D-5L	X			X				X
Correlative sample collection: • blood	X				X	X	X	X
• urine ²	X					X		X
• semen ³	X					X		X
• tissue			X					
Creatinine	X							
PSA ⁴	X				X	X	X	X
Systematic TRUS guided biopsy			X					
MRI								X ⁵
MRI-Targeted Biopsy								X ⁵
Immediate post- biopsy questionnaire			X					
Follow up for results of tests				X				
Treatment decision ⁶				X				
30-day post-biopsy questionnaire				X				
AE/SAE	Complete as required at any time following registration							
Withdrawal Form	Complete as required at any time following registration							
ConMeds Form	Complete as required at any time following registration							

9778 ¹Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative
9779 Science component. See correlative manual for instruction.

9780 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
9781 catch' and post-DRE samples. See the Correlative Science Manual for further details on
9782 collection and processing.

9783 ³Collected at baseline, and annually.

9784 ⁴PSA will have been done prior to visit 1 as part of screening.

9785 ⁵See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue
9786 obtained for correlative science studies if subject has agreed to the Correlative Science
9787 component. See correlative manual for instruction.

9788 ⁶After treatment decision men revert to standard of care.

9789

9790

9791 **10. Trial Interventions and procedures**

9792

9793 The following procedures will be applied as necessary to subjects enrolled in both
9794 arm of the trial.

9795 **10.1 EQ-5D-5L Questionnaires**

9796

9797 **For all subjects enrolled in trial**

9798 Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L
9799 questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to
9800 evaluate health related quality of life. It takes approximately 2 minutes to complete.

- 9801 • All subjects should complete the baseline questionnaire at the screening visit
9802 before leaving the department.
- 9803 • Subjects who have a normal MRI and do not require a biopsy will complete an
9804 EQ-5D-5L questionnaire at Visit 4.
- 9805 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
9806 be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date
9807 that the subject should fill out the questionnaires should be written on top of the
9808 questionnaire. (This can also be done at Visit 4).
- 9809 • All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up
9810 visit.

9811

9812

9813 **10.2 Multiparametric MRI imaging procedure**

9814 **For subjects in Arm A only**

9815

9816 **10.2.1 MRI Protocol**

9817 A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic
9818 phased array coil and an automated injector system with the subject in the supine
9819 position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast
9820 enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS
9821 v2.

9822

9823 Within the specified PI-RADS 2 framework a common protocol will be formulated by
9824 a consensus of the radiologists involved in the trial at each site at a startup meeting.
9825 The highest agreed upon b-value image for DWI (at least 1400s/mm²) will be
9826 selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast
9827 media, injection rates and dynamic scanning temporal resolution will be matched for
9828 all sites. An optional multi b value DWI acquisition will be undertaken as well to
9829 allow for ancillary studies into non log linear apparent diffusion coefficient (ADC)
9830 models for tumor characterization. This is summarized in an MRI Operations Manual
9831
9832
9833 Subjects will be asked to follow their local standard of care MRI examination
9834 preparation instructions for the MRI procedure.

9835 **10.2.2 MRI reporting**

9836 The MRI will be reported by an experienced radiologist using the MRI Reporting
9837 Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored
9838 based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5
9839 point Likert score for purposes of comparison. Biopsy decisions will be based on the
9840 PI-RADS scores.

9841

9842

9843 Lesions in the prostate will be scored on the following scale:

9844 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
9845 present)

9846 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

9847 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
9848 equivocal)

9849 PI-RADS 4 – High (clinically significant cancer is likely to be present)

9850 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
9851 present)

9852

9853 The location of the suspicious areas in the prostate should be marked on a diagram
9854 of the prostate (see Appendix 2) and the sector numbers containing each suspicious
9855 area should be recorded in the case report form.

9856

9857 Radiologists will be blinded to the PSA.

9858

9859

9860 Imaging interpretation will be carried out at each site, however ensuring consistency
9861 and quality of imaging interpretation is crucial. A central imaging site will be
9862 designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site
9863 will perform the interpretation of all images for that site. The designated radiologist
9864 must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A
9865 startup meeting involving all radiologists will be held prior to start of accrual where
9866 each site will bring 5 MRI cases performed at their site for consensus review, scoring
9867 and discussion. This will provide a commonality of approach to interpretation among
9868 the radiologists before the study begins. After this startup meeting each site will

9869 send one set of MRI images and its interpretation for central review for site
9870 qualification.

9871

9872 A copy of all images will be sent on CD/DVD to the central site for archiving.

9873 **10.3 No target identified on MPMRI (PI-RADS 1 or 2)**

9874 **For subjects in Arm A only, who do not require a biopsy**

9875 Men who have MRIs that do not identify any suspicious lesion will not receive a
9876 biopsy. These subjects will benefit from being part of the trial as a result of not
9877 having to undergo an invasive biopsy procedure, avoiding the discomfort associated
9878 with the procedure, the risk of being diagnosed with clinically insignificant cancer
9879 and the risk of sepsis associated with the biopsy procedure. Studies suggest that if
9880 the MRI does not identify areas suspicious for cancer there is an 85-95% chance that
9881 clinically significant cancer is not present [28, 34, 35].

9882

9883 As soon as the results of the MRI are discussed with the subject, their treatment
9884 decision will be recorded and they will return to standard of care management. As
9885 part of standard of care these subjects can undergo further PSA surveillance and / or
9886 prostate biopsies if indicated.

9887 **10.4 MRI-Targeted biopsy**

9888 **For subjects in Arm A who do require a biopsy**

9889 **10.4.1 MRI choice of targets for targeted biopsy**

9890 Men whose prostates contain a suspicious area with a PI-RADS score of 3, 4 or 5 will
9891 subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in
9892 MRI-targeted biopsy. Operator experience (number of targeted biopsies performed
9893 to date) will be recorded before each procedure. The number of biopsy operators
9894 should be kept to the minimum number possible.

9895

9896 Targets will be stratified by PI-RADS score and if the same score then by size and
9897 labeled T1, T2, T3...etc. If there are more than 3 lesions with a score of 3 or more
9898 only T1-T3 will be targeted. The radiologist should record the sectors involved with
9899 tumor in order of most to least involved using the PI-RADS v2 sector scheme.

9900 The number of biopsy operators should be kept to the minimum number possible.

9901

9902 Subjects in the MRI cohort will not have systematic biopsies, with one exception.

9903 Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small
9904 volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core
9905 biopsy will be conducted.

9906 **10.4.2 MRI Biopsy**

9907 The procedure will be performed in the outpatient departments of sites possessing
9908 the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An
9909 operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI
9910 fusion system at their institution before they are qualified to participate as an
9911 operator in the study.

9912
9913 Coumarin anticoagulant, clopidogrel treatment and other relevant
9914 anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and
9915 advice sought as to appropriate substitutes if indicated. Aspirin will be continued at
9916 the discretion of the physician doing the biopsy.
9917
9918 Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will
9919 be performed via the trans-rectal route or via the trans-perineal route depending
9920 upon local practice.
9921
9922 Targeted biopsies should be performed by software-assisted fusion devices
9923 (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This
9924 software is safe and poses no risks to the subject since the same CE-marked
9925 ultrasound probes that are designed to perform the biopsy when performed as
9926 standard of care biopsy are used during targeted biopsy. Should the operator wish to
9927 not use the information provided by the software registration system and use
9928 cognitive (visual) registration alone they can do so, but should indicate this on the
9929 subject’s case report form.
9930
9931 The samples per target will be 4cores spread across the target region for a maximum
9932 total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be
9933 conducted in order meaning T1 then T2 then T3.
9934
9935 Biopsy cores from different suspicious areas will be aliquoted separately. The vials
9936 will be labeled “T1a-d”, “T2a-d” and “T3a-d” (according to how many targets there
9937 are) which should match the assignment of suspicious areas by the radiologist on the
9938 MRI report. The order of lettering a-d should match the order in which the biopsies
9939 were performed in each region. The first biopsy should be at the center of the target
9940 and the remaining fanning out from the center. Each core from the same suspicious
9941 area must be submitted separately. Alternative methods of storing cores that allow
9942 identification of the order of score samples from each target are acceptable.
9943
9944 **10.5 Systematic TRUS guided biopsy**
9945 **For all subjects in Arm B**
9946 Systematic TRUS guided biopsy is the current standard of care for the diagnosis of
9947 prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local
9948 site of recruitment.
9949
9950 A clinician competent in systematic TRUS guided biopsy will perform the procedure.
9951 The experience of the operator (number of systematic TRUS guided biopsies
9952 performed to date) will be recorded prior to each procedure. Software that guides
9953 clinicians in placing biopsy cores should not be used.
9954
9955 Coumarin anticoagulant, clopidogrel treatment and other relevant
9956 anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy
9957 and advice sought as to appropriate substitutes if indicated. Aspirin will be continued
9958 at the discretion of the physician doing the biopsy.

9959

9960 The subject will be positioned in left lateral position. 10-12 core biopsies will be
9961 taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed
9962 to the peripheral zone (See Appendix 3 for standardized method for conducting 12-
9963 core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be
9964 given as per local guidelines.

9965 **10.6 Pathology**

9966 The 2005 International Society of Urological Pathology guidelines for Gleason
9967 Grading of Prostatic Carcinoma will be followed [43].

9968

9969 For men undergoing MRI-targeted biopsy it is required that pathology reported per
9970 suspicious area targeted and per targeted core. For systematic TRUS guided biopsy,
9971 each core will be reported and graded.

9972 **10.7 Post-procedural care**

9973 **For all subjects in ARMS A and B receiving a biopsy**

9974 After a biopsy procedure the subject can be discharged within 2-3 weeks for results
9975 of the histopathology and treatment options to be discussed.

9976 **10.8 Immediate post-biopsy questionnaire**

9977 **For all subjects in ARMS A and B receiving a biopsy**

9978 A modified version of a self-reported questionnaire validated previously [39] in the
9979 assessment of post-biopsy complications will be completed immediately post-biopsy
9980 after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject
9981 should complete the immediate post-biopsy questionnaire before they leave the
9982 department. It aims to assess intensity of discomfort and pain associated with the
9983 procedure.

9984 **10.9 30-day post-biopsy questionnaire**

9985 **For all subjects in ARMS A and B receiving a biopsy**

9986 A modified version of a self-reported questionnaire validated previously [39] in the
9987 assessment of post-biopsy complications at 30 days post-biopsy should be given to
9988 all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home
9989 (Appendix 8). The subject should fill this out on day 30 following the procedure. It
9990 should take 5 minutes to fill out. The date that the participant should complete the
9991 questionnaire should be written on top of the questionnaire. Data on specific biopsy-
9992 related complications including pain, fever, hematuria, hematochezia,
9993 hematospermia, urinary retention and urinary incontinence will be recorded. Any
9994 other adverse events will not be recorded. Contact with healthcare and resource
9995 used data following the biopsy will also be ascertained. The completed questionnaire
9996 can be returned to the investigator in a pre-addressed envelope.

9997

9998 Subjects should be reminded at 30 days to complete this questionnaire.

9999 **10.10 Results and treatment decision (Visit 4)**

10000 The results of the biopsies and/or MRI will be explained to the subject by the clinical
10001 care team during this visit, which is approximately 2-3 weeks after the biopsy.

10002 The research team should record the treatment decision in the subject file.

10003 Possibilities for treatment decision include but are not limited to:

- 10004 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 10005 • Active Surveillance
- 10006 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 10007 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 10008 • Hormone therapy

10009 **10.11 Follow up period**

10010 All study participants will be followed up for up to two years or until they have
10011 radical treatment. Each year, subjects will be surveyed to obtain the following
10012 information:

- 10013 • time to cancer diagnosis
- 10014 • Gleason score progression
- 10015 • time to intervention on active surveillance
- 10016 • time on active surveillance
- 10017 • PSA
- 10018 • All subjects in both Arm A and B who have remained either undiagnosed or
10019 untreated (on active surveillance) will have a follow up MRI 2 years after
10020 study entry.

10021

10022 **10.11.1 Indications for biopsies off protocol**

10023 For subjects who are not biopsied due to a negative MRI, have negative or non-
10024 significant systematic biopsies, or who have a positive MRI but no or non-significant
10025 cancer on targeted biopsy, the following are guidelines for subjects management
10026 during the 2 year follow up period.

10027 It is an accepted standard of care in Ontario for subjects on active surveillance or
10028 with a prior negative biopsy who have a worsening risk profile to undergo mpMRI
10029 followed by targeted biopsy. We propose the following guidelines for risk profile
10030 assessment and consideration of repeat biopsy

10031 Subjects should continue to be followed with semi-annual PSA and DRE. A biopsy
10032 should be considered under one or more of the following circumstances:

- 10033 1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.
- 10034 2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase
10035 in PSA in 1 year.
- 10036 3. Biopsy if a doubling of the risk of high grade cancer according to the NCI
10037 nomogram.

10038 4. Biopsy if development of a suspicious nodule on DRE.
10039
10040 5. For men with a positive study MRI (especially PI-RADS 4 or 5) and a
10041 targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if
10042 there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.
10043
10044 24. For men on the systematic biopsy arm which was negative or showed only
10045 Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or
10046 a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these
10047 subjects.
10048
10049
10050 These are guidelines and should be interpreted with clinical judgment.
10051
10052 Follow-up will cease once treatment beyond active surveillance is undertaken
10053 (prostatectomy, radiation therapy, focal therapy, etc.)
10054 PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI
10055 identifies a target.

10056 **10.12 Additional tests for biomarker discovery - Optional**

10057 Though not related to the primary outcome of this study, this cohort represents a
10058 unique opportunity to obtain human samples for future biomarker discovery studies.
10059 Participants will be consented to provide a blood, urine, semen, and tissue sample
10060 after the consent and screen visit, and subsequent visits for storage and use in future
10061 biomarker studies. In addition, men will be consented for use of the prostate biopsy
10062 tissue in the biomarker discovery studies.
10063

10064 We propose two initial biomarker analyses for men recruited to the PRECISE study.
10065 First we propose testing the utility of several genetic assays. These include the
10066 SELECT MDx test (a urine based genomic assay), the Telo PC test (an analysis of
10067 telomere structure in circulating tumour cells), the Exosome Dx assay (urine based
10068 exosome assay), the Mitomics assay (circulating mitochondrial DNA deletion assay),
10069 and the MDNA test (a urine based microRNA assay). We will test the hypothesis that
10070 alongside conventional PSA measurements, these tests may identify subjects whose
10071 MRI was initially negative for prostate cancer, but who are at high risk of harboring
10072 clinically significant disease as detected by the secondary MRI at 2 years. We will
10073 also test the association between serum biomarkers and clinically significant or
10074 clinically insignificant prostate cancer detected during the PRECISE study. We will
10075 also explore the potential for these assays to provide additional information over
10076 and above Gleason grade. These studies will be separately funded from PRECISE.
10077

10078 Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will
10079 be planned to assess markers which might identify men at higher risk of developing
10080 prostate cancer.

10081 **10.12.1 Samples to be collected for future biomarker discovery work**
10082 **(Optional)**

10083 Participants will be asked to consent to provide a blood, urine, semen, and tissue
10084 sample after the consent and screen visit and subsequent visits for storage and use
10085 in future biomarker studies. This will involve a separate consent form.

10086 Samples include:

- 10087 • Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- 10088 • Urine – 75 mls urine
- 10089 • Semen-1-5 cc (single ejaculate)
- 10090 • Tissue-unstained biopsy sections -15 unstained slides from cancer, and
10091 -15 unstained slide from non-cancer cores
10092 (if possible)

10093

10094 **10.12.2 Correlative Science Component**

10095

10096 Within this protocol biomarker and genetic validation studies and biomarker
10097 discovery research will be incorporated to correlate molecular readouts with the
10098 presence of Gleason 4 or 5 pattern on biopsy. The goal of these studies is to
10099 develop a liquid based assay (serum, plasma, CTCs, urine, or semen) which
10100 accurately predicts the presence of clinically significant cancer. The correlative
10101 science component of Precise constitutes a major initiative, with multiple
10102 collaborators and planned studies. These are briefly summarized below.

10103

10104 Biomaterials (serum, plasma, buffy coat, PRE/POST DRE urine and tissue from
10105 biopsies) will be collected at times specified in the protocol. Sample collection will be
10106 restricted to subjects who have agreed to provide these samples in a separate
10107 optional informed consent. If a subject withdraws consent for the additional
10108 biomarker and genetic testing, subject's samples will be destroyed. The investigator
10109 must notify the sponsor site contact who will request the samples destruction.

10110 Biomaterials for the correlative science studies will be identified with a unique
10111 identification code, date of collection and will not contain any personal identification
10112 information. The samples will be shipped to a secure long-term storage facility,
10113 identified as the Ontario Institute for Cancer Research, located at 661 University Ave,
10114 Suite 510, Toronto, ON M5G 0A3. Samples for the correlative science studies will be shipped
10115 stored and analyzed according to specified, specialized procedures in the Precise Correlative
10116 Science Manual.

10117

10118 A group of investigators led by Drs. Paul Boutros (OICR) and George Rodriguez
10119 (UWO) have obtained funding for a correlative science study nested in the Precise
10120 trial. This study is termed the 'Translational Research Initiative in Prostate Cancer',
10121 or TRIPC. Biomaterial will be collected for these studies as above. A summary of
10122 the planned studies is as follows:

10123

10124 [Urine: The TRIPC project will measure the proteomes of urine specimens using](#)
10125 [either a whole proteome assay or Selective Reaction Monitoring - Mass](#)
10126 [Spectroscopy \(SRM-MS\) or Peptide Reaction Mass Spectroscopy \(PRM-MS\) for a](#)
10127 [panel of ~50 peptides. These peptides will be used to score two published](#)
10128 [biomarkers of disease aggressivity](#)

10129 (<https://www.nature.com/articles/ncomms11906>). The PRECISE data will then be
10130 used to retrain the parameters and weights of the biomarkers as an exploratory
10131 analysis.

10132

10133 Blood: Genotypes will be measured using either DNA-sequencing or genotyping
10134 arrays. The resulting data will be used to score five distinct biomarkers: a germline-
10135 incidence biomarker created by the PRACTICAL GWAS consortium, a biomarker of
10136 aggressive prostate cancer created by the PRACTICAL GWAS consortium, a panel of
10137 DNA repair genes identified by the SU2C group and two biomarkers of disease
10138 aggression identified by the CPC-GENE network. The PRECISE data will then be used
10139 to retrain the parameters and weights of the CPC-GENE biomarkers as an
10140 exploratory analysis. Second, methylation of cell-free DNA will be assessed using
10141 microarray platforms (either tiling or CpG island arrays) to score two existing
10142 signatures of aggressive prostate cancer.

10143

10144 Tissue

10145 Tumour biopsies will be subject to OncoScan microarray profiling and/or DNA
10146 sequencing to measure methylome, somatic single nucleotide variants, copy number
10147 aberrations, genomic rearrangements and mitochondrial copy number. Seven
10148 signatures of aggressive prostate cancer will be scored: the proportion of the
10149 genome altered (PGA, Lalonde et al. Lancet Oncology), 100-locus and 31-locus
10150 signatures (Lalonde et al. European Urology), a multi-modal signature (Fraser et al.
10151 Nature), a mitochondrial signature (Hopkins et al. Nature Communications), and two
10152 unpublished signatures developed by the CPC-GENE network: of tumour evolution
10153 and of the tumour methylome. The PRECISE data will be used to retrain the
10154 parameters and weights of the biomarkers as an exploratory analysis.

10155

10156

10157 A second group, led by Dr. Keith Jarvi, will analyze semen for biomarkers of
10158 significant prostate cancer. They will utilize **deep targeted Next-Generation
10159 sequencing of cell-free DNA and tumor cells Isolated from semen.**

10160

- 10161 • **Contact information:** Dr. Keith Jarvi/Dr. Andrei Drabovich
10162 Murray Koffler Urologic Wellness Centre, 60 Murray Street, 6/F
10163 Toronto, ON M5T 3L9

10164

10165 Semen has potentially high amounts of exfoliated prostate epithelial cells and high
10166 concentrations of prostate-derived cell-free DNA amenable to measurement by the
10167 deep next generation DNA sequencing. The clear advantage of semen is its use as a
10168 fluid for biomarker identification as well as a clinical specimen for non-invasive
10169 diagnostics. In addition, semen and SP analysis may facilitate early cancer diagnosis
10170 since exfoliated PCa cells and PCa-specific cell-free DNA will appear in semen much
10171 earlier and prior to destruction of prostate-blood barrier and diffusion of cells and
10172 cell-free DNA into the blood.

10173 Dr. Jarvi's group will focus on known gene fusions and point mutations in exomes of
10174 genes frequently mutated in PCa. They used the next generation DNA sequencing
10175 data uploaded to the cBioPortal. That included 841 primary prostate cancer tissues

10176 sequenced by the Cancer Genome Atlas, Broad Institute and Memorial Sloan
10177 Kettering Cancer Center. As a result, they identified a panel of 30 genes (26 genes
10178 with 271 recurrent or potentially recurrent missense mutations and 4 gene fusions)
10179 which provided sensitivity of 92% at theoretical 100% specificity for detection of
10180 PCa. Upon protocol optimization, they will first complete a pilot study and sequence
10181 cell-free DNA in 24 SP samples from men with PCa, 12 seminal plasma (SP) samples
10182 from men with a negative biopsy and 12 SP samples from healthy fertile men. They
10183 will then validate the diagnostic performance of the 30-gene panel in 288 SP
10184 samples from men with low-grade, intermediate-grade, high-grade PCa, negative
10185 biopsy, prostate inflammation and healthy men.

10186 They will also develop an approach for immunomagnetic isolation of prostate
10187 epithelial cells and PCa cells from semen. They propose that PCa cells isolated from
10188 semen may function as a non-invasive 'liquid biopsy' tool for the accurate diagnosis
10189 and subtyping of PCa. Exfoliated prostate epithelial cells and PCa cells will be isolated
10190 using magnetic beads coated with monoclonal antibodies or high-affinity aptamers
10191 for the prostate-specific membrane antigen (PSMA). Since PSMA is cell-surface
10192 protein exclusively expressed in prostate cells, this procedure will enrich prostate
10193 epithelial cells and PCa cells, but deplete spermatozoa and leukocytes. Protocols for
10194 cell isolation will include the use of either centrifugation or magnetic-activated cell
10195 sorting. Genomic DNA will be extracted, purified and analyzed by the next
10196 generation sequencing. Using semen samples from post-vasectomy semen, they will
10197 investigate the impact of spermatozoa on the efficiency of isolation of prostate
10198 epithelial cells.

10199
10200 The following collaborators will also be receiving biomaterial specimens (blood
10201 and/or urine and/or semen). The goals of each of these groups is to correlate a
10202 biomarker readout with the likelihood of prostate cancer, and of clinically significant
10203 cancer. The planned assays are summarized briefly as follows

- 10204
- 10205 • 3D Signatures
- 10206 MaRS Centre, South Tower
10207 101 College Street, Suite 200
10208 Toronto, Ontario, Canada M5G 1L7

10209
10210 This group will be examining the telomere structure of circulating tumour cells
10211 (CTCs) using an established assay, the Telo PC test. The results of a 50 patient
10212 prostate cancer pilot study in men with intermediate risk prostate cancer who
10213 underwent radical prostatectomy showed that the TeloPC assay correctly predicted
10214 the status/aggressiveness of disease in each of the study's patients.¹ While all
10215 patients were diagnosed as intermediate risk using conventional biopsies prior to
10216 surgery, only 21 of the 50 patients who underwent RP showed disease upgrading
10217 upon post-surgical analysis and therefore were suitable for prostate removal. The
10218 TeloPC assay correctly predicted that 29 of the 50 patients had a stable form of
10219 prostate cancer.

10220
10221 The TeloPC assay includes filtration-based circulating tumour cell (CTC) enrichment
10222 combined with 3-dimensional (3D) analysis of telomeres to obtain 3D telomere

-
- 10223 profiles of PCa patients with low-intermediate risk category.
- 10224 • MiR Diagnostics
10225 1 Discovery Drive
10226 Rensselaer, NY 12144
- 10227 This group will be examining urinary microRNAs. A panel of 56 miRNAs and
10228 snoRNAs, which have been demonstrated to be predictive of clinically significant
10229 prostate cancer, will be interrogated.
- 10230
10231
10232
- 10233 • Exosome Diagnostics, Inc.
10234 266 2 nd Ave.
10235 Waltham, MA 02451
- 10236
10237 This group will be interrogating non-coding RNAs extracted from urinary exosomes.
10238 They will assay exosomal RNA for three biomarkers known to be expressed in men
10239 with high-grade prostate cancer, using an algorithm that integrates this three-gene
10240 signature,
- 10241
- 10242 • MDNA Life Sciences, Inc.
10243 2054 Vista Parkway, Suite 400
10244 West Palm Beach, FL 33411
- 10245
10246 This group will evaluate the performance of the Prostate Mitomics test. This is a
10247 blood-based screening test which evaluates free plasma DNA for the presence of a
10248 mitochondrial DNA deletion. This deletion has been demonstrated to be associated
10249 with high grade prostate cancer. Nucleic acids will be extracted from each plasma
10250 sample using a commercially available reagent kit. The Prostate Mitomic Test is a
10251 quantitative real-time PCR test for a 3.4kb mitochondrial DNA deletion correlated
10252 with prostate cancer. Each sample will also be profiled for novel mitochondrial
10253 DNA mutations using standard laboratory techniques such as quantitative real-time
10254 PCR. Mutation frequency will be compared to clinical outcomes.
- 10255
- 10256 • Dr. Keith Jarvi/Dr. Andrei Drabovich
10257 Murray Koffler Urologic Wellness Centre
10258 60 Murray Street, 6/F
10259 Toronto, ON M5T 3L9
- 10260
10261 This group will interrogate prostatic epithelial cells in seminal fluid for the presence
10262 of genetic alterations known to be associated with high grade prostate cancer.
- 10263
- 10264 • MDx Health. Inc
10265 15279 Alton Parkway, Suite 100
10266 Irvine, CA 926188
- 10267

10268 This group will perform the Select MDx assay, a two gene mRNA assay performed on
10269 urine, to evaluate its performance in predicting the presence of clinically significant
10270 prostate cancer.
10271

10272 **10.13 Long-term data linkage – Permission to Contact**

10273 The cohort of men who consent to participate in this study represent a uniquely
10274 characterized group. Their long-term outcomes will contribute to our understanding
10275 of the epidemiology of prostate cancer beyond the questions being addressed in this
10276 study.

10277
10278 Permission to Contact (PTC) is a feasible mechanism to engage subjects in research
10279 programs. This will allow researchers to contact study participants in the future to
10280 assess their willingness to respond to questionnaires. This potentially enables
10281 research that would complement the planned long-term follow up in terms of health
10282 status, for obtaining information about future biopsies not included in the study, and
10283 allow assessment of quality of life.

10284 **10.14 End of Study**

10285 The end of study assessment comprises an essential safety evaluation that should be
10286 completed prior to discharging any subject from the study.

- 10287
- 10288 • Adverse events;
 - 10289 • PSA measurement;
 - 10290 • EQ-5D-5L questionnaire;
 - 10291 • An MRI in those who did NOT have a biopsy;
 - Complete CRF.

10292 **10.15 Risks and Benefits to Participants**

10293 An important consideration of this study is that men are being randomized to one of
10294 two biopsy techniques when it is not known which will be more effective. Both
10295 diagnostic tests are currently used in clinical practice at the institutions involved in
10296 the trial. Though systematic TRUS guided biopsy could be considered standard of
10297 care, there is enough evidence to support the concept that MRI-targeted biopsy may
10298 be at least as effective as systematic TRUS guided biopsy[27].

10299 **10.15.1 Risks to subjects**

10300 The intervention proposed in this trial (MRI-biopsy) do not offer participants any
10301 more risk than if they underwent standard of care (systematic TRUS guided biopsy)
10302 for the diagnosis of prostate cancer.

10303 **10.15.1.1 Risk of Systematic TRUS guided biopsy**

10304 Systematic TRUS guided biopsy can be associated with discomfort, haematuria,
10305 haematospermia and dysuria in a large proportion of subjects, which is self-resolving
10306 (See Table 4). There is a 4% risk of systemic urosepsis[46].

10307

10.15.1.2 Risks of MPMRI

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MRI is associated with few risks. It is a safe procedure used in everyday clinical practice (See Table 4). Small risks of allergic reactions are associated with the intravenous administration of gadolinium, the contrast agent used in MRI scans. The study uses a low molecular weight Gd chelate as a contrast agent (Gadovist, Bayer, gadobutrol – generic). This contrast agent is used routinely for contrast enhanced MRI and is approved by Health Canada. Subjects will be screened for any contraindications to Gd injection or to MRI as per current clinical Dept of Medical Imaging protocols at each institution. The commonest reported sides effects are of limited duration and mild to moderate in intensity and include headache, vasodilation, injection site pain, nausea, dizziness, rash, and dyspnea. The incidence of these are <1%. Severe life threatening reactions such as severe anaphylaxis occur very rarely, about 1:10,000-1: 100,000. These are treatable with epinephrine and steroids. The risk of death is <1:100,000. There is a known risk of nephrogenic systemic fibrosis, a potentially fatal condition in subjects with impaired renal function, with an eGFR<30ml/min/1.73m². These subjects are ineligible for this study.

10324

10.15.1.3 Risks of MRI-targeted biopsy

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10332

MRI-targeted biopsy is associated with similar risks to the standard of care systematic TRUS guided biopsy. As fewer biopsy cores are being taken with MRI-targeted biopsy, the theoretical risk of adverse events associated may be less than that of systematic TRUS guided biopsy. In addition, as a proportion of men may not require a biopsy (approximately 30%) on a group level there will be reduced number of men experiencing these complications, which is one of the major advantages of an MRI-based approach.

10333

Table 4: Adverse events associated with procedures

10334

Side Effect \ Procedure	Systematic TRUS guided biopsy (Standard of care)	MRI	MRI-targeted biopsy
Pain / discomfort	Some have discomfort Some have pain	Intravenous cannulation (to allow contrast administration) can cause minimal discomfort	Similar / reduced compared to systematic TRUS guided biopsy
Dysuria	Majority have dysuria (self-resolving in 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematuria	Majority (self-resolving, 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haemospermia	Majority (self-resolving, 1-2 weeks)	No	Similar / reduced compared to systematic TRUS guided biopsy
Erectile dysfunction	30% (self resolving after 1-2 months)	No	Similar / reduced compared to systematic TRUS guided biopsy

Urinary Tract infection	1-8 %	No	Similar / reduced compared to systematic TRUS guided biopsy
Systemic urosepsis	2-4%	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary retention	1%	No	Similar / reduced compared to systematic TRUS guided biopsy
Contrast allergy	N/A	Rare < 1 in 10000 – severe allergic reaction (breathing problems) < 1 in 2000 – moderate allergic reaction (nausea and vomiting) < 1 in 250 – mild allergic reaction (rash, itching)	N/A
Adverse effects of antibiotics	Rare <1%	N/A	Rare <1%

10335
10336
10337

10338 **10.15.2 Benefits to subjects**

10339 Subjects enrolled in this trial will benefit from the following:

- 10340 • Subjects in both arms may benefit from receiving a diagnostic test for suspected prostate cancer and will receive further treatment if required. The research team
- 10341 will also ensure streamlined diagnostic investigations to promptly conduct the
- 10342 diagnostic test and communicate the test outcome for the subject.
- 10343
- 10344 • Subjects enrolled in the trial will benefit from the dedicated research team
- 10345 involved in their care in addition to the clinical team normally involved in their
- 10346 care.
- 10347 • Subjects will benefit from additional discussions regarding the trial, which could
- 10348 increase their understanding of prostate cancer and help them to make a more
- 10349 informed decision about their health.
- 10350 • Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will
- 10351 remove any risk of post-biopsy infection. MRI-randomized subjects may also
- 10352 benefit from a reduced probability of having a clinically insignificant prostate
- 10353 cancer diagnosed. Clinically insignificant prostate cancer is often treated
- 10354 definitively per subject preference despite the lack of evidence supporting the
- 10355 need. All definitive local therapies for prostate cancer carry the risk of peri-
- 10356 operative complications as well as long-term risk of incontinence and erectile
- 10357 dysfunction.
- 10358

10359 **10.16 Concomitant medications**

10360 **10.16.1 Permitted Medications**

10361 All concomitant medications taken during the study will be recorded in the CRF with
10362 indication, dose information and dates of administration. The definition of which
10363 medication would be considered outside the routine medical practice is up to the
10364 discretion of the investigator. All dietary and herbal supplement usage will be
10365 recorded in the CRF.

10366 **10.16.2 Non-Drug Therapies**

10367 Any occurrence of prostate-related surgical and/or non-surgical (or minimally
10368 invasive) intervention during the conduct of the study will be recorded in the CRF.
10369

10370 **11. Schedule of Study Visits**

10371 **11.1 Visit 1 (Screening/Randomization): Screening, Consent,**
10372 **Randomization**

10373 **For all subjects enrolled in trial**

10374 Screening will occur any time following the referral of the subject. Ideally, this will be
10375 performed as soon as possible following receipt of referral.

10376 Subjects will be consented only after they have had time to consider the study. This
10377 may happen on the same visit as the screening visit.

10378 Randomization can happen immediately after the consent form is signed and
10379 eligibility is confirmed.

10380

10381 Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L
10382 questionnaire (Appendix 4), which is a validated 2-page questionnaire representing
10383 health related quality of life. It takes approximately 2 minutes to complete. This
10384 questionnaires should be completed at the screening visit before the subject leaves
10385 the clinic.

10386

10387 If a subject agrees to the optional informed consent, from randomization until any
10388 point prior to a biopsy, optional blood, urine, semen and tissue samples will be
10389 collected for correlative studies.

10390

10391 Even if PSA testing was done prior to Visit 1, PSA should be obtained at Visit 1.

10392

10393 **11.2 Visit 2 (MRI): ARM A, for men randomized to MRI**

10394 This will occur approximately within one week of randomization. Men will receive an
10395 MRI (see Section 10.2.)

10396 **11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate**

10397 **For men randomized to ARM A, who have a lesion identified by MRI.** This
10398 appointment will follow approximately one-two weeks of MRI.

10399

10400 Depending on local Urology service structure, an appointment for a biopsy may need
10401 to be booked at the same time as the MRI is booked (i.e. immediately after
10402 randomization) in order for a biopsy to occur in timely fashion. If the results of the
10403 MRI show that a biopsy is not required, then the biopsy appointment can be used
10404 instead of Visit 4 for follow up of results and treatment decision.

10405
10406 Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy
10407 of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy
10408 Questionnaire (Appendix 7) ideally completed and returned immediately after a
10409 biopsy, before the subject leaves the department.

10410
10411 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
10412 and complete as instructed on day 30 post-biopsy. This is to be returned by post or
10413 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
10414 biopsy then this questionnaire can be given to the research team when 30 days is
10415 finally complete. If Visit 4 is on or later than 30 days then this can be returned at the
10416 Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-
10417 biopsy, it will be acceptable, however, the questionnaire should be completed as
10418 close as possible to 30 days post-biopsy.

10419
10420 At the 30-days post biopsy interval, a member of the research team will call the
10421 subject to remind them to complete and return the 30-day questionnaires.

10422 **11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic** 10423 **TRUS-biopsy**

10424 **For men randomized to ARM B only.**

10425
10426 Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will
10427 complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed
10428 and returned immediately after the biopsy.

10429 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
10430 and it is to be completed as instructed on day 30 post-biopsy. This is to be returned
10431 by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30
10432 days post biopsy then this questionnaire can be given to the research team when 30
10433 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the
10434 Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-
10435 biopsy, it will be acceptable, however the questionnaire should be completed as
10436 close as possible to 30 days post-biopsy.

10437
10438 At 30-days post biopsy a member of the research team will call the subject to remind
10439 them to complete and return the 30-day questionnaires.

10440 **11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a** 10441 **biopsy**

10442 This appointment will include a follow up meeting with the investigator to discuss
10443 the results of the MRI as well as treatment decisions. This follow up should occur

10444 after the availability of the MRI report. At this visit the subject will also complete a
10445 30-day post intervention EQ-5D-5L Questionnaire.
10446
10447 Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8), which has been
10448 posted to them by the research team. If Visit 4 is earlier than 30 days post MRI then
10449 this questionnaire can be given to the research team when 30-days is finally
10450 complete. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
10451 appointment. As long as the questionnaire is completed at 30-60 days post-MRI, it
10452 will be acceptable, however the questionnaire should be completed as close as
10453 possible to 30 days post-MRI.
10454
10455 At 30-days post MRI, a member of the research team will call the subject to remind
10456 them to complete the 30-day questionnaires.

10457 **11.6 Visit 4 (Post-test follow up): For all men who received a biopsy**

10458 This appointment will include a follow up meeting with the investigator to discuss
10459 the results of the biopsy as well as treatment decisions. This should be completed as
10460 soon as possible following the availability of any pathology results. The follow up
10461 appointment should be within 1 month of the biopsy. Depending on local Urology
10462 service structure, these results may need to be discussed at an MDT meeting to
10463 inform treatment decision.
10464

10465 The research team should record the treatment decision in the subject file.
10466

10467 Possibilities for treatment decision include but are not limited to:

- 10468 • Further diagnostic test (e.g. PSA, biopsy, MRI)
 - 10469 • Active Surveillance
 - 10470 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
 - 10471 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
 - 10472 • Hormone therapy
- 10473

10474 At this visit the subject will also receive a 30-day post intervention EQ-5D-5L
10475 Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy
10476 questionnaire (Appendix 8), which has been posted to them by the research team.
10477 The questionnaire needs to be completed on the 30th day post-intervention (i.e. post
10478 biopsy). However it will be accepted if completed up to 72 hours prior to or after the
10479 30th day. A telephone reminder from the research team to the subject can take
10480 place.
10481

10482 **11.7 Visit 5 (6 month follow up):26 week follow up**

10483 All subjects will have a 26 week visit

10484 Subjects will have the following:

- 10485 • Vitals, DRE
- 10486 • PSA
- 10487 • Optional sample collection (blood)

10488 **11.8 Visit 6 (1 year follow up): 52 week follow up**

10489 All subjects are planned to have a 52 week follow up visit.

10490 Subjects will be followed to obtain the following information on an annual basis:

- 10491 • Vitals, DRE
- 10492 • time to cancer diagnosis;
- 10493 • Gleason score progression;
- 10494 • time to intervention on active surveillance;
- 10495 • time on active surveillance;
- 10496 • results of PSA tests.
- 10497 • Time to follow up biopsy and/or mpMRI if performed (see follow up
- 10498 guidelines)
- 10499 • Indication for follow up biopsy
- 10500 • Was MRI performed prior to follow up biopsy
- 10501 • Was the biopsy systematic, targeted only or both systematic + targets, not
- 10502 done because of negative MRI
- 10503 • Optional sample collection (blood, urine)

10504

10505 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
10506 will have an additional MRI at Visit 6 (year 2).

10507 **11.9 Visit 7 (18 month follow up): 78 week follow up**

10508 All subjects will have a 78 week visit

10509 Subjects will have the following:

- 10510 • Vitals, DRE
- 10511 • PSA
- 10512 • Optional sample collection (blood)

10513

10514 **11.10 Visit 8 (2 year follow up): End of study**

10515 All study participants will be followed for up to two years or until they undergo
10516 radical treatment

10517 Subjects will be followed to obtain the following information on an annual basis:

- 10518 • Vitals, DRE
- 10519 • time to cancer diagnosis;
- 10520 • Gleason score progression;
- 10521 • time to intervention on active surveillance;
- 10522 • time on active surveillance;
- 10523 • results of PSA tests.
- 10524 • Optional sample collection (blood, urine)
- 10525
- 10526 • Time to follow up biopsy and/or mpMRI if performed (see follow up
- 10527 guidelines)
- 10528 ○ Indication for follow up biopsy
- 10529 ○ Was MRI performed prior to follow up biopsy

10530 ○ Was the biopsy systematic, targets only or both systematic + targets,
10531 not done because of negative mpMRI

10532

10533

10534 Follow-up will cease once treatment beyond active surveillance is undertaken
10535 (prostatectomy, radiation therapy, focal therapy, etc.).

10536

10537 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
10538 will have an additional MRI at Visit 8.

10539

10540 **12. Randomization**

10541 **12.1 Randomization Procedure**

10542 Written informed consent will be obtained from all eligible subjects prior to
10543 commencing any study related procedures. The Ontario Clinical Oncology Group
10544 (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre,
10545 Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate
10546 subject randomization. Subjects will be allocated to the two treatment arms in an
10547 approximate 1:1 ratio by use of a dynamic allocation scheme[47].

10548

10549 After documentation of written informed consent and confirmation of subject
10550 eligibility, clinical centres will randomize the subject by accessing the CMC's web-
10551 based Interactive Registration/Randomization System (IRIS). Prior to randomization
10552 and treatment allocation, the subjects' individualized risk of high-grade prostate
10553 cancer, obtained using the PCPTRC 2.0 calculator found at
10554 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> must be determined.

10555 **12.2 Stratification**

10556 Eligible, consenting subjects will be stratified by: (1) individualized risk of high-grade
10557 prostate cancer (5% to 25%, >25%); and (2) clinical centre

10558 **12.3 Blinding and measures taken to avoid bias**

10559 This study is unblinded, and all subjects will be aware of the treatment that they are
10560 receiving. As the MRI scan is unique to one of the arms it will not be possible to blind
10561 the participants or investigators as to what intervention is being received. Therefore,
10562 participants will be informed which arm they have been allocated to. Where
10563 possible, the data will be coded so as to blind individuals analyzing the data from
10564 which of the groups the data was from. Summary details of randomized allocation
10565 and outcomes will not be made available (unless specifically authorized by the Trial
10566 Steering Committee and/or Data Monitoring Committee) in order to maintain the
10567 overall blind of the trial.

10568

10569 Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be
10570 aware that the subject is part of the trial.

10571 Pathologists will be blinded to the cohort allocation. Concealment may be
10572 challenging due to the different number of cores in the two groups, but this is
10573 unavoidable. This is unlikely to represent a significant source of bias.

10574

10575

10576 **13. Data**

10577

10578 Type of data to be collected:

- 10579 • EQ-5D–5L questionnaires. These will measure quality of life and which will be
- 10580 measured at specific times throughout the trial.
- 10581 • Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and
- 10582 continuous data
- 10583 • MRI – diagram representing MRI; categorical data for areas and scores of
- 10584 suspicion (e.g. Sector 1p, score of suspicion 4/5)
- 10585 • MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and
- 10586 continuous data
- 10587 • Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers
- 10588 yes/no)
- 10589 • Treatment decisions – categorical data (e.g. radical treatment)
- 10590 • PSA – continuous data (e.g. value of PSA in ng/ml)

10591

10592 Please see **Appendix1** for the time window for data collection.

10593

10594 **14. Statistical Considerations**

10595 **14.1 Sample Size Calculation**

10596 **STATISTICAL methods**

10597 **Primary Analysis**

10598 Absolute differences in the proportion of clinically significant cancer detected

10599 between arms will be calculated and compared using the Clopper-Pearson method.

10600 If the lower boundary of an one-sided, 97.5% confidence interval for the difference

10601 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less

10602 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower

10603 bound is greater than zero, superiority can be claimed.

10604

10605 A supportive analysis will be performed by using a logistic regression model,

10606 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification

10607 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of

10608 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower

10609 bound was calculated to approximate an absolute 5% difference of interest (NOTE:

10610 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

10611

10612 **Secondary Analyses**

10613 For each secondary outcome, where appropriate, a difference in proportions with

10614 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

10615 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for

10616 time-to-event outcomes.

10617

10618 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
10619 differences between allocation arms in secondary outcomes. Logistic regression and
10620 Cox proportional hazards regression will be used to examine the effect of allocation
10621 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
10622 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
10623 adjustments will be made due to multiple testing, however, results for secondary
10624 outcomes will be interpreted cautiously, acknowledging that tests were performed
10625 on secondary outcomes and numerous secondary tests were performed. Figures and
10626 tables will be used to illustrate results of interest.

10627

10628 **Treatment Allocation and Stratification**

10629 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
10630 use of a dynamic allocation scheme. Specifically, the first 20 subjects will be
10631 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a
10632 biased coin method will be used, whereby the number of subjects within each
10633 stratum will be calculated, and the next eligible subject will be allocated (with
10634 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
10635 allocation to each arm will occur with probability $p=0.5$.

10636

10637 Stratification

10638 For treatment allocation, the subjects' individualized risk of high-grade prostate
10639 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
10640 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
10641 subjects will be stratified by:

- 10642 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);
- 10643 (2) clinical centre.

10644

10645 **Sample Size**

10646 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
10647 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
10648 50% from another study [36].

10649

10650 Rates of clinically significant cancer detection from one the largest studies of
10651 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
10652 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will
10653 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
10654 systematic TRUS guided biopsy.

10655

10656 For this study, it will be conservatively hypothesized that systematic TRUS guided
10657 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
10658 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
10659 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
10660 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
10661 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
10662 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
10663 choice of 5% as the margin of non-inferiority represents a difference that would be
10664 considered clinically important.

10665

10666 Thus total men required in study = **422**.

10667

10668 To account for potential withdrawal / loss to follow up and the effect of
10669 stratification, the sample size will be inflated by 5%, and a target of **450 men** will be
10670 recruited.

10671

10672 Note that the rate of clinically significant cancers is very dependent on the
10673 population registered for this study. It is possible that fewer (or more) subjects will
10674 have clinically significant cancers than what is initially hypothesized. However, if the
10675 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
10676 biopsy detection rate is <30%) and other statistical assumptions remain as stated
10677 previously, the statistical power will increase. The minimum statistical power would
10678 be obtained if the clinically significant cancer detection rate was 45% for systematic
10679 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
10680 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
10681 rate of clinically significant cancer in the population is miss-specified, assuming an
10682 absolute difference of 10% between targeted and systematic TRUS guided
10683 biopsydetection rates, and a 5% margin of non-inferiority.

10684

10685 **Statistical Conventions**

10686 For categorical data, tables will be presented showing the n and percentage
10687 (n/N*100%) of subjects. Analyses will be presented by study allocation arm
10688 separately.

10689

10690 Duration of time will be described in either years, months or weeks, and calculated
10691 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or
10692 X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date –
10693 date of birth + 1)/365.25.

10694

10695 Transformations of the data in order to meet statistical assumptions may be
10696 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
10697 assess any of the model fittings. All the statistical analysis will be carried out using
10698 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-
10699 project.org) or higher.

10700

10701 **Missing Data**

10702 Missing values for the primary endpoint will be examined closely. Sources and
10703 reasons for the absence of data incurred as a result of subjects lost-to-follow up,
10704 dropouts, and intermittent missing values will be described and explored by various
10705 summary statistics as well as graphical displays between the two allocation arms.
10706 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
10707 those subjects will be described by allocation arm and tested using Fisher's exact
10708 tests or Wilcoxon rank sum tests.

10709

10710 Missing data for secondary endpoints will be described. The methods for evaluating
10711 missing data of the primary endpoint may be employed for endpoints of interest. For
10712 summarization of baseline data, the following conventions will be used for partial
10713 missing date information occurring prior to randomization (e.g. for medical history

10714 or prior treatment). If year is missing, the date will be set at missing. If year is
10715 available, but month and date is missing, the month and date will be set to July 1st of
10716 the respective year. If date is missing, but year and month available, the day will be
10717 set to the 15th of the respective month.

10718 **14.2 Interim Analyses**

10719

10720 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
10721 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
10722 conduct if there are concerns about subject safety or futility. Unless otherwise
10723 specified by one of these bodies, a futility analysis will be performed after
10724 approximately 200 subjects are enrolled and have their primary outcome
10725 ascertained. Simulation will be used to estimate the conditional probability of futility
10726 assuming the study was to continue to completion, and assuming the clinically
10727 significant cancer detection rate is 30% in both arms. If the conditional probability is
10728 0.95 or higher that continuation of the study will result in a negative result, the
10729 DSMC will recommend a suspension of recruitment to the trial, and initiation of a
10730 quality assurance review. A decision to permanently close the study or continue with
10731 accrual will be determined by the Steering Committee, based on the results of the
10732 quality assurance review, and the recommendation of the DSMC.

10733

10734 **Timing of Final Analysis**

10735 A single, final, analysis will occur after all subjects have undergone their initial biopsy
10736 and all data related to the initial biopsy is documented and validated. Follow-up
10737 analyses will be conducted after all subjects have completed two years of follow-up.

10738 **14.3 Populations:**

10739 The per protocol, study population will consist of all subjects who satisfy all eligibility
10740 criteria and are randomized to the study, who undergo MPMRI-TB or systematic
10741 TRUS guided biopsy and have their primary outcome measured. This population will
10742 be used for the primary analysis of non-inferiority.

10743 The intent-to-treat (ITT) population will consist of all subjects randomized to the
10744 study, regardless of any protocol violations or if they do not complete the study as
10745 defined in the protocol. The ITT population will be used as a supportive analysis of
10746 the primary analysis, for all safety analyses, and for any analysis investigating
10747 superiority.

10748 **14.4 Primary Outcome**

10749 **14.4.1 Detection rate of clinically significant cancer**

10750 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will
10751 be calculated based on histology results from biopsy procedures. Analysis will be on
10752 the intention to treat population.

10753

10754 Absolute differences in proportion of clinically significant cancer detected between
10755 arms will be calculated and compared. If the lower boundary of the 97.5%
10756 confidence interval for the difference in detection rates of MPMRI-TB compared to

10757 systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-
10758 inferior. In the event that the lower bound is greater than zero, superiority can be
10759 claimed.

10760

10761 The primary analysis will be conducted once all subjects have completed visit 4,
10762 when the results of the biopsy or MRI are given to the subject.

10763

10764 **14.5 Secondary Outcomes**

10765 For each secondary outcome, where appropriate, a difference in proportions with
10766 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

10767

10768 **14.5.1 Proportion of men in each arm with clinically insignificant 10769 cancer detected**

10770 The proportion of men in each arm with clinically insignificant cancer (Gleason <7)
10771 will be calculated based on histology results from biopsy procedures. In addition, the
10772 numbers with clinically insignificant cancer identified by MRI alone will also be
10773 included.

10774

10775 **14.5.2 Proportion of men in each arm with Gleason $\geq 4+3$ detected**

10776 The proportion of men in each arm with Gleason $\geq 4+3$ will be calculated based on
10777 histology results from biopsy procedures. In addition, the numbers with clinically
10778 insignificant cancer identified by MRI alone will also be included.

10779

10780 **14.5.3 Proportion of men in MPMRI arm who avoid biopsy.**

10781

10782 **14.5.4 Proportion of men in the MRI arm whom the PI-RADS score for 10783 suspicion of clinically significant cancer was 3, 4 or 5 but no clinically 10784 significant cancer was detected.**

10785 The proportion of men in each arm whom the PI-RADS score for suspicion of
10786 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
10787 detected, will be calculated based on histology results from biopsy procedures.

10788

10789 **14.5.5 Proportion of men in each arm who go on to definitive local 10790 treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or 10791 systemic treatment (e.g. hormone therapy, chemotherapy)**

10792

10793

10794

10795 **14.5.8 Proportion of men with a negative MRI who progress within 24 10796 months after their study MRI, or who are upgraded within 24 months**

10797 Men with a negative MRI who do not undergo a biopsy will have a follow-up MRI 2
10798 years after their study MRI. We will determine the proportion of men whose
10799 subsequent MRI shows a PI-RADS 3 or greater lesion. The results of targeted biopsy

10800 of those lesions will be recorded and analyzed. The number of men who are
10801 upgraded to Gleason ≥ 7 due to an off-protocol biopsy will also be recorded.
10802

10803 **14.5.9 Proportion of men with post-biopsy adverse events**

10804 Immediate post-biopsy discomfort and pain will be characterized by intensity using
10805 the numerical analogue score. Scores for each arm will be compared. 30-day biopsy
10806 specific complications and adverse events will be characterized according to their
10807 presence, absence, duration and how much of a problem the symptoms caused the
10808 subject. Whether the subject had contact with health care providers/system will also
10809 be recorded. The proportion of individuals experiencing each symptom, proportion
10810 in whom that symptom caused a problem and proportion who had contact with
10811 healthcare providers/system will be calculated and compared qualitatively between
10812 arms utilizing classification systems validated in previous studies [39]. The biopsy
10813 specific complications that will be compared include pain, urinary retention, fever,
10814 pain, erectile dysfunction, urinary incontinence, haematuria, haematochezia
10815 and haematospermia.

10816
10817 Any post-biopsy complications up to 30-days post biopsy procedure will be tabulated
10818 and listed by duration and management.
10819

10820 **14.5.10 Health related quality of life**

10821 EQ-5D-5L descriptive domain summary indices and visual analogue scores will be
10822 assessed at baseline, at 2 years and changes will be compared between arms.
10823

10824 EQ-5D was selected as a simple, low burden quality of life instrument that will
10825 provide validated information on symptoms, particularly anxiety, that could be
10826 compared across disease states and studies. Other subject-reported outcomes
10827 directly linked to the interventions will be captured in the post-biopsy surveys. Since
10828 it provides utilities, these will be incorporated into a secondary economic analysis if
10829 the results permit.
10830

10831 **14.5.11 Proportion Gleason score upgrading in men undergoing radical 10832 prostatectomy**

10833 Of the men who undergo radical prostatectomy, the proportion who have cancer
10834 upgraded from the biopsy histopathology to the radical prostatectomy
10835 histopathology in each arm will be calculated and compared.
10836

10837 **14.5.12 Cost Outcomes**

10838 As the study design for clinical outcomes is one of non-inferiority, the primary
10839 economic analysis will be **cost minimization analysis**. The perspective of the
10840 economic analysis will be that of the public payer. The primary goal of the analysis
10841 will be to support arguments for public funding. Thus the costs of participant
10842 burden, logistical challenges, and expense of obtaining societal costs, will not be
10843 evaluated.
10844

10845 **14.5.12.1 Data collection:**

10846 As part of the informed consent process, participants in Ontario will also
10847 consent to having their Ontario Health Insurance Number recorded, to be
10848 later transferred to the Institute for Clinical Evaluative Sciences (ICES) where
10849 it will be linked to a number of administrative claims databases recording
10850 health system resource utilization such as physician billing [Ontario Health
10851 Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization
10852 and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug
10853 Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity
10854 Level Reporting (ALR)]; clinic and emergency department visits [National
10855 Ambulatory Care Reporting System (NACRS), Emergency Department visits];
10856 radiation (ALR); homecare (Home Care databases) and a few additional ones
10857 as determined necessary (e.g., Long-term care, Mental Health, Diabetes. The
10858 overall, number and proportion of health system resources will be
10859 determined. In this way we can capture comprehensive resource utilization
10860 related to on-trial management including any adverse events.

10861 **14.5.12.2 Health Insurance number handling and security**

10862 As the economic implications of this study are of prime importance to some
10863 of the funders, the request for data linkage will be part of the main consent
10864 form. If a participant indicates to the study team that they decline or
10865 withdraw consent, the OHIP number will be recorded as 9999-999-999-XX.
10866 The OHIP numbers will stay with the participating institution until after
10867 accrual is complete, and then they will all be transferred at one time under
10868 data sharing agreements between ICES and each institution. Data will be
10869 transferred using a secure electronic file transfer system established by ICES
10870 and managed by authorized ICES personnel responsible for receiving
10871 data. The file transfer system uses security safeguards including encryption
10872 and authentication.

10873
10874 ICES is a Prescribed Entity under the Personal Health Information Protection
10875 Act (PHIPA), and can receive and use personal health information for
10876 purposes of analysis and compiling statistical information and other research.
10877 Its policies and procedures for privacy protection and data security have been
10878 approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-
10879 monitored and requiring passkeys to access private offices and
10880 computers. ICES has extensive experience in the protection of confidentiality
10881 when using such data. It has a UNIX-based network that cannot be accessed
10882 externally. ICES data facilities are fully 'moated' (no connections to other
10883 computers). At ICES, routine procedures for data backup are instituted by a
10884 data management team. The data is burned onto a CD or placed on an
10885 external hard drive and placed in a locked vault. All ICES staff and scientific
10886 affiliates are required to sign agreements of confidentiality annually. Internal
10887 audits are conducted to monitor compliance with ICES policies, standards and
10888 procedures.

10889
10890 Study data with direct personal identifiers such as OHIP numbers will
10891 reside on a dedicated and secure server at ICES and will only be
10892 accessible by a named Data Covenantor. The Covenantor will encode

10893 the OHIP number, replacing it with an ICES key number (IKN) (a code)
10894 and transferring it to a “moated” server for the study project. (The
10895 Data Covenantor is an ICES person named in our data sharing
10896 agreements and identified to the Office of the Information and
10897 Privacy Commissioner, who can access personal health information at
10898 ICES for the purposes of receiving, coding, transferring or destroying
10899 personal health information.) The coded study data will only be made
10900 available to the Principal Investigator and project staff directly
10901 responsible for data analysis (under the supervision of the
10902 investigator). No subject, physician or institution will be identified in
10903 the reporting of results
10904

10905 **14.5.12.3 Cost calculation**

10906 Once the utilization of health services is determined from those cases linked
10907 to administrative databases, publicly available costs (2016\$CAN) will be
10908 applied to health services. Costs for physician and laboratory services will be
10909 determined by applying that year’s fee code. Costs for hospital care will be
10910 estimated using the Canadian Institute for Health Information (CIHI) Resource
10911 Intensity Weight method for the most recently available year. Outpatient
10912 prescription drug costs for participants not covered by ODB (those under age
10913 65 and not on social assistance) will be considered to be the same as the trial
10914 arm-specific average for those with coverage. Costs will then be inflated
10915 using the healthcare-specific Consumer Price Index reported by Statistics
10916 Canada into constant Canadian dollars for the year the study ends. Due to the
10917 short time horizon, discounting will not be applied.

10918 **14.5.12.4 Primary Analysis**

10919 A within-trial analysis will be conducted to calculate the total cost for each
10920 arm and mean cost per subject for each arm. Frequency distributions and
10921 measures of central tendency (e.g. means and medians) will be determined
10922 for each resource category (e.g. hospitalizations) for each arm of the study.
10923 Confidence intervals for the difference in costs and resource utilization
10924 between the strategies overall and for each resource category will also be
10925 calculated. Univariate comparisons between the groups will be made
10926 primarily using nonparametric tests, such as Wilcoxon rank-sum test. In the
10927 primary analysis, assuming equivalence in the primary outcome, an arm with
10928 significantly lower mean costs will be considered the economically most
10929 attractive approach.

10930
10931 Should the clinical trial find a difference between the two arms on the
10932 primary endpoint, an incremental cost-benefit analysis will be calculated by
10933 deriving the additional cost per case of clinically significant cancer diagnosed,
10934 according to the following equation:

10935

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\quad}$$

10936 The cost of avoiding each additional case of clinically insignificant cancer
10937 diagnosed may also be similarly calculated. Consideration will be given to
10938 extending this analysis using economic modeling with incorporation of utility
10939 values from the EQ-5D to allow a lifetime perspective to be taken and the
10940 estimation of quality adjusted life years (QALYs).

10941 **14.5.12.5 Secondary Cost Analyses**

10942 One and multi-way sensitivity analyses will be carried out around major cost
10943 drivers by varying the costs over their observed ranges and conducting
10944 threshold analyses where appropriate. Sensitivity analyses will also be
10945 performed to evaluate potential limitations in the data, such as ODB costs as
10946 described above (though the proportion without ODB coverage should be
10947 similar in the two arms, and it is not expected to be a major cost-driver).

10948

10949

10950

10951 **14.5.13 Missing Data**

10952 The impact of missing data will be explored in all analyses; sensitivity
10953 analyses/multiple imputation will be performed as appropriate.

10954

10955 **15. Participant compliance and withdrawal**

10956

10957 The study will be completed when at least 422 subjects have been randomized, have
10958 undergone a diagnostic test and completed follow up. Compliance to randomized
10959 treatment will be assessed by monitoring the completed forms, e.g. the systematic
10960 TRUS guided biopsy form or the MRI-targeted biopsy form.

10961

10962 In consenting to the study, subjects are consenting to study monitoring, imaging and
10963 biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to
10964 withdraw consent at any stage and their care will not be affected in any way. All
10965 communication surrounding the withdrawal and its reasons should be noted in the
10966 subject's record. Such cases should be reported to the PRECISE Study Operations
10967 Office. Data up to the time of withdrawal can be included in the study.

10968

10969 As the study diagnostic tests are for suspected cancer it is not anticipated that there
10970 will be significant loss to follow up.

10971

10972 **15.1 Subject Withdrawal from Study**

10973 A subject may discontinue participation in this study at any time at the investigator's
10974 discretion or at the request of the subject.

10975

10976 If a subject discontinues at or before Visit 1 (randomization), he is not required to
10977 complete end of study assessments.

10978

10979 If a subject discontinues after Visit 1 (randomization) for any reason, the investigator
10980 should make every effort to complete the activities bulleted below.
10981
10982 • End of study assessments as outlined in **Section 10.17**.
10983 • Any occurrence of death, prostatic surgical intervention, non-surgical treatment
10984 for prostate cancer after study withdrawal should be documented in the CRF and
10985 source documents.
10986
10987 Subjects who are discontinued from the study after randomization will not be
10988 replaced. Subjects withdrawn from the study retain their subject number if already
10989 given. New subjects will be allocated a new subject number.
10990
10991 In the event that a subject is prematurely discontinued from the study at any time
10992 due to an AE, the procedures describe in **Section 16.3** must be followed.
10993
10994 Subjects should be withdrawn from the study for any of the following criteria:
10995 • Non-compliance with the requirements of the study.
10996 • Request to discontinue treatment. This request can be made by either the
10997 subject or the investigator.
10998 • Develops progressive disease.
10999

11000 **15.2 Study completion**

11001 The primary end point will be reached when the last subject entered has their
11002 systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be
11003 followed for up to 2 years following study entry or until they have radical treatment.
11004 Subjects who are found to have significant prostate cancer and are treated will not
11005 be included in follow up for this period. This includes subjects diagnosed as part of
11006 study protocol, and subjects diagnosed during the follow up period by standard-of-
11007 care procedures. However, post MRI/biopsy questionnaires will not be required
11008 following non-protocol based procedures.
11009

11010 **16. Data Monitoring, Quality Control and Safety**

11011 **16.1 Stopping / discontinuation rules**

11012 The study will be completed when 450 participants have been randomized,
11013 undergone a diagnostic test and completed follow up.
11014

11015 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
11016 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
11017 conduct if there are concerns about subject safety or futility. See Section 14.2.1 for
11018 further details on the interim analysis. Appropriate documentation as per the PI's
11019 requirement will be completed if stopping the trial is necessary and the ethics
11020 committee will be informed.
11021

11022 As the study is unblinded there will be no need for randomization code breaks.
11023

11024 **16.2 Monitoring, quality control and assurance**

11025

11026 Members of the trial team will be Good Clinical Practice (or equivalent) trained.

11027

11028 An independent DSMC will be appointed to monitor subject safety and the rate of
11029 recruitment of subjects in the study. They will meet at least once a year whilst the
11030 trial is ongoing for routine review of safety data and trial progression. They have the
11031 power to call additional meetings and review data at any point in the trial should
11032 they wish to do so.

11033

11034 The PI may also arrange an independent trial monitor to review the study data.

11035 **16.3 Assessment of safety**

11036 The investigator is responsible for the detection and documentation of events
11037 meeting the criteria and definition of an AE or SAE as provided in this protocol.

11038 During this study, when there is a safety evaluation, the investigator or site staff will
11039 be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

11040 **16.3.1 Definition of an Adverse Event (AE)**

11041 Adverse events (AE) will be defined as “any untoward medical occurrence in a
11042 clinical trial subject undergoing any intervention in the trial, which does not
11043 necessarily have a causal relationship with this treatment”.

11044

11045 Only adverse events specific to biopsy-related complications including pain, fever,
11046 hematuria, hematochezia, hematospermia, urinary retention and urinary
11047 incontinence will be recorded. Any other adverse events will not be recorded. Please
11048 refer to section 16.3.6 of the protocol.

11049 **16.3.2 Definition of a Serious Adverse Event (SAE)**

11050 Serious adverse events (SAE) will be defined as “any untoward medical occurrence as
11051 a result of any intervention in the trial that:

11052 **(a) results in death**

11053 **(b) is life-threatening**

11054 The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which
11055 the subject was at risk of death at the time of the event. It does not refer to an
11056 event, which hypothetically might have caused death, if it were more severe.

11057 **(c) requires hospitalisation or prolongation of existing hospitalisation**

11058 In general, hospitalization signifies that the subject has been detained (usually
11059 involving at least an overnight stay) at a hospital or emergency ward for observation
11060 and/or treatment that would not have been appropriate in the physicians’ office or
11061 outpatient setting. Complications that occur during hospitalization are AEs. If a
11062 complication prolongs hospitalization or fulfils any other serious criteria, the event is
11063 serious. When in doubt as to whether ‘hospitalization’; occurred or was necessary,
11064 the AE should be considered serious. Hospitalization for elective treatment of a pre-
11065 existing condition that did not worsen form baseline is not considered an AE.

11066 **(d) results in disability / incapacity**

11067 The term disability means substantial disruption of a person’s ability to conduct
11068 normal life functions. This definition is not intended to include experiences of
11069 relatively minor medical significance such as uncomplicated headache, nausea,
11070 vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may
11071 interfere or prevent everyday life functions but do not constitute a substantial
11072 disruption.

11073 **(e) is a congenital abnormality/birth defect.**

11074 Medical or scientific judgement should be exercised in deciding whether reporting is
11075 appropriate in other situations, such as important medical events that may not be
11076 immediately life threatening or result in death or hospitalization but may jeopardise
11077 the subject or may require medical or surgical intervention to prevent one of the
11078 outcomes listed in the above definition. These should also be considered serious.
11079 Examples of such events are invasive or malignant cancers, intensive treatment in an
11080 emergency room or at home for allergic bronchospasm, blood dyscrasias or
11081 convulsions that do not result in hospitalization, or development of drug
11082 dependence or drug abuse.

11083 **16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs**

11084 An event which is part of the natural course of the disease under study (i.e., disease
11085 progression) does not need to be reported as a serious adverse event. Progression of
11086 the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death
11087 due to progressive disease is to be recorded on 'Record of Death' CRF page and not
11088 as an SAE. However, if the progression of the underlying disease is greater than that
11089 which would normally be expected for the subject, or if the investigator considers
11090 that there was a causal relationship between treatment with study medication or
11091 protocol design/procedures and the disease progression, then this must be reported
11092 as an SAE. Any new primary cancer must be reported as an SAE.

11093 **16.3.4 Lack of Efficacy**

11094 “Lack of efficacy” will not be reported as an AE. The signs and symptoms or clinical
11095 sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE
11096 definition (including clarifications).

11097 **16.3.5 Clinical Laboratory Abnormalities and Other Abnormal 11098 Assessments as AEs and SAEs**

11099 Abnormal laboratory findings or other abnormal assessments that are judged by the
11100 investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet
11101 the definition of an AE or SAE. Clinically significant abnormal laboratory findings or
11102 other abnormal assessments that are detected during the study or are present at
11103 baseline and significantly worsen following the start of the study will be reported as
11104 AEs or SAEs. However, clinically significant abnormal findings or other abnormal
11105 assessments that are associated with the disease being studied, unless judged by the
11106 investigator as more severe than expected for the subject’s condition or that are
11107 present or detected at the start of the study and do not worsen, will not be reported
11108 as AEs or SAEs.
11109

11110 The trial interventions are routinely carried out in clinical practice for investigation of
11111 suspected cancer and the risks of the interventions are therefore not any greater
11112 than if a man was not part of the trial. The risks of the procedures are relatively low,
11113 as detailed in Section 11.

11114
11115 The investigator will exercise his or her medical and scientific judgment in deciding
11116 whether an abnormal laboratory finding or other abnormal assessment is clinically
11117 significant.

11118 **16.3.6 Recording/Reporting AEs and SAEs**

11119 The AE reporting period for this study begins at randomization and
11120 will be recorded until 30-days post-biopsy. In the event that the subject does not
11121 undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

11122
11123 Only adverse events specific to biopsy-related complications including pain, fever,
11124 hematuria, hematochezia, hematospermia, urinary retention and urinary
11125 incontinence will be recorded. Any other adverse events will not be recorded.

11126
11127 AEs will be recorded by a member of the research team or clinical team on an AE
11128 report form. All SAEs must be recorded on a SAE report form. SAE report forms
11129 should be sent to the CTG who will keep a log of AEs and SAEs. AE and SAE logs will
11130 be reviewed by the DSMC.

11131
11132 For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or
11133 DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria
11134 as a SAE, will be collected and reported.

11135
11136 Expected AEs includes the following:

- 11137 • Pain
- 11138 • Blood in the urine
- 11139 • Blood in the semen
- 11140 • Blood in the stool or back passage
- 11141 • Erectile dysfunction
- 11142 • Urinary incontinence
- 11143 • Urinary tract infection
- 11144 • Fevers

11145
11146 In addition, small risks of allergic reactions are associated with the intravenous
11147 administration of gadolinium, the contrast agent used in MRI scans, as described in
11148 section 10.18.1.2. This contrast agent is used consistently in MRI scanning and is not
11149 limited to this trial.

11150
11151 If any of these symptoms are accompanied by events consistent with the definition
11152 of an SAE as specified above, then the event will be considered an SAE.

11153
11154 The Trial Coordinator, Principle Investigator or Chief Investigator should be informed
11155 of any SAE within 24 hours.

11156 All SAE report forms must be completed and the SAE logs updated. All SAEs must be
11157 followed up until a resolution is reached (i.e. recovered, recovering, recovered with
11158 sequelae, fatal, not recovered or unknown).

11159

11160 Local sites may have specific institutional protocols for reporting SAEs, which should
11161 be followed in addition.

11162

11163 When an AE/SAE occurs, it is the responsibility of the investigator to review all
11164 documentation relative to the event. The investigator will then record all relevant
11165 information regarding an AE/SAE on the CRF.

11166

11167 The investigator will attempt to establish a diagnosis of the event based on signs,
11168 symptoms and/or other clinical information. In such cases, the diagnosis should be
11169 documented as the AE/SAE and not the individual signs/symptoms.

11170 **16.3.7 Evaluating AEs and SAEs**

11171 **16.3.7.1 Assessment of Intensity**

11172

11173 The investigator will make an assessment of intensity for each AE and SAE reported
11174 during the study. Degree of severity and change in severity will be recorded by
11175 means of National Cancer Institute, Common Terminology Criteria for Adverse
11176 Events (NCI CTCAE), version 4.03.

11177

11178 If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on
11179 the investigator's clinical judgment. The intensity of each AE and SAE recorded in the
11180 CRF should be assigned to one of the following categories:

11181

11182 **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort
11183 and not interfering with everyday activities.

11184 **Moderate:** An event that is sufficiently discomforting to interfere with normal
11185 everyday activities.

11186 **Severe:** An event that prevents normal everyday activities.

11187

11188 An event that is classified as severe should not be confused with a SAE. Severity is a
11189 category utilized for rating the intensity of an event; both AEs and SAEs can be
11190 assessed as severe.

11191 **16.3.7.2 Assessment of Causality**

11192 The investigator is obligated to assess the relationship between investigational
11193 product and the occurrence of each AE/SAE. The investigator will use clinical
11194 judgment to determine the relationship. Alternative causes and the temporal
11195 relationship of the event to the investigational product will be considered and
11196 investigated. The investigator will also consult the CIB and or Product Information,
11197 for marketed products, in the determination of his/her assessment.

11198 **16.3.8 Follow-up of AEs and SAEs**

11199 After the initial AE/SAE report, the investigator is required to proactively follow each
11200 subject and provide further information to the PI of the study, on the subject's
11201 condition.

11202

11203 All AEs and SAEs documented at a previous visit/contact and are ongoing, will be
11204 reviewed at subsequent visits/contacts.

11205

11206 All AEs and SAEs will be followed until resolution, until the condition stabilizes, until
11207 the event is otherwise explained or until the subject is lost to follow-up. Once
11208 resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will
11209 ensure that follow-up includes any supplemental investigations as may be indicated
11210 to elucidate the nature and/or causality of the AE or SAE.

11211

11212 The PI may request that the investigator perform or arrange for the conduct of
11213 supplemental measurements and/or evaluations to elucidate as fully as possible the
11214 nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a
11215 subject dies during participation in the study or during a recognized follow-up
11216 period, the PI will be provided with any post-mortem findings.

11217

11218 New or updated information will be recorded on the originally completed SAE CRF,
11219 with all changes signed and dated by the investigator or designate. The updated SAE
11220 CRF should be resent to the PI.

11221 **16.3.9 Prompt Reporting of SAEs**

11222 Once the investigator determines that an event meets the protocol definition of an
11223 SAE, the SAE will be reported to the PI (CURC) within 24 hours.

11224

11225 **16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI**

11226 The Site Investigator must immediately inform the PI (CURC) of all SAEs (within 24
11227 hours) at the following fax number: 1-416-480-6121.

11228

11229 The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing
11230 addresses is as follows:

11231 Dr. Laurence Klotz

11232 c/o Marlene Kebabdjian

11233 Sunnybrook Health Sciences Centre

11234 2075 Bayview Avenue A304

11235 Toronto, Ontario M4N 3M5 Canada

11236 Phone: (416) 480-6100 ext 2890

11237 E-mail: Laurence.Klotz@sunnybrook.ca

11238 Marlene.kebabdjian@sunnybrook.ca

11239 **16.3.9.2 Completion and Transmission of the SAE Reports**

11240 Once an investigator becomes aware that an SAE has occurred in a study subject,
11241 she/he will report the information to the PI within 24 hours. The SAE CRF will always
11242 be completed as thoroughly as possible with all available details of the event, signed

11243 by the investigator (or designee), and forwarded to the PI within the designated time
11244 frames. If the investigator does not have all information regarding as SAE, he/she will
11245 not wait to receive additional information before notifying the PI of the event and
11246 completing the form. The form will be updated when additional information is
11247 received.

11248
11249 The investigator will always provide an assessment of causality at the time of the
11250 initial report as described in Section 16.3.6.2.

11251 **16.3.10 Post-study AEs and SAEs**

11252 If the investigator learns of any SAE at any time after a subject has been discharged
11253 from the study, and such event(s) is (are) reasonably related to the study
11254 intervention, the investigator should promptly notify the PI (CURC).

11255

11256 **17. Study Administration**

11257 **17.1 Regulatory and Ethical Considerations**

11258 An important consideration is that men are being randomized to one of two biopsy
11259 techniques when it is not known which will be more effective in diagnosing clinically
11260 significant prostate cancer. Both diagnostic tests are currently used in everyday
11261 clinical practice at the institutions involved in the trial. Though systematic TRUS
11262 guided biopsy could be considered standard of care, there is enough evidence to
11263 support the concept that MPMRI-targeted biopsy may be as effective, if not more so,
11264 than systematic TRUS guided biopsy[27]. This study aims to confirm this.

11265 **17.1.1 Ethical Conduct of the Study and Ethics Approval**

11266 The PI and each participating site will obtain approval to conduct the study from the
11267 Research Ethics Board (REB) prior to initiating the study.

11268

11269 Participating sites from Ontario will use the Ontario Cancer Research Ethics Board
11270 (OCREB) as their Board of Record.

11271 This study will be conducted in accordance with 'good clinical practice' (GCP) and all
11272 applicable regulatory requirements, including where applicable, the 2013 version of
11273 the Declaration of Helsinki.

11274

11275 The investigator is responsible for ensuring that this protocol, the site's informed
11276 consent form and any other information that will be present to potential subjects
11277 are reviewed and approved by the appropriate REB. The investigator agrees to allow
11278 the REB direct access to all relevant regulatory documents. The PI will provide the
11279 site investigator(s) with relevant document(s)/data that are needed for REB review
11280 and approval of the study. Before CRFs can be shipped to the site, the PI must
11281 receive copies of the REB approval, the approved informed consent form and any
11282 other information that the REB has approved for presentation to potential subjects.

11283

11284 If the protocol, the informed consent form or any other information that the REB has
11285 approved for presentation to potential subjects is amended during the study, the
11286 site investigator(s) is responsible for ensuring the REB reviews and approves, where

11287 applicable, these amended documents. The site investigator(s) must follow all
11288 applicable regulatory requirements pertaining to the use of an amended informed
11289 consent form including obtaining the REB approval of the amended form before new
11290 subjects consent to take part in the study using this version of the form. Copies of
11291 the REB approval of the amended informed consent form/other information and the
11292 approved amended informed consent form/other information must be forwarded to
11293 the PI promptly.

11294 **17.1.2 Informed Consent**

11295 Informed consent will be obtained before the subject can participate in the study.
11296 The contents and process of obtaining informed consent will be in accordance with
11297 all applicable regulatory requirements.

11298
11299 The subject's consent to participate in the study should be obtained after a full
11300 explanation has been provided of the procedures to be given. Subjects should be
11301 given sufficient time (at least 24 hours) after being given the study subject
11302 information sheet to consider and discuss participation in the study with family and
11303 friends.

11304
11305 A contact number will be given to the subject should he wish to discuss any aspect of
11306 the study. Following this, the clinician will determine that the subject is fully
11307 informed of the study and their participation, in accordance with Good Clinical
11308 Practice Guidelines. Subjects will always be asked to sign a consent form. One copy
11309 will be given to the subject, one copy will be kept with subject's hospital notes and
11310 one copy should be kept in the local investigator's file.

11311 **17.1.3 Investigator Reporting Requirements**

11312 The investigator is responsible for reporting SAEs to the REB in accordance with all
11313 applicable regulations. Furthermore, the investigator may be required to provide
11314 periodic safety updates on the conduct of the study at his or her site and notification
11315 of study closure to the REB.

11316 **17.2 Study Monitoring**

11317 This study will be monitored by a CRA. The CRA will contact the sites by telephone
11318 on a predetermined basis and would conduct a monitoring visits based on the data
11319 entered in the EDC and queries.

11320
11321 During these contacts, the monitor will:

- 11322 • Check the progress of the study
- 11323 • Review study data collected
- 11324 • Conduct source document verification
- 11325 • Identify any issues and address their resolution

11326
11327 This will be done in order to verify that the:

- 11328 • Data are authentic, accurate and complete
- 11329 • Safety and rights of subjects are being protected
- 11330 • Study is conducted in accordance with the currently approved protocol (and

11331 any amendments), GCP and all applicable regulatory requirements

11332

11333 The investigator agrees to allow CRA personnel direct access to all relevant
11334 documents and to allocate his/her time and the time of his/her staff to CRA
11335 personnel to discuss findings and any relevant issues.

11336 **17.3 Quality Assurance**

11337 To ensure compliance with GCP and all applicable regulatory requirements,
11338 regulatory agencies may conduct a regulatory inspection of the study. Such
11339 audits/inspections can occur at any time during or after completion of the study. If
11340 an audit or inspection occurs, the investigator and institution agree to allow the
11341 auditor/inspector direct access to all relevant documents and to allocate his/her
11342 time and the time of his/her staff to the auditor/inspector to discuss findings and
11343 any relevant issues.

11344 **17.4 Study and Site Closure**

11345 Upon completion of the study, the site investigator(s) will conduct the following
11346 activities:

- 11347 • Return of all study data to the Sponsor (CURC)
- 11348 • Submission of all study data and data queries to OCOG
- 11349 • Review of site study records for completeness

11350

11351 In addition, the Principal Investigator has the right to temporarily suspend or
11352 prematurely discontinue this study either at a single site or at all sites at any time for
11353 reasons including but not limited to, safety or ethical issues or severe non-
11354 compliance. If the PI determines such action is needed, the PI will discuss this with
11355 the site investigator (including the reasons for taking such action) at that time. When
11356 feasible, the PI will provide advance notification to the site investigator of the
11357 impending action prior to it taking effect.

11358

11359 Individual site Investigators may also terminate their participation in the study at any
11360 time. If the investigator determines such action is needed, the investigator will
11361 discuss this with the PI(including the reasons for taking such action) at that time.
11362 When feasible, the investigator will provide advance notification to the PI of the
11363 impending action prior to it taking effect.

11364

11365 The PI will promptly inform all other investigators and/or institutions conducting the
11366 study if the study is suspended or terminated for safety reasons and will also inform
11367 the regulatory authorities of the suspension or termination of the study and the
11368 reason(s) for the action. If required by applicable regulations, the investigator must
11369 inform the REB promptly and provide the reason for the suspension or termination.

11370

11371 If the study is prematurely discontinued, all study data must be returned to the PI. In
11372 addition, the investigator has the responsibility to return any used/unused clinical
11373 supplies.

11374

11375 Financial compensation to investigators and/or institutions will be in accordance
11376 with the agreement established between the investigator and the PI.

11377 **17.5 Records Retention**

11378 Following closure of the study, the site investigator(s) must maintain all site study
11379 records in a safe and secure location. The records must be maintained to allow easy
11380 and timely retrieval when needed and whenever feasible, to allow any subsequent
11381 review of data in conjunction with assessment of the facility, supporting systems and
11382 staff.

11383
11384 The site investigator(s) will retain study records to comply with all applicable
11385 regulatory requirements. The minimum retention time will meet the strictest
11386 standard applicable to that site for the study as dictated by any institutional
11387 requirements or local laws or regulations of Health Canada standards/procedures;
11388 otherwise, the retention period will default to 25 years.

11389
11390 The site investigator(s) must inform the PI of any changes in the archival
11391 arrangements, including but not limited to the following: archival at an off-site
11392 facility, transfer of ownership of the records in the event the investigator leaves the
11393 site. The PI should be informed of this change if it affects their access to the
11394 information in case of an audit.

11395 **17.6 Data Management**

11396 Subject data are collected by the investigator or designee using the CRF within an
11397 Electronic Data Capture (EDC) system. Subject data necessary for analysis and
11398 reporting will be entered/transmitted into a validated database. Clinical data
11399 management will be performed in accordance with applicable standards and data
11400 cleaning procedures. Database lock will occur when data management quality
11401 control procedures are completed.

11402 **17.7 Publication**

11403 The results from the study will be analyzed and published as soon as possible and is
11404 appropriate. All study-related communications can only be presented or published
11405 after approval from all relevant members involved in the trial.

11406
11407 All publications shall include appropriate indication named authors as agreed on by
11408 the members involved in the trial. For the main study reports, senior and first
11409 authorship will be determined by agreement of the Chief Investigator, the Principle
11410 Investigator at time of manuscript drafting. Authorship will be based on
11411 recommendations of the International Committee of Medical Journal Editors
11412 (www.ICMJE.org) where all authors meet the following for criteria:

- 11413
11414 13. Substantial contributions to the conception or design of the work; or the
11415 acquisition, analysis, or interpretation of data for the work; AND
11416 14. Drafting the work or revising it critically for important intellectual content;
11417 AND
11418 15. Final approval of the version to be published; AND

11419 16. Agreement to be accountable for all aspects of the work in ensuring that
11420 questions related to the accuracy or integrity of any part of the work are
11421 appropriately investigated and resolved.
11422
11423 If there are no named authors (i.e. group authorship) then a writing committee will
11424 be identified that would usually include these people. The clinical trials.gov
11425 registration number that will be allocated to this trial will be attached to any
11426 publications resulting from this trial.
11427
11428 Trial funding agencies (OICR, PCC and collaborators as appropriate) will be
11429 acknowledged in all publications.
11430
11431 The members of the trial steering committee will be listed with their affiliations in
11432 the acknowledgements/appendix of the main publication.
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Appendices

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Appendix 1: Time windows for data collection

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11645 For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3

11646 For details on time windows permitted for each trial intervention to be completed

11647 please see Table 5 below.

11648

11649 Table 5: Details of time windows permitted for all trial interventions.

11650

Contact and Purpose if not clear	Time window permitted +/-30 days of scheduled visit
Visit 1 Screening (eligibility review, med hx,)	Any time following referral of subject. Ideally perform as soon as possible following receipt of referral.
Visit 1 Consent Vitals, DRE Randomization EQ-5D-5L Questionnaire (baseline) Optional blood, urine, semen and tissue sample	Complete only once subject has had 24 hours after receiving the patient information to fully consider the study. Ideally on same visit as screening. Complete at screening Immediately after consent form signed and eligibility is confirmed. Complete immediately after consent form is signed Complete after additional informed consent signed, after randomization and up until any point prior to a biopsy.
Visit 2 MRI	Only for men randomized to this arm. Any time following randomization. Ideally within 1 week of randomization.

<p>Visit 3</p> <p>MRI-Targeted Biopsy of Prostate</p>	<p>Only for men randomized to this arm who have a lesion on MRI that needs a biopsy.</p> <p>Any time following the MRI being reported, ideally within 1 week of MRI.</p> <p>Depending on local Urology service structure, an appointment for a biopsy may need to be booked at the same time as the MRI is booked (i.e. immediately after randomization) in order for a slot to be secured for a biopsy to occur in timely fashion.</p> <p>If it is determined from the MRI that a biopsy is not required then the biopsy appointment can be used instead of Visit 4 for follow up of results and treatment decision.</p>
<p>Visit 3</p> <p>Systematic TRUS guided biopsy</p>	<p>Only for men randomized to this arm.</p> <p>Any time following randomization. Ideally within 4 weeks of randomization.</p>
<p>Visit 3</p> <p>Immediate post-biopsy questionnaire</p> <p>30-day post-biopsy questionnaire</p>	<p>Should be completed and returned immediately after a biopsy, before the subject leaves the department. As long as questionnaire completed within 24 hours it will be acceptable.</p> <p>To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy.</p> <p>To be returned by post or at follow up appointment (Visit 4).</p> <p>If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as</p>

Telephone reminder	<p>possible to 30 days post-biopsy.</p> <p>At 30-days post biopsy a member of the research team will phone the subject to remind them to fill out the 30-day questionnaires</p>
<p>Visit 4</p> <p>Follow up for results And treatment Decision</p> <p>EQ-5D-5L Questionnaire</p>	<p>Should be completed as soon as possible following the availability of any pathology results. Alternatively, if a man is in the MRI arm and the MRI is negative, this follow up should occur after the availability of the MRI report. Ideally the follow up appointment should be within 6 weeks of randomization.</p> <p>Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.</p> <p>To be completed</p>
<p>Visit 5 26 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood
<p>Visit 6 1 year follow up 52 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • Vitals, DRE • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
<p>Visit 7 78 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood

Visit 8

104 week follow up visit

The following information will be obtained on an annual basis:

- Vitals, DRE
- time to cancer diagnosis;
- Gleason score progression;
- time to intervention on active surveillance;
- time on active surveillance;
- results of PSA tests.
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MPMRI-targeted biopsy will have an additional MPMRI at Visit 8. This will be followed by a targeted-biopsy if results of MRI are positive (PI-RADS 3-5).

All patients in both Arm A and B who have remained undiagnosed or untreated (on active surveillance) will have a follow up MRI 2 years after study entry.

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

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Appendix 2: MPMRI Reporting Proforma

Date of MRI scan:

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day			month			year		

Reporting Radiologist:

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Form Completion Instructions:

11661 Radiologists should annotate this diagram with up to 3 suspicious areas
11662 scoring 3 or greater on the PI-RADS v2 scale of suspicion. The three most
11663 suspicious areas should be annotated, each with the score clearly marked.
11664

11665 "T1" should be the area with the greatest degree of suspicion. If
11666 applicable, "T2" should be the area with the next greatest degree of
11667 suspicion and finally if applicable, "T3" should be the area with the next
11668 greatest degree of suspicion.

11669
11670 For each suspicious area, triaxial measurements should be recorded with
11671 all 3 measurements in orthogonal planes provided whenever possible. In
11672 the PZ, lesions should be measured on ADC. In the TZ, lesions should be
11673 measured on T2W.
11674

11675 If lesion measurement is difficult or compromised on ADC (for PZ) or T2W
11676 (for TZ), measurement should be made on the sequence that show the
11677 lesion best. For example, coronal measurements may be best performed
11678 in the peripheral zone on T2 images.
11679

11680

IMPORTANT SUBMISSION INSTRUCTIONS:

11681

11682
11683 **Please send this completed case report form and a DVD with the images AND**
11684 **completed MRI Report to:**

11685

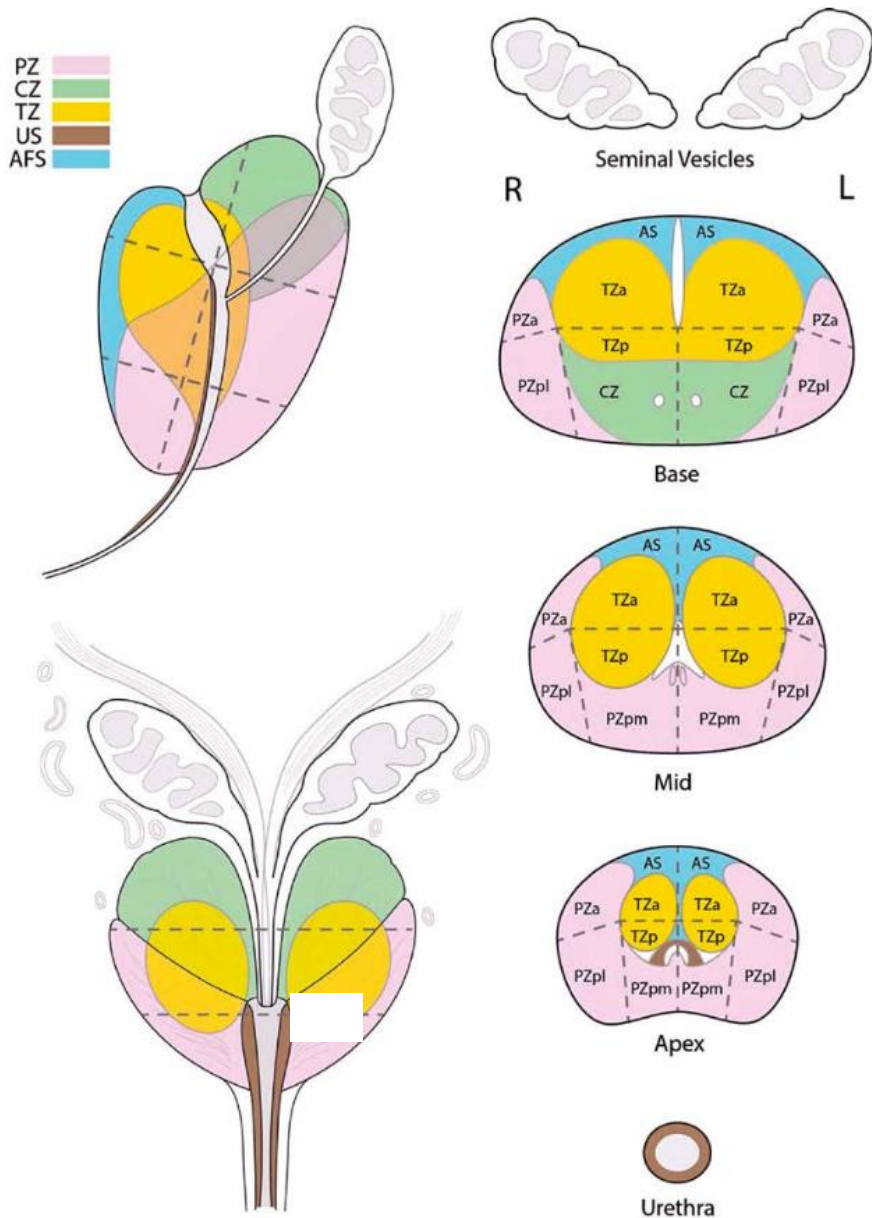
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11687 Sunnybrook Health Sciences Centre
11688 Urology Research, A304
11689 2075 Bayview Avenue, A304
11690 Toronto, Ontario, M4N 3M5

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**NO DCE (Part 1 or 2) – T2/DWI/ADC
 DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE
 PSA**

Draw lesions on diagram below annotating each with the T index (i.e T1; T2...)



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NO DCE (Part 1 or 2) – T2/DWI/ADC
**DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE
PSA**

- Image quality:** Good
(DWI + T2) Minor image quality issues (still acceptable)
 Unacceptable but some lesions seen warranting biopsy
 Unacceptable, can't interpret at all

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If image quality is not good please comment:

11756

How to record locations

11757
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11759

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

11760

Number of candidate tumor sites: _____ I

11761

If none, please proceed to Section B

11762

11763

11764

11765

Section A:

11766

Target 1 (*Highest Pi-Rads score and then largest*):

11767

Present (Y/N): _____

11768

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

11769

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

11770

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

11771

x10⁻⁶
Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

11772

Location(s) (largest to smallest area involved):

11773

_____, _____, _____, _____

11774

_____, _____, _____, _____ (as per location code
format above)

11775

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Extraprostatic extension: No Yes Equivocal _____

11779

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Target 2:

11781

Present (Y/N): _____

11782

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

11783

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

11784

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

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x10⁻⁶
Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

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11788 Location(s) (largest to smallest area involved):
 11789 _____/_____/_____/_____
 11790 _____/_____/_____/_____ (as per location code
 11791 format above)
 11792 Extraprostatic extension: No Yes Equivocal
 11793
 11794

11795 **Target 3:**

11796 Present (Y/N): _____
 11797 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____
 11798 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____
 11799 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
 11800 x10⁻⁶

11801 Size: _____x_____x_____mm (Ax1 > Ax2 x SI)
 11802 Location(s) (largest to smallest area involved):
 11803 _____/_____/_____/_____
 11804 _____/_____/_____/_____ (as per location code
 11805 format above)
 11806

11807 Extraprostatic extension: No Yes Equivocal
 11808

11809 There are more than 3 targets seen (Y/N): _____
 11810 If yes give describe:

11811 _____
 11812 _____
 11813 _____

11814 **Section B:**

LSV invasion: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal	RSV invasion: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal
Adenopathy: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal	Worst PI-RADS Score: _____

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 11823

Other Findings:

_____	(SI)	_____	(AP)	_____	(LR)	Volume:	_____	cc
cm	x	cm	x	cm				

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DCE (Part 2 or 2) – T2/DWI/ADC/DCE
VIEW DCE – YOU SHOULD NOT KNOW THE PSA

**Image quality
of DCE + DWI +
T2:**

- Good**
- Minor image quality issues (still acceptable)**
- Unacceptable but some lesions seen warranting biopsy**
- Unacceptable, can't interpret at all**

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If image quality is not good please comment:

11848

Number of candidate tumor sites: _____

11849

If none, please proceed to Section C

11850

11851

There was a change in lesions number or rank when adding DCE

11852

sequence: No Yes

11853

If Yes, please give the correspondence between Target numbers

11854

with and without DCE (i.e. Target 1 without DCE = Target x with

11855

DCE) and **fill in all fields below to avoid confusion. Also draw**

11856

lesions on diagram below again

11857

11858

Also draw lesions on diagram on next page again.

11859

11860

11861

11862

Correspondence:

11863

Old T1 = New T_____

Old T2 = New T_____

Old T3 = New

11864

T_____

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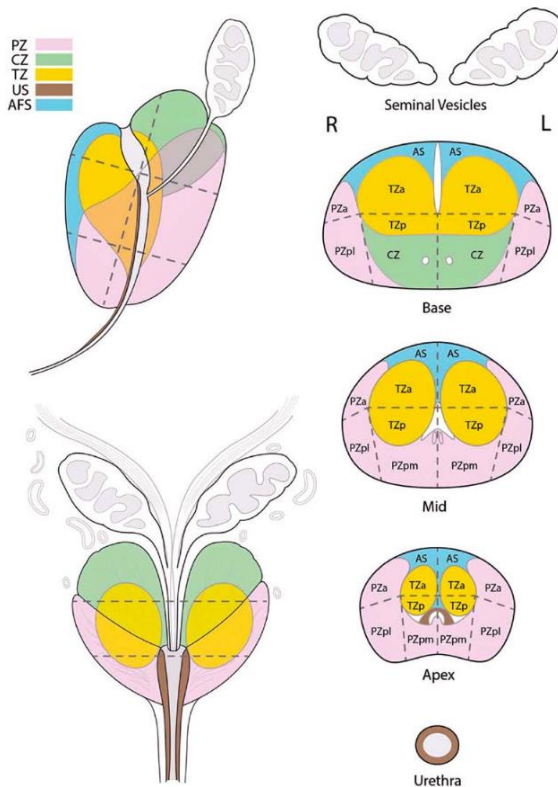
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If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2...)



11887

Target 1:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

11897

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
 x10⁻⁶

Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____, _____, _____, _____

_____, _____, _____, _____

Extraprostatic extension: No Yes Equivocal

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Target 2:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
x10⁻⁶

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____ / _____ / _____ / _____

_____ / _____ / _____ / _____

Extraprostatic extension: No Yes Equivocal

Target 3:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
x10⁻⁶

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____ / _____ / _____ / _____

_____ / _____ / _____ / _____

Extraprostatic extension: No Yes

There are more than 3 targets seen (Y/N): _____

If yes give describe:

Section C:

LSV invasion: No Yes Equivocal

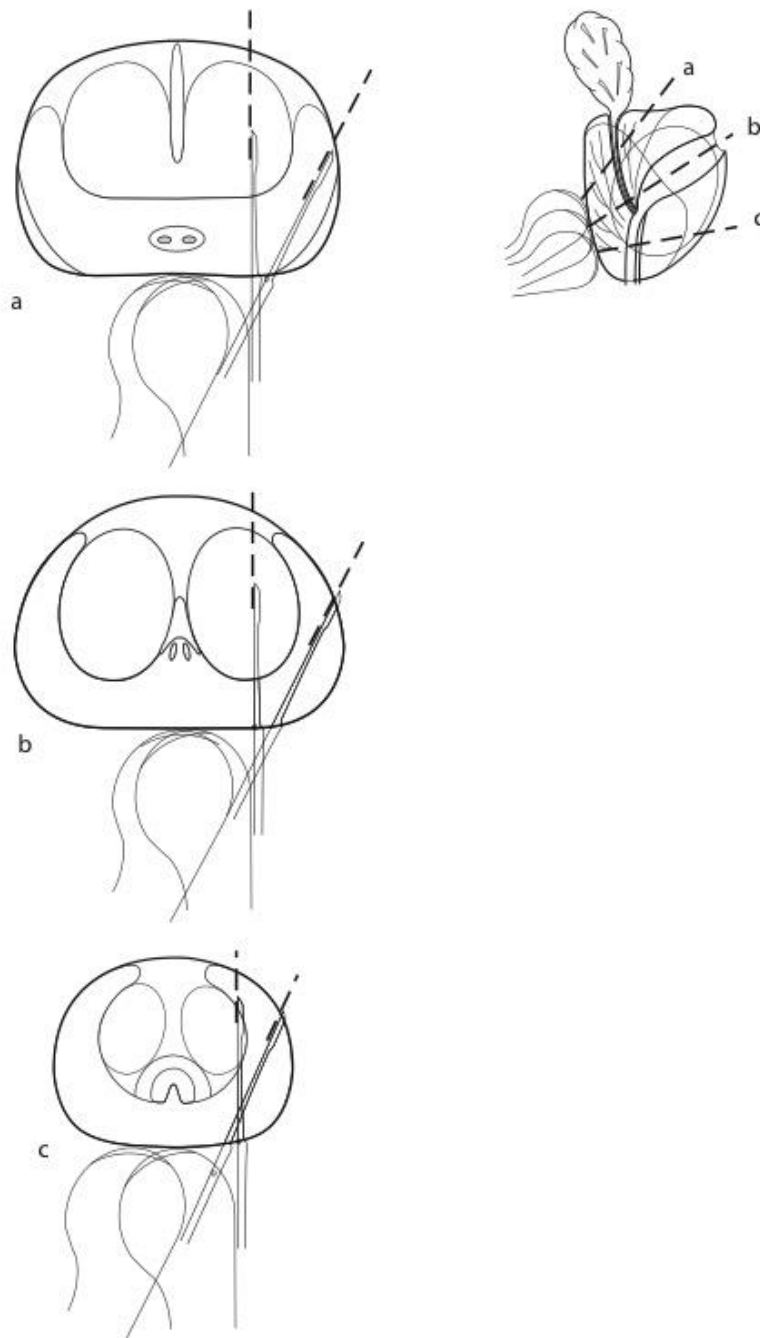
RSV invasion: No Yes
Equivocal

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12011 **Appendix 3: Example of systematic TRUS guided biopsy schema**

12012

12013 Figure depicting 12-core systematic TRUS guided biopsyschema that sites are
12014 recommended to follow. Axial/coronal sections of a prostate gland (left) showing
12015 biopsy courses of the 12 biopsies performed under ultrasound guidance with an end
12016 fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,



12018

12019 **Appendix 4: 2-page EQ-5D-5L Questionnaire**

12020 Under each heading, please tick the ONE box that best describes your health TODAY

12021

12022 **MOBILITY**

12023 I have no problems in walking about

12024 I have slight problems in walking about

-
- 12025 I have moderate problems in walking about
- 12026 I have severe problems in walking about
- 12027 I am unable to walk about
- 12028
- 12029 **SELF-CARE**
- 12030 I have no problems washing or dressing myself
- 12031 I have slight problems washing or dressing myself
- 12032 I have moderate problems washing or dressing myself
- 12033 I have severe problems washing or dressing myself
- 12034 I am unable to wash or dress myself
- 12035
- 12036 **USUAL ACTIVITIES** (*e.g. work, study, housework,*
12037 *family or leisure activities*)
- 12038 I have no problems doing my usual activities
- 12039 I have slight problems doing my usual activities
- 12040 I have moderate problems doing my usual activities
- 12041 I have severe problems doing my usual activities
- 12042 I am unable to do my usual activities
- 12043
- 12044 **PAIN / DISCOMFORT**
- 12045 I have no pain or discomfort
- 12046 I have slight pain or discomfort
- 12047 I have moderate pain or discomfort
- 12048 I have severe pain or discomfort
- 12049 I have extreme pain or discomfort
- 12050
- 12051 **ANXIETY / DEPRESSION**
- 12052 I am not anxious or depressed
- 12053 I am slightly anxious or depressed
- 12054 I am moderately anxious or depressed
- 12055 I am severely anxious or depressed
- 12056 I am extremely anxious or depressed
- 12057
- 12058 © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

12059

12060 • We would like to know how good or bad your health
12061 is TODAY.

The best health
you can imagine

12062 • This scale is numbered from 0 to 100.

12063 • 100 means the best health you can imagine.

12064 0 means the worst health you can imagine.

12065 • Mark an X on the scale to indicate how your health is
12066 TODAY.

12067 • Now, please write the number you marked on the
12068 scale in the box below.

12069

12070

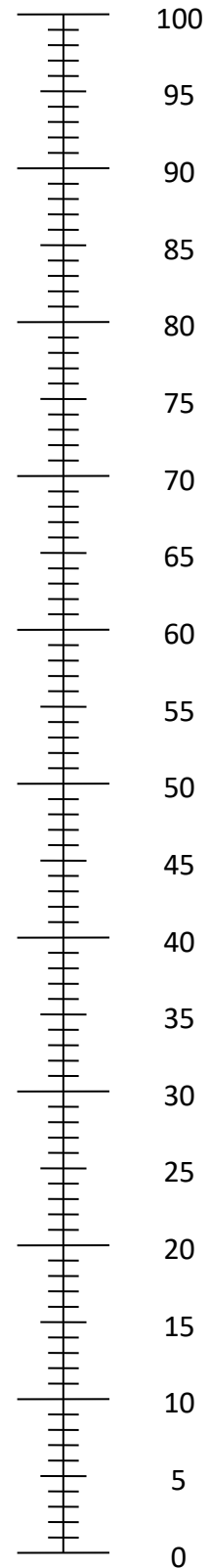
12071

12072

12073

12074

YOUR HEALTH TODAY=



The worst health
you can imagine

Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

Please ask the patient to fill this out after the biopsy, before they leave the department.

Please tick the box corresponding to the number, which describes how you felt immediately after the biopsy procedure:

1. Overall, how much discomfort did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Discomfort			Moderate Discomfort					Worst Discomfort Possible		

2. Overall, how much pain did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Pain			Moderate Pain					Worst pain Possible		

- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?
- ?

Please complete the next page of questions

Did you experience any of the following in the month **before** your biopsy procedure.
For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

11. Pain at the site where the biopsies were taken from

Yes

1

No

2

Thank you for completing the questionnaire. Please hand this to a member of staff before you leave. Please ensure you are given the 30-day questionnaire for completion at 30 days following the biopsy.

12078

Appendix 6: 30-day post biopsy questionnaire

30-day post biopsy questionnaire

30-days after the biopsy procedure, the patient should complete this questionnaire:

Did you experience the following problem in the 30-days after the biopsy procedure:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the biopsy did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

12081

Did you experience the following problem in the 30-days after the biopsy procedure:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the biopsy did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

25. Pain at the site where the biopsies were taken from

Yes No
1 2

26. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

12082

28. Please list any **new** medications that you have taken **since the biopsy**. Do not list your regular medications but do list any **new** medications started related to the biopsy. Think especially about any painkillers or antibiotics that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. ciprofloxacin</i>	<i>500mg</i>	<i>2</i>	<i>3</i>

29. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

No

1

2

30. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over fevers*)

(iii) manner of contact (*e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency*)

(iv) any treatment you received (please be as specific as possible *e.g. "I was admitted to the ward and treated for an infection of the blood stream for 5 days of intravenous antibiotics with 1.2g co-amoxiclav three times a day and I had 2 days of painkillers with intravenous paracetamol 1g four times a day"*):

12083

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the biopsy, have you had contact with the community healthcare team for reasons related to the biopsy?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at GP surgery/home visit)

(iv) any treatment you received (please be as specific as possible e.g. "I received 5 days of oral antibiotics for a urinary tract infection- 625mg co-amoxiclav three times a day and I had 2 days of painkillers with paracetamol 1g four times a day"):

12084

12085

37. Have you felt unwell in any other way that we have not asked that you feel is due to the biopsy?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2	3-5	6-10	11-15	16-20	21-30
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another biopsy** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

?

Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

?

12086
12087

12088 April 10, 2018

12089

PRECISE Trial: Amendment 4

12090

Protocol version 5.0: 10 April 2018

12091

Summary of Changes

12092

12093 Minor administrative changes were made throughout the current protocol to avoid
12094 discrepancy. Minor errors were corrected.

12095 The following changes were made:

12096

- **Version date to reflect:** Amendment 4: 10 April 2018

12097

- **The following has been amended throughout the protocol:** *Inclusion criteria:*

12098

Addition of stipulation: Serum PSA \leq 20ng/ml; **within 3 months of**

12099

randomization

12100

Rationale: to clarify the need for PSA at screening, without duplicating PSA
12101 bloodwork

12102

12103

- **ADDITION of EOS/Withdrawal visit on Table 1, 2, 3:** now includes:

12104

EOS/Withdrawal visit, documenting all requirements for this visit.

12105

Rationale: to clarify/separate what is needed at a withdrawal visit, and
12106 EOS study visit independent of the study completion.

12107

- **ADDITION of stipulation to section 10.11.1 Indications for biopsies**
12108 **off protocol:**

12109

now includes: Subjects should continue to be followed with semi-annual

12110

PSA and DRE (not required, at the discretion of the PI).

12111

Rationale: to clarify that the DRE is not mandatory and left up to the
12112 discretion of the PI.

12113

- **ADDITION of tumour bank information to section 10.12.2**
12114 **Correlative Science Component:**

12115

the following has been added: Biomaterial will be stored, anonymized, at

12116

the Ontario Institute of Cancer Research (OICR) Biobank, under the

12117

direction of Dr. John Bartlett. Dr. Bartlett is the Program Director,

12118

[Diagnostic Development](#), at OICR. The material will not be used for

12119

commercial purposes. No personal information will be kept at

12120

OICR. Personal identifying information on the patients in the PRECISE

12121

trial is held by the Ontario Clinical Oncology Group (OCOG), who are

12122

performing the data management function for the study. Access to the

12123

biomaterial will be under the control of the PRECISE steering

12124

committee. Access has already been approved for the Translational

12125

Research in Prostate Cancer (TRIPC) research group led by Dr. Paul

12126

Boutros. Future researchers interested in using the biomaterial will apply

12127

to the Precise steering committee for approval, based on the scientific

12128

merit of the study.

12129

Rationale: to provide more information regarding the storage of samples

12130

at OICR.

12131

- **ADDITION of vendor information to section 10.12.2 Correlative**
12132 **Science Component:**

12133

The following has been added (3D Signatures): The urine samples will be

12134

used to establish the sensitivity of the procedures and the precision of the

12135

analytic algorithms to identify those with significant prostate cancer.

12136 The long term goal of the project is to develop a non-invasive
12137 methodology that can be used to identify genetic alterations that identify
12138 a group of patients at high risk for clinically significant prostate cancer.
12139 **Rationale:** to provide more information regarding the 3D Signatures
12140 collection purposes.
12141 July 24, 2018
12142

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1. Title Page

Full title:

A phase III multi-centre open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.

4. Short title: Prostate Evaluation for Clinically Important disease: MRI vs Standard Evaluation procedures. (PRECISE)

Date: 10 April 2018

Version 5.0

Sponsor:

Canadian Urology Research Consortium (CURC)

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12191
12192

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12195 solely for the guidance of the clinical investigation. Reproduction or disclosure of this
12196 document - whether in part or in full - to parties not associated with the clinical
12197 investigation, or its use for any other purpose, without the prior written consent of
12198 the PI is not permitted.

12199
12200

12201 **2. Signature of Investigators**

12202

12203 **A phase III multi-centre open-label randomized controlled trial of**
12204 **multi-parametric magnetic resonance imaging (MRI)-targeted biopsy**
12205 **compared to systematic trans-rectal ultrasound (TRUS) guided biopsy**
12206 **for the diagnosis of prostate cancer in men without prior biopsy.**

12207

12208 **Date: 10 April 2018**

12209 **Version 5.0**

12210
12211
12212

12213 The signatory agrees to the content of the final clinical study protocol as presented.

12214
12215

12216 Signature: _____

12217

12218 Name: _____

12219

12220 Title: _____

12221

12222 Date: _____

12223

12224 Site name: _____

12225
12226
12227

3. Synopsis

Title	A phase III multi-centre, open-label randomized controlled trial of multi-parametric magnetic resonance imaging (MRI)-targeted biopsy compared to systematic trans-rectal ultrasound (TRUS) guided biopsy for the diagnosis of prostate cancer in men without prior biopsy.
Short Title	<u>P</u> rostate <u>E</u> valuation for <u>C</u> linically <u>I</u> mportant disease: MRI vs <u>S</u> tandard <u>E</u> valuation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	<p>Primary Objective</p> <p>To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.</p> <p>Secondary Objectives</p> <p>53. To determine whether the proportion of men with clinically significant cancer (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy.</p> <p>54. Proportion of men in each arm with clinically insignificant cancer detected.</p> <p>55. Proportion of men in each arm with Gleason $\geq 4+3$ detected.</p> <p>56. Proportion of men in MRI arm who avoid biopsy.</p> <p>57. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected.</p> <p>58. Proportion of men in each arm who go on to definitive local treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g. hormone therapy, chemotherapy).</p> <p>59. Proportion of men in each arm who do not have significant cancer found at baseline who develop a positive MRI and/or have a progressive lesion found on MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or targeted) by 2 years</p> <p>60. Proportion of men with post-biopsy adverse events</p> <p>61. Health-related quality of life scores.</p> <p>62. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.</p> <p>63. To determine the cost per diagnosis of cancer.</p> <p>64. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield</p> <p>65. To determine if a radiologist Likert score not based on PI-</p>

	RADS has a better target yield than PI-RADS_ alone
Test procedures	<p>Subjects will be randomized to either</p> <p>ARM A: multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy.</p> <p>ARM B: systematic trans-rectal ultrasound (TRUS) guided biopsy.</p> <p>Subjects in both arms will complete a number of different questionnaires and will have PSA measurements taken. If subjects consent to participate in correlative studies, they will also need to provide blood, urine semen and tissue samples at pre-specified time points.</p>
Indication	Clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy.
Diagnosis and main criteria for inclusion	<p>In order to be eligible, <u>all</u> inclusion criteria must be met.</p> <p>21. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;</p> <p>22. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk assessment of prostate cancer calculator, PCPTRC 2.0, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp; For men under age 55, the default age of 55 should be entered on the risk calculator.</p> <p>23. Serum PSA ≤ 20ng/ml; within 3 months of randomization</p> <p>24. Fit to undergo all procedures listed in protocol;</p> <p>25. Able to provide written informed consent.</p>
Exclusion Criteria	<p>Men who meet the following criteria at the time of screening will be excluded:</p> <p>25. Prior prostate biopsy;</p> <p>26. Prior treatment for prostate cancer;</p> <p>27. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min);</p> <p>28. Contraindication to prostate biopsy;</p> <p>29. Men in whom artifact would reduce the quality of the MRI; i.e, previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work;</p> <p>30. Unfit to undergo any procedures listed in protocol.</p>
Study Design	This is a multi-centre open-label, randomized two arm study. Men are either randomized to receive MRI or a systematic trans-rectal ultrasound (TRUS) guided biopsy.
Methodology	<p>Eligible subjects will be randomized in a 1:1 ratio to receive either (ARM A) multi-parametric magnetic resonance imaging (MRI) which, depending on outcome, may be followed by (MRI)-targeted biopsy, or (ARM B) systematic trans-rectal ultrasound (TRUS) guided biopsy. The time frame for data collection is shown in Appendix 1.</p> <p><u>All subjects</u> will have a PSA test prior to, or at Visit 1, and will</p>

	<p>complete a baseline EQ-5D-5L questionnaire. In addition, they will contribute optional blood, urine semen and tissue samples if they consent to correlative studies.</p> <p><u>All subjects in ARM A</u> will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI.</p> <p><u>Subjects in ARM A who do not receive a subsequent biopsy</u> will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (\pm 1 week) after the procedure. They will have another MRI and PSA test 2 years after the initial MRI. When they complete the study after 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>Subjects in ARM A who do receive a MRI-targeted biopsy</u> will complete an immediate post-biopsy questionnaire at the time of the biopsy, another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p> <p><u>All subjects in ARM B</u> will complete an immediate post-biopsy questionnaire following the standardized TRUS-guided biopsy. They will complete another EQ-5D-5L questionnaire and a 30-day post biopsy questionnaire when they find out the results of the biopsy, 3 weeks (\pm 1 week) after the procedure. They will have an additional PSA test every 6 months for two years, and at the end of 2 years of follow up, they will complete another EQ-5D-5L questionnaire.</p>
Type of control	This is an open-label randomized study.
Number of subjects	This study requires 422 subjects (211 in each arm). To account for potential withdrawal / loss to follow up and the effect of stratification, the sample size will be inflated by 5%, and a target of 450 men will be recruited.
Primary endpoint	The proportion of men in each arm with clinically significant cancer (Gleason \geq 7) will be calculated based on histology results from biopsy procedures. Analysis will be on the per protocol study population.
Secondary endpoints	See section 7.4
Plan for statistical analysis	See section 14.0.
Funding	The total budget for this trial is \$3,000,000. (see attached).Ontario Institute for Cancer Research (OICR) has committed to \$1,500,000 in support of this study (letter appended).We hope to obtain the additional \$1,500,000 from the Movember Accelerated Translational Research Grant Competition

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12360 **4. Abbreviations and definitions**

12361 **Abbreviations:**

12362		
12363	ADC	Apparent diffusion coefficient
12364	CI	Confidence interval
12365	CRF	Case report form
12366	DSMC	Data Safety and Monitoring Committee
12367	DRE	Digital rectal examination
12368	DWI	Diffusion weighted imaging
12369	DCE	Dynamic contrast enhancement
12370	EDC	Electronic Data Capture
12371	ITT	Intention to treat
12372	MCCL	Maximum cancer core length
12373	MPMRI	Multi-parametric MRI, used interchangeably with MRI
12374		in this protocol.
12375	MPMRI-TB	Multi-parametric magnetic resonance image-targeted
12376		biopsy of the prostate
12377	MRI	Magnetic resonance imaging, used interchangeably
12378		with MPMRI in this protocol
12379	MRI-TB	Magnetic resonance imaging targeted biopsy
12380	MRS	Magnetic resonance spectroscopy
12381	PI	Principal Investigator
12382	PI-RADS	Prostate Imaging Reporting and Data System
12383	PTC	Permission to Contact
12384	PSA	Prostate specific antigen
12385	REB	Research Ethics Board
12386	STARD	Standards for the reporting of diagnostic studies
12387	TRUS	Trans-rectal ultrasound
12388	TSC	Trial Steering Committee
12389	T2W	T2-weighted imaging

12390

12391

12392 **Definitions:**

12393

12394	MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is
12395		used to determine the location of a suspicious
12396		target prior to biopsy.

12397

12398	Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure
12399		is not influenced by findings on MRI imaging.
12400		Currently this is the standard of care for
12401		prostate cancer in the province of Ontario.

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5. Trial summary

5.1 Aim and Rationale

12408

12409 The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided
12410 (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is
12411 performed primarily for anatomic guidance as the ultrasound poorly discriminates
12412 between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are
12413 concentrated in areas of the peripheral zone, thought to harbor the majority of
12414 cancer.

12415

12416 An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to
12417 perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer.
12418 This information is used to direct a subsequent biopsy, known as an MRI-targeted
12419 biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a
12420 similar or greater amount of clinically significant cancer than systematic TRUS guided
12421 biopsy and has several other potential advantages including: the ability to
12422 differentiate between clinically significant and insignificant cancer, reducing
12423 unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related
12424 side-effects.

12425

12426 A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an
12427 individual's life expectancy and therefore does not warrant treatment. However
12428 when diagnosed with low grade cancer that is likely to be insignificant, a large
12429 proportion of subjects request treatment in case a more significant cancer is
12430 present[1]. A challenge in this area is that subjects are typically not aware that their
12431 cancer is clinically insignificant, and often view the early diagnosis and aggressive
12432 treatment they have been subjected to as life-saving.

12433 A prostate cancer detection procedure that differentiates clinically significant cancer
12434 from clinically insignificant cancer is therefore a major unmet need.

12435

12436 The potential implications of this trial include:

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- A redefinition of the prostate cancer diagnostic pathway;
- A reduction in the number of subjects undergoing prostate biopsy;
- A reduction in the number of biopsy cores taken per subject;
- A reduction in biopsy-related adverse events including sepsis and pain;
- A reduction in the over-diagnosis of clinically insignificant prostate cancer;
- A reduction in the economic burden of diagnosing and treating prostate cancer.

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5.2 Methods

Men referred with clinical suspicion of prostate cancer who have had no prior biopsy are randomized to either systematic TRUS guided biopsy(standard of care) or to a multi-parametric MRI (MPMRI) arm (the investigational arm). In the MRI arm, areas of the prostate are scored on a 5-point scale of suspicion for clinically significant cancer based on the Prostate Imaging Reporting and Data System

(PI-RADS) v2[2]:

PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be present)

PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)

PI-RADS 3 – Intermediate (the presence of clinically significant cancer is equivocal)

PI-RADS 4 – High (clinically significant cancer is likely to be present)

PI-RADS 5 – Very high (clinically significant cancer is highly likely to be present)

Each suspicious area will be given a separate score as described by consensus meeting recommendations [2, 3]. Lesions scoring 3, 4 or 5 will undergo targeted biopsy; up to three suspicious areas will be targeted.

In the control arm, subjects will undergo a standard 12 core systematic TRUS guided biopsy as per standard recommendations[4]. Suspicious sonographic lesions will be targeted (12 cores *in toto*).

Pathologic findings from all biopsies will be recorded and will undergo statistical analysis (see statistics section, 14.0).

In both arms, self-reported questionnaires to capture biopsy-specific side effects will be administered immediately post-procedure, and at the post-procedure appointment which will take place 3 weeks (\pm 1 week) after the procedure. Euro QOL group 5 domain EQ-5D-5L questionnaires or a comparable QOL instrument will also be completed at baseline (prior to MRI or TRUS biopsy), 24 hours post MRI and 24 hours post-biopsy. Men will be followed up for 30-days post intervention and until a treatment decision is made and recorded. Pathology results from men requiring a radical prostatectomy will be recorded.

Men will complete the trial after they complete treatment for prostate cancer (radical prostatectomy) or the required follow-up procedures for each arm are met (see study timelines, section 9.3). Once men complete the trial, they revert to standard of care.

Annual questionnaires will be administered for all men with negative biopsy in both arms during a two-year follow-up period to determine cancer and treatment status.

12493 No diagnostic test is perfect, and even with the best test some cancers may be
12494 missed. To minimize the risk of false negatives, men with negative biopsy results will
12495 be followed with serial PSA testing; PSA levels will increase if cancer is present.
12496 In both arms in addition to serial PSA testing all men who have no cancer found at
12497 systematic biopsy or targeted biopsy, have a negative MRI or enter active
12498 surveillance will have a followup MRI at 24 months. If a new Pi-Rads ≥ 3 lesion is
12499 found on the followup MRI or there is progression of an existing lesion this lesion will
12500 undergo targeted biopsy as part of standard of care.

12501
12502 As recruitment is expected to take up to 24 months (see section 7.6) and each
12503 subject will be followed up for two years, the estimated maximal duration of this
12504 study is four years in total. The primary endpoint will be reached at approximately 2
12505 years after study initiation.

12506 **5.3 Participating Sites**

12507 This is a multi-centre study. Institutions participating in the study must be able to
12508 perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able
12509 to randomize men to one of these two diagnostic tests.

12510
12511 We expect to recruit 3-6 subjects per month per site, based on recruitment rates
12512 from previous diagnostic trials performed by the centers involved. A typical centre
12513 sees 15-30 eligible men per month. We expect 5 recruitment sites, with 100 men to
12514 be recruited at each site over an 18-24 month period (see section 7.6).

12515 **5.4 Study outcomes**

12516 **5.4.1 Primary outcome**

12517 To determine whether the proportion of men with clinically significant cancer
12518 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
12519 guided biopsy.

12520 **5.4.2 Secondary outcomes**

- 12521 53. To determine whether the proportion of men with clinically significant cancer
12522 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
12523 guided biopsy.
- 12524 54. Proportion of men in each arm with clinically insignificant cancer detected.
- 12525 55. Proportion of men in each arm with Gleason $\geq 4+3$ detected.
- 12526 56. Proportion of men in MRI arm who avoid biopsy.
- 12527 57. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
12528 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
12529 detected.
- 12530 58. Proportion of men in each arm who go on to definitive local treatment (e.g.
12531 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
12532 hormone therapy, chemotherapy).
- 12533 59. Proportion of men in each arm who do not have significant cancer found at
12534 baseline who develop a positive MRI and/or have a progressive lesion found on
12535 MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or

-
- 12536 targeted) by 2 years.
- 12537 60. Proportion of men with post-biopsy adverse events
- 12538 61. Health-related quality of life scores.
- 12539 62. Proportion with Gleason grade upgrading in men undergoing radical
- 12540 prostatectomy.
- 12541 63. To determine the cost per diagnosis of cancer.
- 12542 64. To determine the impact of the addition of Gd based contrast compared to a non
- 12543 contrast abbreviated MRI protocol on target yield
- 12544 65. To determine if a radiologist Likert score not based on PI-RADS has a better
- 12545 target yield than PI-RADS alone
- 12546
- 12547

12548 **6. Background**

12549 **6.1 Prostate cancer diagnosis**

12550 Prostate cancer is the most common male cancer in the Western world with an

12551 incidence of 24,000 new cases in Canada and 233,000 in the USA[5, 6]. It is the

12552 second most common cause of cancer death in European and North American men,

12553 with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe[5, 6].

12554 The incidence of the disease has increased by 22% over the last decade due to the

12555 widespread use of the prostate specific antigen (PSA) blood test; by 2030 the

12556 Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.As

12557 prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal

12558 digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one

12559 million prostate biopsies are performed in North America and Europe every year[7].

12560

12561 **6.2 Clinically significant versus clinically insignificant prostate cancer**

12562

12563 Clinically significant prostate cancer is cancer that is likely to progress and affect a

12564 man's life expectancy if left untreated. Though there is no universally agreed upon

12565 definition on what histological parameters define clinically significant cancer, most

12566 agree that larger volume cancers with a higher Gleason grade are more likely to be

12567 clinically significant; an historically accepted threshold is a tumour volume above

12568 0.5milliliters or any Gleason pattern 4 or 5 cancer[8-11].

12569

12570 This definition is likely overly stringent. An increasing consensus views all Gleason

12571 pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of

12572 pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate

12573 cancers fall into this category, and are unlikely to progress and affect a man's life

12574 expectancy if left untreated. The widespread use of PSA testing has led to more men

12575 being diagnosed with insignificant cancer that does not warrant any treatment [13];

12576 however they are typically monitored closely with active surveillance. This is

12577 associated with anxiety about harbouring untreated cancer, and the negative

12578 psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate

12579 cancer are also subjected to serial biopsies and other tests, requiring long term

12580 follow up. Further, many men with low risk disease receive radical treatment, either

12581 because their physicians are not advocates of surveillance or because of anxiety
12582 [15].These treatments may expose them to morbidity including urinary incontinence
12583 and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate
12584 clinically significant cancer from clinically insignificant cancer will help reduce patient
12585 anxiety, alleviate further testing, and avoid radical treatment and associated
12586 morbidities.
12587

12588 **6.3 Current standard of care: systematic TRUS guided biopsy**

12589 The European association of Urology and NICE guidelines recommend systematic
12590 TRUS guided biopsy as the current standard of care for the diagnosis of prostate
12591 cancer [4, 17].This procedure has several advantages: it can be delivered quickly in
12592 an outpatient clinic under local anesthetic, it can be offered at most Urology centres,
12593 and the expertise is widely distributed.
12594

12595 Limitations of systematic TRUS guided biopsy are as follows: the procedure requires
12596 the operator to take 10-12 samples in the peripheral zone, where it is thought that
12597 the majority of prostate cancer can be found (See Appendix 2)[18]. The ultrasound
12598 guidance used during the procedure is useful for visualizing the prostate and
12599 assessing the location of the needle within the prostate but has a poor ability to
12600 discriminate tumour from normal tissue [19], which means that the systematic TRUS
12601 guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has
12602 been shown to have a high false negative rate of 30-45% [20, 21].As a systematic
12603 TRUS guided biopsy is not specifically targeted to the location of a suspected
12604 significant cancer, there is also a greater chance that a significant cancer may be
12605 missed.

12606 **6.4 The emerging role of MRI in prostate cancer diagnosis and** 12607 **treatment**

12608 **6.4.1 The role of imaging in prostate cancer diagnosis**

12609 Although used to diagnose many other solid organ cancers such as breast, renal and
12610 colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic
12611 pathway. Imaging in prostate cancer, is typically limited to stage the disease
12612 following histological diagnosis. Magnetic resonance imaging (MRI) is used in many
12613 centres to assess for extra-capsular extension during prostate cancer staging. In the
12614 past five years however, the possibility of using multi-parametric MRI (MPMRI)for
12615 diagnosing prostate cancer prior to biopsy, has generated tremendous interest[22].

12616 **6.4.2 Limitations of early MRI studies in prostate cancer**

12617 Early literature reported conflicting results on the ability of MRI to detect prostate
12618 cancer. A recent systematic review of the literature showed that the quality of
12619 studies evaluating MRI was disappointing [22]. Limitations of reported studies
12620 include:

- 12621 • **Poor reporting standards.** Many early studies failed to closely follow
12622 published guidelines for the standards of reporting of diagnostic studies
12623 (STARD) [23].

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- **Biopsy artifact.** The majority of early studies evaluated MRI after biopsy. Evidence has shown that post-biopsy hemorrhage can remain for several months and affect interpretation of the image [24].
 - **Poor reference standards.** Many early studies use systematic TRUS guided biopsy as a reference standard, which due to its limitations, can influence the validity of the index test of MRI. Using radical prostatectomy specimens as reference standards can lead to a selection bias, as MRI is only validated in men with disease characteristics that require radical prostatectomy. Further, correlation of radical prostatectomy specimen with an MRI image is not without difficulty given the shrinkage (10-20%), distortion, absent perfusion, orientation and tissue loss as a result of specimen trimming.
 - **Incomplete analysis of the prostate.** Many early studies only evaluate the validity of MRI in the peripheral zone, even though studies have shown that around 25% of prostate cancers may be located in the transition zone [18].
 - **Segmentation.** Many early studies artificially divide the prostate into a number of segments in order to increase the amount of data obtained and the power of the analysis. Segments should not be treated as independent regions of interest, and this should be factored into the analysis.

12643 **6.4.3 Emerging role of MRI in the diagnosis of prostate cancer**

12644 Since the publication of these early reports, improvements in diagnostic technology
12645 have changed the field and more evidence supporting the role of pre-biopsy MRI has
12646 been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla
12647 and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image
12648 acquisition and the addition of functional sequences including magnetic resonance
12649 spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast
12650 enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for
12651 biopsy artifacts.

12652

12653 The combination of anatomical sequences (T2-weighted imaging) and functional
12654 sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI.
12655 Combining the sequences improves the validity of the test [25, 26].

12656

12657 A systematic review determined that 60% of men with a clinical suspicion of prostate
12658 cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI
12659 with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity,
12660 positive predictive value and negative predictive value of 90%, 88%, 77% and 95%
12661 respectively for the identification of prostate tumours greater than 0.5ml [28].

12662 Systematic reviews and meta-analysis of recent studies have demonstrated
12663 sensitivity and specificity consistently between 70-90% for the detection of clinically
12664 significant prostate cancer[26, 29-31].

12665

12666 As a result of this accumulating evidence, MRI is increasingly used in clinical practice
12667 in the diagnostic pathway for prostate cancer. The results of MRI can influence the
12668 decision to perform a prostate biopsy, as well as the technique and targeting used
12669 during the biopsy.

12670

12671 MRI has tremendous potential to enhance the outcome of men on active
12672 surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA <
12673 10) harbor higher-grade disease. This occult high-grade disease “*the wolf in sheep’s*
12674 *clothing*”, is responsible for the 3-5% of prostate cancer deaths that have been
12675 reported in long term surveillance series that did not incorporate MRI[32, 33]. The
12676 early use of MRI in men on surveillance has the potential both to reduce the need
12677 for confirmatory biopsies, and to identify the *wolf in sheep’s clothing* earlier, prior to
12678 the development of metastasis.

12679

12680 This was the rationale for the very successful ASIST study, which recently successfully
12681 completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in*
12682 *toto* by the Ontario Institute of Cancer Research. The project was managed by the
12683 Canadian Urology Research Consortium (CURC). It randomized 273 men recently
12684 diagnosed with low risk prostate cancer, on surveillance, between systematic
12685 confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end
12686 point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or
12687 higher prostate cancer. The study had numerous secondary end points and
12688 correlative science components. We expect to report the initial results by 3Q
12689 2016. We believe that the success and potential impact of the ASIST trial has created
12690 strong momentum to proceed with the PRECISE trial, which has even greater
12691 potential to substantially influence prostate cancer screening and diagnosis.

12692 **6.4.3.1 MRI can influence the decision to perform a prostate biopsy**

12693 With reported negative predictive values of 95% [28, 34,35], MRI can help determine
12694 whether a prostate biopsy is necessary; if the MRI does not identify a suspicious area
12695 the biopsy can be avoided. Using MRI, 40-50% of men referred with clinical suspicion
12696 of prostate cancer might avoid a biopsy [27]. The recent National Institute for Health
12697 Research (NIHR) Health Technology Assessment (HTA) report [11] acknowledged the
12698 value of MRI in this context. The NIHR HTA report suggests that using MRI to reduce
12699 the number of men who undergo biopsy, can be cost effective despite the costs
12700 associated with MRI[11]. Cost savings for the publically funded health care system
12701 accrue as a result of reduced number of biopsies and costs of attendant
12702 complications, and reduced treatment of clinically insignificant cancer.

12703 **6.4.3.2 MRI can influence the biopsy technique**

12704 For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI
12705 information is used to influence the prostate biopsy technique. This is known as MRI-
12706 targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of
12707 ways.

12708

12709 The biopsy operator can use the MRI images or report to direct biopsies into the
12710 area of the prostate where the tumour is located. The location of the tumour on the
12711 MRI (carried out in advance) is registered to the real-time ultrasound images with
12712 the use of software (software assisted registration or image-fusion) or without the
12713 use of software (visual registration or cognitive registration), while the prostate is
12714 visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted
12715 directly “in-bore”, where the biopsy is conducted within an MRI scanner where the

12716 target identified on MRI during a prior diagnostic scan is biopsied using guidance
12717 from serial MRI scans during the biopsy procedure, performed in an open magnet.
12718

12719 For the PRECISE study, the biopsy will be performed using an image fusion-targeting
12720 device. Two devices have been FDA approved: the Artemis, made by Eigen, and the
12721 Urostation, made by Koelis. These devices import the MR target into the TRUS
12722 image, and direct the biopsy needle into the target.

12723 **6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are** 12724 **similar to other methods**

12725 A systematic review determined that 60% of men with a clinical suspicion of prostate
12726 cancer will have a suspicious area identified on MRI [27]. One study found that a
12727 prostate biopsy strategy using only MPMRI-targeted cores resulted in the same
12728 detection rate of clinically significant cancer as 20-sector transperineal biopsies[36].
12729 Other studies also show that a targeted-alone approach would detect a similar
12730 amount of clinically significant cancer when compared to a 10-12 core systematic
12731 TRUS guided biopsy[37]. A targeted-alone approach detects 17% less clinically
12732 insignificant cancer compared to systematic TRUS guided biopsy[38].
12733

12734 The detection rates achieved with a targeted-alone biopsy strategy require fewer
12735 biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis,
12736 targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer
12737 detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores
12738 compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of
12739 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material
12740 for histopathological analysis as the maximum cancer core length obtained from
12741 targeted biopsies can be greater than that obtained from systematic biopsies[37].
12742

12743 Robust comparative evidence from randomized controlled trials is needed to
12744 determine if MRI scans can improve our ability over systematic TRUS guided biopsy
12745 to diagnose clinically significant cancer and our ability to avoid detecting clinically
12746 insignificant cancer.
12747

12748 **6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy**

12749 Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine
12750 clinical practice for prostate cancer diagnosis. Most existing studies have cohort
12751 study designs which make interpretation difficult as they do not conform well to
12752 STARD [23] recommendations [27]. Limitations of these studies include:

- 12753 • **Broad definition of the study population.** The cancer detection rates depend on
12754 the prevalence of the condition in the population being investigated. This varies
12755 amongst men with no prior biopsy, prior negative biopsy and prior positive
12756 biopsy. In many studies the detection rates are not attributable to a clearly
12757 defined population.
- 12758 • **MRI conduct and reporting.** The detail in which MRI is conducted and
12759 interpreted varies greatly amongst published studies.

12760 • **Reporting of cancer detection.** The cancer detection by systematic and targeted
12761 cores is not always presented separately and cancer detection is not always
12762 specified by clinical significance. These are both essential in order to evaluate the
12763 technique.
12764 There is a strong need for a randomized controlled trial comparing MRI-targeted
12765 biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical
12766 practice can be established.

12767 **6.5 Novelty of PRECISE**

12768 PRECISE is the first randomized study in biopsy-naïve men in which men are
12769 randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal
12770 areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic
12771 TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-
12772 targeted biopsy approach in the detection of clinically significant cancer. In order to
12773 evaluate a biopsy technique that could replace standard of care, the standard of care
12774 test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to
12775 allow a direct comparison.

12776
12777 Other constituencies with an interest in MRI in prostate cancer (University College,
12778 London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New
12779 York) have considered similar studies, however in these centres MRI has largely
12780 replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to
12781 date. As a result, these centres have acknowledged that randomization to a standard
12782 biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as
12783 equipoise has been lost.

12784
12785 In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not
12786 recommended for the indication of an elevated PSA in men who have not had a
12787 biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed
12788 to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a
12789 biopsy will make entry into this trial very appealing to potential candidates. Further,
12790 the barriers, both financial and physical, to obtaining a quality MRI outside of the
12791 health care system are substantial. Thus we believe men who are randomized to the
12792 systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant
12793 contamination (i.e. men randomized to the systematic biopsy arm seeking out an
12794 MRI instead).

12795

12796 **7. Trial objectives**

12797 **7.1 Overall aim**

12798 The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to
12799 standard of care systematic TRUS guided biopsy in the detection of clinically
12800 significant and clinically insignificant prostate cancer in men without prior biopsy.
12801 The implication of this trial is that MRI-targeted biopsy could replace systematic
12802 TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

12803 **7.2 Hypotheses**

12804 The proportion of men with clinically significant cancer detected by MRI-targeted
12805 biopsy will be no less than that detected by systematic TRUS guided biopsy.

12806 **7.3 Primary Objective**

12807 To determine whether the proportion of men with clinically significant cancer
12808 (Gleason ≥ 7) detected by MRI-targeted biopsy is no less than systematic TRUS
12809 guided biopsy.

12810 **7.4 Secondary Objectives**

12811 66. To determine whether the proportion of men with clinically significant cancer
12812 (Gleason ≥ 7) detected by MRI-targeted biopsy is greater than systematic TRUS
12813 guided biopsy.

12814 67. Proportion of men in each arm with clinically insignificant cancer detected.

12815 68. Proportion of men in each arm with Gleason $\geq 4+3$ detected.

12816 69. Proportion of men in MRI arm who avoid biopsy.

12817 70. Proportion of men in the MRI arm whom the PI-RADS score for suspicion of
12818 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
12819 detected.

12820 71. Proportion of men in each arm who go on to definitive local treatment (e.g.
12821 radical prostatectomy, radiotherapy, brachytherapy) or systemic treatment (e.g.
12822 hormone therapy, chemotherapy).

12823 72. Proportion of men in each arm who do not have significant cancer found at
12824 baseline who develop a positive MRI and/or have a progressive lesion found on
12825 MRI and/or have Gleason ≥ 7 cancer detected on a repeat biopsy (systematic or
12826 targeted) by 2 years.

12827 73. Proportion of men with post-biopsy adverse events

12828 74. Health-related quality of life scores.

12829 75. Proportion with Gleason grade upgrading in men undergoing radical
12830 prostatectomy.

12831 76. To determine the cost per diagnosis of cancer.

12832 77. To determine the impact of the addition of Gd based contrast compared to a non
12833 contrast abbreviated MRI protocol on target yield

12834 78. To determine if a radiologist Likert score not based on Pi-Rads has a better target
12835 yield than Pi_Rads alone

12836

12837

12838 **7.5 Explanation for non-inferiority hypothesis**

12839 Due to the putative advantages of MRI-TB in reducing the number of men who
12840 require a biopsy, reducing the number of cores required in each man who is
12841 biopsied, more accurate representation of disease burden, less insignificant disease
12842 detected and reducing the number of men at risk of complications of biopsy, the
12843 primary outcome of detection of clinically significant cancer in each arm will be
12844 compared using a non-inferiority hypothesis. Even if a similar amount of clinically
12845 significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these

12846 advantages would support the use of MRI-TB instead of systematic TRUS guided
12847 biopsy in clinical practice.
12848

12849 **7.6 Anticipated timeline of study progression**

12850 The study will commence once sponsorship, ethical approval and local approvals
12851 have been obtained at a participating site and once site initiation training has
12852 occurred and a letter of site activation has been issued from the coordinating centre.
12853 Additional sites may join after the study has commenced. At this time, five sites will
12854 participate. Assuming a minimum recruitment rate of 3-6 men per site per month,
12855 recruitment will be complete by 24 months, if not sooner. If accrual is slower than
12856 expected, an additional 1-2 sites will be recruited for year 2.
12857

Month	Number of Sites	Total recruitment
0	2	0
3	4	18-36
6	5	54-108
9	5	99-198
12	5	144-288
15	5	189-378
18	5	234-468
21	5	279-558
24	5	324-648

12858

12859 **8. Study Population**

12860 **8.1 Number of Subjects**

12861 Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or
12862 results of digital rectal exam, with no prior biopsy will be eligible for participation.
12863 Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be
12864 enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

12865 **8.2 Subject inclusion criteria**

12866 In order to be eligible, all inclusion criteria must be met:

- 12867 25. Men at least 18 years of age referred with clinical suspicion of prostate cancer
12868 who have been advised to have a prostate biopsy;
- 12869 26. $\geq 5\%$ chance of high-grade prostate cancer as calculated using individualized risk
12870 assessment of prostate cancer calculator, PCPTRC 2.0, found at
12871 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> For men under age 55,
12872 the default age of 55 should be entered on the risk calculator.
- 12873 27. Serum PSA ≤ 20 ng/ml within 3 months of randomization
- 12874 28. Fit to undergo all procedures listed in protocol;
- 12875 29. Able to provide written informed consent.

12876 **8.3 Subject exclusion criteria**

12877 Men who meet the following criteria at the time of screening will be excluded:

- 12878 25. Prior prostate biopsy

-
- 12879 26. Prior treatment for prostate cancer
12880 27. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR
12881 ≤50mls/min)
12882 28. Contraindication to prostate biopsy
12883 29. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip
12884 replacement surgery, metallic hip replacement or extensive pelvic orthopaedic
12885 metal work
12886 30. Unfit to undergo any procedures listed in protocol.

12887

12888 **9. Study design**

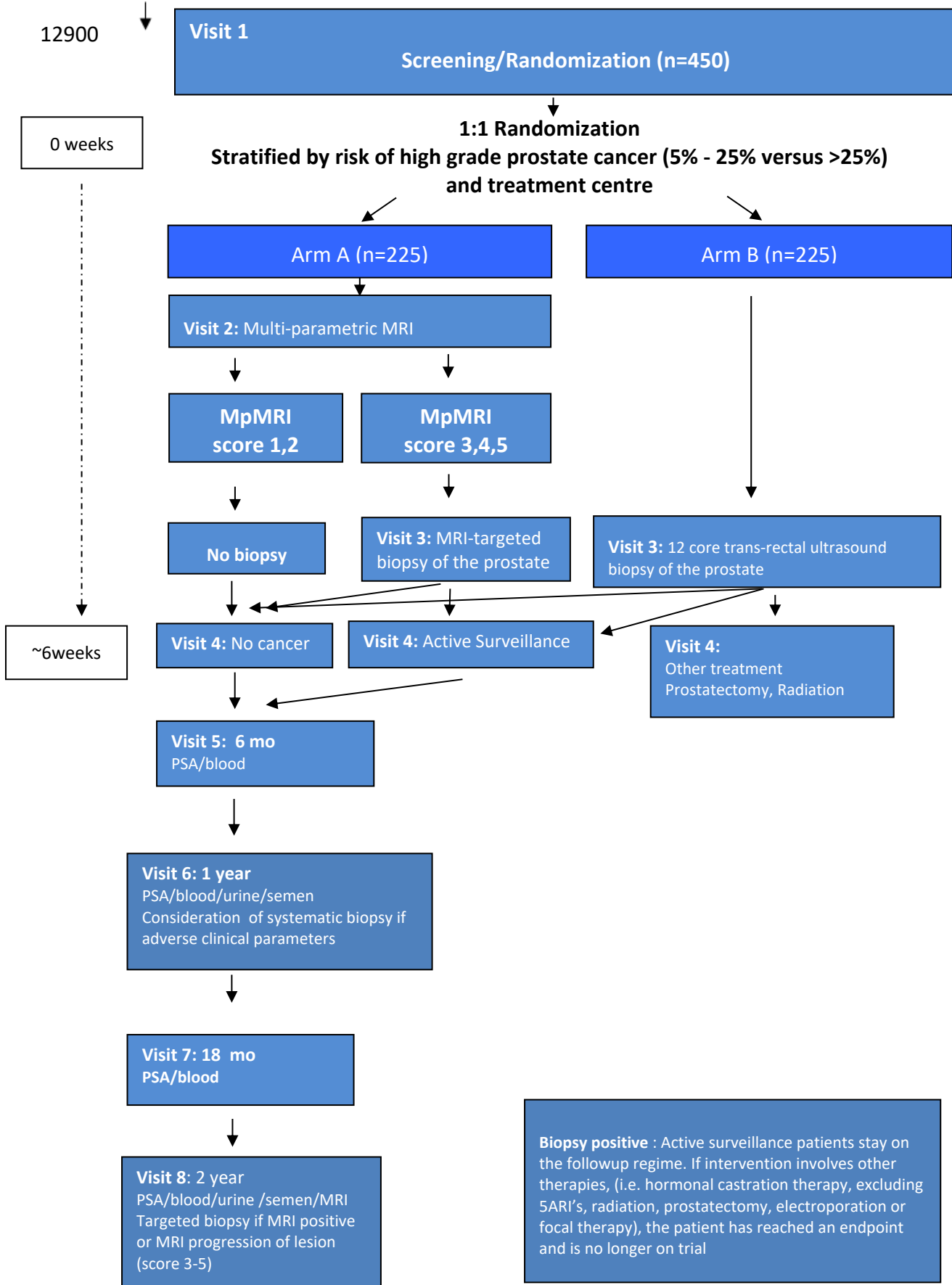
12889 **9.1 Study design**

12890 The study is a multi-centre, open-label randomized controlled trial, with men
12891 randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in
12892 Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or
12893 will be followed for two years if there is no suspicious areas identified by MRI. The
12894 unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-
12895 core systematic TRUS guided biopsy. All men in the study will be followed for two
12896 years or until they have had radical treatment (whichever comes first).

12897

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12900

9.2 Study Trial Schema



12901 **9.3 Timeline of subject contact**

12902 Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial.

12903 The individual pathway that each subject experiences is dependent on both the arm he is randomized to and results of the tests.

12905

12906 **Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require**
 12907 **a biopsy**

	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3 N/A	Visit 4 Post- Test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follow up	EOS/ withdrawal
Weeks:	0	1	2	5	26	52	78	104	
Consent	X								
Screening (eligibility review, med hx,	X								
Vitals,	X					X		X	
DRE ¹	X ¹					X		X	
Randomization	X								
EQ-5D-5L	X			X				X	X
Correlative sample collection:									
• blood	X				X	X	X	X	
• urine ²	X					X		X	
• semen	X					X		X	
• tissue-NA									
Creatinine ⁴	X ⁴								
PSA ⁵	X ⁵				X	X	X	X	X
Systematic TRUS guided biopsy									
MRI		X						X ⁶	
MRI-Targeted Biopsy								X if target	
Immediate post-biopsy questionnaire									
Follow up for results of tests				X					
Treatment decision ⁷				X					
30-day post-biopsy questionnaire									
AE/SAE	Complete as required at any time following registration								
Withdrawal Form	Complete as required at any time following registration								
ConMeds Form	Complete as required at any time following registration								

12908

12909 ¹Urine sample will be required ONLY if the subject has agreed to the Correlative Science
12910 collection, for PRE and POST DRE urine samples. See correlative manual for instruction.
12911 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
12912 catch' and post-DRE samples. See the Correlative Science Manual for further details on
12913 collection and processing.
12914 ³Collected at baseline, and annually.
12915 ⁴Creatinine requirements as per institutional Radiology (MRI) SOPs
12916 ⁵PSA greater than 3 months of randomization, must be repeated at screening .
12917 ⁶ If MRI indicates a target, biopsy must be done
12918 ⁷After treatment decision men revert to standard of care.
12919

12920
12921

Table 2: ARM A: Men randomized to MRI arm who have a lesion on MRI and require a biopsy

	Visit 1 Screening / Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post- test	Visit 5 6 mos	Visit 6 1 year follow up	Visit 7 18 mos	Visit 8 2 year follow up	EOS Intervention / withdrawal
Weeks:	0	1	2	6	26	52	78	104	
Consent	X								
Screening (eligibility review, med hx)	X								
Vitals,	X					X		X	
DRE ¹	X ¹					X		X	
Randomization	X								
EQ-5D-5L	X			X				X	X
Correlative sample collection: • blood	X				X	X	X	X	
• urine ²	X					X		X	
• semen	X					X		X	
• tissue ⁴			X					X	
Creatinine ⁵	X ⁵								
PSA ⁶	X ⁶				X	X	X	X	X
Systematic TRUS guided biopsy									
MRI ⁷		X						X ⁷	
MRI-Targeted Biopsy			X					X ⁷	
Immediate post- biopsy questionnaire			X						
Follow up for results of tests				X					
Treatment decision ⁸				X					
30-day post- biopsy questionnaire				X					
AE/SAE	Complete as required at any time following registration								X
Withdrawal Form	Complete as required at any time following registration								
ConMeds Form	Complete as required at any time following registration								

12922
12923

12924 ¹Urine sample will be required ONLY if the subject has agreed to the Correlative Science
12925 collection, for PRE and POST DRE urine samples. See correlative manual for instruction.
12926 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
12927 catch' and post-DRE samples. See the Correlative Science Manual for further details on
12928 collection and processing.
12929 ³Collected at baseline, and annually.
12930 ⁴ tissue should be obtained if subject has agreed to the Correlative Science component. See
12931 correlative manual for instruction.
12932 ⁵ Creatinine requirements as per institutional Radiology (MRI) SOPs
12933 ⁶PSA greater than 3 months of randomization, must be repeated at screening
12934 ⁷ See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue
12935 obtained for correlative science studies if subject has agreed to the Correlative Science
12936 component. See correlative manual for instruction.
12937 ⁸After treatment decision men revert to standard of care.
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Table 3: ARM B: Men randomized to systematic TRUS guided biopsy arm

	<u>Visit 1</u> Screening/ Randomization	<u>Visit 2</u>	<u>Visit 3</u> Biopsy	<u>Visit 4</u> Post- test visit	<u>Visit 5</u> 6 mos	<u>Visit 6</u> 1 year follow up	<u>Visit 7</u> 18 mos	<u>Visit 8</u> 2 year follow up	EOS Intervention /withdrawal
Weeks:	0	1	2	6	26	52	52	104	
Consent	X								
Screening (eligibility review, med hx)	X								
Vitals,	X					X		X	
DRE ¹	X ¹					X		X	
Randomization	X								
EQ-5D-5L	X			X				X	X
Correlative sample collection: • blood	X				X	X	X	X	
• urine ²	X					X		X	
• Semen	X					X		X	
• tissue			X						
Creatinine ⁴	X ⁴								
PSA ⁵	X ⁵				X	X	X	X	X
Systematic TRUS guided biopsy			X						
MRI ⁶								X ⁶	
MRI-Targeted Biopsy								X ⁶	
Immediate post- biopsy questionnaire			X						
Follow up for results of tests				X					
Treatment decision ⁷				X					
30-day post- biopsy questionnaire				X					
AE/SAE	Complete as required at any time following registration								X
Withdrawal Form	Complete as required at any time following registration								
ConMeds Form	Complete as required at any time following registration								

12979

12980 ¹Urine sample will be required ONLY if the subject has agreed to the Correlative Science
12981 collection, for PRE and POST DRE urine samples. See correlative manual for instruction.

12982 ²Urine samples will be collected at select visits, this may include 2 samples, 'Random-First
12983 catch' and post-DRE samples. See the Correlative Science Manual for further details on
12984 collection and processing.

12985 ³Collected at baseline, and annually.

12986 ⁴ Creatinine requirements as per institutional Radiology (MRI) SOPs

12987 ⁵PSA greater than 3 months of randomization, must be repeated at screening

12988 ⁶ See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue
12989 obtained for correlative science studies if subject has agreed to the Correlative Science
12990 component. See correlative manual for instruction.

12991 ⁷After treatment decision men revert to standard of care.

12992

12993

12994 **10. Trial Interventions and procedures**

12995

12996 The following procedures will be applied as necessary to subjects enrolled in both
12997 arm of the trial.

12998 **10.1 EQ-5D-5L Questionnaires**

12999

13000 **For all subjects enrolled in trial**

13001 Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L
13002 questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to
13003 evaluate health related quality of life. It takes approximately 2 minutes to complete.

- 13004 • All subjects should complete the baseline questionnaire at the screening visit
13005 before leaving the department.
- 13006 • Subjects who have a normal MRI and do not require a biopsy will complete an
13007 EQ-5D-5L questionnaire at Visit 4.
- 13008 • Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will
13009 be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date
13010 that the subject should fill out the questionnaires should be written on top of the
13011 questionnaire. (This can also be done at Visit 4).
- 13012 • All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up
13013 visit.

13014

13015

13016 **10.2 Multiparametric MRI imaging procedure**

13017 **For subjects in Arm A only**

13018

13019 **10.2.1 MRI Protocol**

13020 A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic
13021 phased array coil and an automated injector system with the subject in the supine
13022 position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast

13023 enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS
13024 v2.
13025
13026 Within the specified PI-RADS 2 framework a common protocol will be formulated by
13027 a consensus of the radiologists involved in the trial at each site at a startup meeting.
13028 The highest agreed upon b-value image for DWI (at least 1400s/mm²) will be
13029 selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast
13030 media, injection rates and dynamic scanning temporal resolution will be matched for
13031 all sites. An optional multi b value DWI acquisition will be undertaken as well to
13032 allow for ancillary studies into non log linear apparent diffusion coefficient (ADC)
13033 models for tumor characterization. This is summarized in an MRI Operations Manual
13034
13035
13036 Subjects will be asked to follow their local standard of care MRI examination
13037 preparation instructions for the MRI procedure.

13038 **10.2.2 MRI reporting**

13039 The MRI will be reported by an experienced radiologist using the MRI Reporting
13040 Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored
13041 based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5
13042 pointLikert score for purposes of comparison. Biopsy decisions will be based on the
13043 PI-RADS scores.

13044
13045

13046 Lesions in the prostate will be scored on the following scale:

- 13047 PI-RADS 1 – Very low (clinically significant cancer is highly unlikely to be
13048 present)
- 13049 PI-RADS 2 – Low (clinically significant cancer is unlikely to be present)
- 13050 PI-RADS 3 – Intermediate (the presence of clinically significant cancer is
13051 equivocal)
- 13052 PI-RADS 4 – High (clinically significant cancer is likely to be present)
- 13053 PI-RADS 5 – Very high (clinically significant cancer is highly likely to be
13054 present)

13055

13056 The location of the suspicious areas in the prostate should be marked on a diagram
13057 of the prostate (see Appendix2) and the sector numbers containing each suspicious
13058 area should be recorded in the case report form.

13059

13060 Radiologists will be blinded to the PSA.

13061

13062

13063 Imaging interpretation will be carried out at each site, however ensuring consistency
13064 and quality of imaging interpretation is crucial. A central imaging site will be
13065 designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site
13066 will perform the interpretation of all images for that site. The designated radiologist
13067 must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A
13068 startup meeting involving all radiologists will be held prior to start of accrual where
13069 each site will bring 5 MRI cases performed at their site for consensus review, scoring

13070 and discussion. This will provide a commonality of approach to interpretation among
13071 the radiologists before the study begins. After this startup meeting each site will
13072 send one set of MRI images and its interpretation for central review for site
13073 qualification.

13074
13075 A copy of all images will be sent on CD/DVD to the central site for archiving.

13076 **10.3 No target identified on MPMRI (PI-RADS 1 or 2)**

13077 **For subjects in Arm A only, who do not require a biopsy**

13078 Men who have MRIs that do not identify any suspicious lesion will not receive a
13079 biopsy. These subjects will benefit from being part of the trial as a result of not
13080 having to undergo an invasive biopsy procedure, avoiding the discomfort associated
13081 with the procedure, the risk of being diagnosed with clinically insignificant cancer
13082 and the risk of sepsis associated with the biopsy procedure. Studies suggest that if
13083 the MRI does not identify areas suspicious for cancer there is an 85-95% chance that
13084 clinically significant cancer is not present [28, 34, 35].

13085
13086 As soon as the results of the MRI are discussed with the subject, their treatment
13087 decision will be recorded and they will return to standard of care management. As
13088 part of standard of care these subjects can undergo further PSA surveillance and / or
13089 prostate biopsies if indicated.

13090 **10.4 MRI-Targeted biopsy**

13091 **For subjects in Arm A who do require a biopsy**

13092 **10.4.1 MRI choice of targets for targeted biopsy**

13093 Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will
13094 subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in
13095 MRI-targeted biopsy. Operator experience (number of targeted biopsies performed
13096 to date) will be recorded before each procedure. The number of biopsy operators
13097 should be kept to the minimum number possible.

13098
13099 Targets will be stratified by PI-RADS score and if the same score then by size and
13100 labeled T1, T2, T3...etc. If there are more than 3 lesions with a score of 3 or more
13101 only T1-T3 will be targeted. The radiologist should record the sectors involved with
13102 tumor in order of most to least involved using the PI-RADS v2 sector scheme.
13103 The number of biopsy operators should be kept to the minimum number possible.

13104
13105 Subjects in the MRI cohort will not have systematic biopsies, with one exception.
13106 Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small
13107 volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core
13108 biopsy will be conducted.

13109 **10.4.2 MRI Biopsy**

13110 The procedure will be performed in the outpatient departments of sites possessing
13111 the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An
13112 operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI

13113 fusion system at their institution before they are qualified to participate as an
13114 operator in the study.
13115
13116 Coumarin anticoagulant, clopidogrel treatment and other relevant
13117 anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and
13118 advice sought as to appropriate substitutes if indicated. Aspirin will be continued at
13119 the discretion of the physician doing the biopsy.
13120
13121 Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will
13122 be performed via the trans-rectal route or via the trans-perineal route depending
13123 upon local practice.
13124
13125 Targeted biopsies should be performed by software-assisted fusion devices
13126 (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This
13127 software is safe and poses no risks to the subject since the same CE-marked
13128 ultrasound probes that are designed to perform the biopsy when performed as
13129 standard of care biopsy are used during targeted biopsy. Should the operator wish to
13130 not use the information provided by the software registration system and use
13131 cognitive (visual) registration alone they can do so, but should indicate this on the
13132 subject's case report form.
13133
13134 The samples per target will be 4cores spread across the target region for a maximum
13135 total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be
13136 conducted in order meaning T1 then T2 then T3.
13137
13138 Biopsy cores from different suspicious areas will be aliquoted separately. The vials
13139 will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there
13140 are) which should match the assignment of suspicious areas by the radiologist on the
13141 MRI report. The order of lettering a-d should match the order in which the biopsies
13142 were performed in each region. The first biopsy should be at the center of the target
13143 and the remaining fanning out from the center. Each core from the same suspicious
13144 area must be submitted separately. Alternative methods of storing cores that allow
13145 identification of the order of score samples from each target are acceptable.
13146

13147 **10.5 Systematic TRUS guided biopsy**

13148 **For all subjects in Arm B**

13149 Systematic TRUS guided biopsy is the current standard of care for the diagnosis of
13150 prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local
13151 site of recruitment.
13152

13153 A clinician competent in systematic TRUS guided biopsy will perform the procedure.
13154 The experience of the operator (number of systematic TRUS guided biopsies
13155 performed to date) will be recorded prior to each procedure. Software that guides
13156 clinicians in placing biopsy cores should not be used.
13157

13158 Coumarin anticoagulant, clopidogrel treatment and other relevant
13159 anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy

13160 and advice sought as to appropriate substitutes if indicated. Aspirin will be continued
13161 at the discretion of the physician doing the biopsy.

13162

13163 The subject will be positioned in left lateral position. 10-12 core biopsies will be
13164 taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed
13165 to the peripheral zone (See Appendix 3 for standardized method for conducting 12-
13166 core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be
13167 given as per local guidelines.

13168 **10.6 Pathology**

13169 The 2005 International Society of Urological Pathology guidelines for Gleason
13170 Grading of Prostatic Carcinoma will be followed [43].

13171

13172 For men undergoing MRI-targeted biopsy it is required that pathology reported per
13173 suspicious area targeted and per targeted core. For systematic TRUS guided biopsy,
13174 each core will be reported and graded.

13175 **10.7 Post-procedural care**

13176 **For all subjects in ARMS A and B receiving a biopsy**

13177 After a biopsy procedure the subject can be discharged within 2-3 weeks for results
13178 of the histopathology and treatment options to be discussed.

13179 **10.8 Immediate post-biopsy questionnaire**

13180 **For all subjects in ARMS A and B receiving a biopsy**

13181 A modified version of a self-reported questionnaire validated previously [39] in the
13182 assessment of post-biopsy complications will be completed immediately post-biopsy
13183 after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject
13184 should complete the immediate post-biopsy questionnaire before they leave the
13185 department. It aims to assess intensity of discomfort and pain associated with the
13186 procedure.

13187 **10.9 30-day post-biopsy questionnaire**

13188 **For all subjects in ARMS A and B receiving a biopsy**

13189 A modified version of a self-reported questionnaire validated previously [39] in the
13190 assessment of post-biopsy complications at 30 days post-biopsy should be given to
13191 all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home
13192 (Appendix 8). The subject should fill this out on day 30 following the procedure. It
13193 should take 5 minutes to fill out. The date that the participant should complete the
13194 questionnaire should be written on top of the questionnaire. Data on specific biopsy-
13195 related complications including pain, fever, hematuria, hematochezia,
13196 hematospermia, urinary retention and urinary incontinence will be recorded. Any
13197 other adverse events will not be recorded. Contact with healthcare and resource
13198 used data following the biopsy will also be ascertained. The completed questionnaire
13199 can be returned to the investigator in a pre-addressed envelope.

13200

13201 Subjects should be reminded at 30 days to complete this questionnaire.

13202 **10.10 Results and treatment decision (Visit 4)**

13203 The results of the biopsies and/or MRI will be explained to the subject by the clinical
13204 care team during this visit, which is approximately 2-3 weeks after the biopsy.

13205 The research team should record the treatment decision in the subject file.

13206 Possibilities for treatment decision include but are not limited to:

- 13207 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 13208 • Active Surveillance
- 13209 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 13210 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 13211 • Hormone therapy

13212 **10.11 Follow up period**

13213 All study participants will be followed up for up to two years or until they have
13214 radical treatment. Each year, subjects will be surveyed to obtain the following
13215 information:

- 13216 • time to cancer diagnosis
- 13217 • Gleason score progression
- 13218 • time to intervention on active surveillance
- 13219 • time on active surveillance
- 13220 • PSA
- 13221 • All subjects in both Arm A and B who have remained either undiagnosed or
13222 untreated (on active surveillance) will have a follow up MRI 2 years after
13223 study entry.

13224

13225 **10.11.1 Indications for biopsies off protocol**

13226 For subjects who are not biopsied due to a negative MRI, have negative or non-
13227 significant systematic biopsies, or who have a positive MRI but no or non-significant
13228 cancer on targeted biopsy, the following are guidelines for subjects management
13229 during the 2 year follow up period.

13230 It is an accepted standard of care in Ontario for subjects on active surveillance or
13231 with a prior negative biopsy who have a worsening risk profile to undergo mpMRI
13232 followed by targeted biopsy. We propose the following guidelines for risk profile
13233 assessment and consideration of repeat biopsy

13234 Subjects should continue to be followed with semi-annual PSA and DRE (not
13235 required, at the discretion of the PI). A biopsy should be considered under one or
13236 more of the following circumstances:

- 13237 1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.
- 13238 2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase
13239 in PSA in 1 year.
- 13240 3. Biopsy if a doubling of the risk of high grade cancer according to the NCI
13241 nomogram.

13242 4. Biopsy if development of a suspicious nodule on DRE.
13243
13244 5. For men with a positive study MRI (especially PI-RADS 4 or 5) and a
13245 targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if
13246 there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.
13247
13248 30. For men on the systematic biopsy arm which was negative or showed only
13249 Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or
13250 a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these
13251 subjects.
13252
13253
13254 These are guidelines and should be interpreted with clinical judgment.
13255
13256 Follow-up will cease once treatment beyond active surveillance is undertaken
13257 (prostatectomy, radiation therapy, focal therapy, etc.)
13258 PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI
13259 identifies a target.

13260 **10.12 Additional tests for biomarker discovery - Optional**

13261 Though not related to the primary outcome of this study, this cohort represents a
13262 unique opportunity to obtain human samples for future biomarker discovery studies.
13263 Participants will be consented to provide a blood, urinesemen, and tissue sample
13264 after the consent and screen visit, and subsequent visits for storage and use in future
13265 biomarker studies. In addition, men will be consented for use of the prostate biopsy
13266 tissue in the biomarker discovery studies.
13267

13268 We propose two initial biomarker analyses for men recruited to the PRECISE study.
13269 First we propose testing the utility of several genetic assays. These include the
13270 SELECT MDx test (a urine based genomic assay), the Telo PC test (an analysis of
13271 telomere structure in circulating tumour cells), the Exosome Dx assay (urine based
13272 exosome assay), the Mitomics assay (circulating mitochondrial DNA deletion assay),
13273 and the MDNA test (a urine based microRNA assay). We will test the hypothesis that
13274 alongside conventional PSA measurements, these tests may identify subjects whose
13275 MRI was initially negative for prostate cancer, but who are at high risk of harboring
13276 clinically significant disease as detected by the secondary MRI at 2 years. We will
13277 also test the association between serum biomarkers and clinically significant or
13278 clinically insignificant prostate cancer detected during the PRECISE study. We will
13279 also explore the potential for these assays to provide additional information over
13280 and above Gleason grade. These studies will be separately funded from PRECISE.
13281

13282 Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will
13283 be planned to assess markers which might identify men at higher risk of developing
13284 prostate cancer.

13285 **10.12.1 Samples to be collected for future biomarker discovery work**
13286 **(Optional)**

13287 Participants will be asked to consent to provide a blood, urinesemen and tissue
13288 sample after the consent and screen visit and subsequent visits for storage and use
13289 in future biomarker studies. This will involve a separate consent form.

13290 Samples include:

- 13291 • Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- 13292 • Urine – 75 mls urine
- 13293 • Semen 1-5cc (single ejaculate)
- 13294 • Tissue-unstained biopsy sections -15 unstained slides from cancer, and
13295 -15 unstained slide from non-cancer cores
13296 (if possible)

13297

13298 **10.12.2 Correlative Science Component**

13299

13300 Within this protocol biomarker and genetic validation studies and biomarker
13301 discovery research will be incorporated to correlate molecular readouts with the
13302 presence of Gleason 4 or 5 pattern on biopsy. The goal of these studies is to
13303 develop a liquid based assay (serum, plasma, CTCs, urine semen
13304) which accurately predicts the presence of clinically significant cancer. The
13305 correlative science component of Precise constitutes a major initiative, with multiple
13306 collaborators and planned studies. These are briefly summarized below.

13307

13308 Biomaterials (serum, plasma, buffy coat, PRE/POST DRE urine and tissue from
13309 biopsies) will be collected at times specified in the protocol. Sample collection will be
13310 restricted to subjects who have agreed to provide these samples in a separate
13311 optional informed consent. If a subject withdraws consent for the additional
13312 biomarker and genetic testing, subject's samples will be destroyed. The investigator
13313 must notify the sponsor site contact who will request the samples destruction.

13314 Biomaterials for the correlative science studies will be identified with a unique
13315 identification code, date of collection and will not contain any personal identification
13316 information. The samples will be shipped to a secure long-term storage facility,
13317 identified as the Ontario Institute for Cancer Research, located at 661 University Ave,
13318 Suite 510, Toronto, ON M5G 0A3. Samples for the correlative science studies will be
13319 shipped stored and analyzed according to specified, specialized procedures in the
13320 Precise Correlative Science Manual.

13321

13322 Biomaterial will be stored, anonymized, at the Ontario Institute of Cancer Research
13323 (OICR) Biobank, under the direction of Dr. John Bartlett. Dr. Bartlett is the Program
13324 Director, [Diagnostic Development](#), at OICR. The material will not be used for
13325 commercial purposes. No personal information will be kept at OICR. Personal
13326 identifying information on the patients in the PRECISE trial is held by the Ontario
13327 Clinical Oncology Group (OCOG), who are performing the data management function
13328 for the study. Access to the biomaterial will be under the control of the PRECISE
13329 steering committee. Access has already been approved for the Translational
13330 Research in Prostate Cancer (TRIPC) research group led by Dr. Paul Boutros. Future

13331 researchers interested in using the biomaterial will apply to the Precise steering
13332 committee for approval, based on the scientific merit of the study.
13333
13334 A group of investigators led by Drs. Paul Boutros (OICR) and George Rodriguez
13335 (UWO) have obtained funding for a correlative science study nested in the Precise
13336 trial. This study is termed the 'Translational Research Initiative in Prostate Cancer',
13337 or TRIPC. Biomaterial will be collected for these studies as above. A summary of
13338 the planned studies is as follows:
13339
13340 Urine: The TRIPC project will measure the proteomes of urine specimens using
13341 either a whole proteome assay or Selective Reaction Monitoring - Mass
13342 Spectroscopy (SRM-MS) or Peptide Reaction Mass Spectroscopy (PRM-MS) for a
13343 panel of ~50 peptides. These peptides will be used to score two published
13344 biomarkers of disease aggressivity
13345 (<https://www.nature.com/articles/ncomms11906>). The PRECISE data will then be
13346 used to retrain the parameters and weights of the biomarkers as an exploratory
13347 analysis.
13348
13349 Blood: Genotypes will be measured using either DNA-sequencing or genotyping
13350 arrays. The resulting data will be used to score five distinct biomarkers: a germline-
13351 incidence biomarker created by the PRACTICAL GWAS consortium, a biomarker of
13352 aggressive prostate cancer created by the PRACTICAL GWAS consortium, a panel of
13353 DNA repair genes identified by the SU2C group and two biomarkers of disease
13354 aggression identified by the CPC-GENE network. The PRECISE data will then be used
13355 to retrain the parameters and weights of the CPC-GENE biomarkers as an
13356 exploratory analysis. Second, methylation of cell-free DNA will be assessed using
13357 microarray platforms (either tiling or CpG island arrays) to score two existing
13358 signatures of aggressive prostate cancer.
13359
13360 Tissue
13361 Tumour biopsies will be subject to OncoScan microarray profiling and/or DNA
13362 sequencing to measure methylome, somatic single nucleotide variants, copy number
13363 aberrations, genomic rearrangements and mitochondrial copy number. Seven
13364 signatures of aggressive prostate cancer will be scored: the proportion of the
13365 genome altered (PGA, Lalonde et al. Lancet Oncology), 100-locus and 31-locus
13366 signatures (Lalonde et al. European Urology), a multi-modal signature (Fraser et al.
13367 Nature), a mitochondrial signature (Hopkins et al. Nature Communications), and two
13368 unpublished signatures developed by the CPC-GENE network: of tumour evolution
13369 and of the tumour methylome. The PRECISE data will be used to retrain the
13370 parameters and weights of the biomarkers as an exploratory analysis.
13371
13372
13373 A second group led by Dr. Keith Jarvi, will analyze semen for biomarkers of
13374 significant prostate cancer. They will utilize **deep targeted Next Generation**
13375 **sequencing of cell free DNA and tumor cells isolated from semen.**
13376
13377 • **Contact Information:** Dr. Keith Jarvi
13378 Murray Koffler Urologic Wellness Centre, 60 Murray Street, 6/F

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Toronto, ON M5T 3L9

Semen has potentially high amounts of exfoliated prostate epithelial cells and high concentrations of prostate derived cell free DNA amenable to measurement by the deep next generation DNA sequencing. The clear advantage of semen is its use as a fluid for biomarker identification as well as a clinical specimen for non-invasive diagnostics. In addition, semen and SP analysis may facilitate early cancer diagnosis since exfoliated PCa cells and PCa specific cell free DNA will appear in semen much earlier and prior to destruction of prostate blood barrier and diffusion of cells and cell free DNA into the blood.

Dr. Jarvi's group will focus on known gene fusions and point mutations in exomes of genes frequently mutated in PCa. They used the next generation DNA sequencing data uploaded to the cBioPortal. That included 841 primary prostate cancer tissues sequences by the Cancer Genome Atlas, Broad Institute and Memorial Sloan Kettering Cancer Centre. As a result, they identified a panel of 30 genes (26 genes with 271 recurrent or potentially recurrent missense mutations and 4 gene fusions) which provided sensitivity of 92 % at theoretical 100% specificity for detection of PCa. Upon protocol optimization, they will first complete a pilot study and sequence cell free DNA in 24 SP samples from men with PCa, 12 seminal plasma (SP) samples from men with a negative biopsy and 12 SP samples from healthy fertile men. They will then validate the diagnostic performance of the 30 gene panel in 288 SP samples from men with low grade, intermediate grade, high grade PCa, negative biopsy, prostate inflammation and healthy men.

They will also develop an approach for immunomagnetic isolation of prostate epithelial cells and PCa cells from semen. They propose that PCa cells isolated from semen may function as a non invasive 'liquid biopsy' tool for the accurate diagnosis and subtyping of PCa. Exfoliated prostate epithelial cells and PCa cells will be isolated using magnetic beads coated with monoclonal antibodies or high affinity aptamers for the prostate specific membrane antigen (PSMA). Since PSMA is cell surface protein exclusively expressed in prostate cells, this procedure will enrich prostate epithelial cells and PCa cells, but despite spermatozoa and leukocytes. Protocols for cell isolation will include the use of either centrifugation or magnetic activated cell sorting. Genomic DNA will be extracted, purified and analyzed by the next generation sequencing. Using semen samples from post vasectomy semen, they will investigate the impact of spermatozoa on the efficiency of isolation of prostate epithelial cells.

The following collaborators will also be receiving biomaterial specimens (blood and/or urine semen). The goals of each of these groups is to correlate a biomarker readout with the likelihood of prostate cancer, and of clinically significant cancer. The planned assays are summarized briefly as follows

- 3D Signatures
MaRS Centre, South Tower
101 College Street, Suite 200
Toronto, Ontario, Canada M5G 1L7

13427

13428 This group will be examining the telomere structure of circulating tumour cells
13429 (CTCs) using an established assay, the Telo PC test. The results of a 50 patient
13430 prostate cancer pilot study in men with intermediate risk prostate cancer who
13431 underwent radical prostatectomy showed that the TeloPC assay correctly predicted
13432 the status/aggressiveness of disease in each of the study's patients.¹ While all
13433 patients were diagnosed as intermediate risk using conventional biopsies prior to
13434 surgery, only 21 of the 50 patients who underwent RP showed disease upgrading
13435 upon post-surgical analysis and therefore were suitable for prostate removal. The
13436 TeloPC assay correctly predicted that 29 of the 50 patients had a stable form of
13437 prostate cancer.

13438

13439 The TeloPC assay includes filtration-based circulating tumour cell (CTC) enrichment
13440 combined with 3-dimensional (3D) analysis of telomeres to obtain 3D telomere
13441 profiles of PCa patients with low-intermediate risk category.

13442

- MiR Diagnostics
13443 1 Discovery Drive
13444 Rensselaer, NY 12144

13445

13446 This group will be examining urinary microRNAs and other non-coding RNAs from
13447 urinary exosomes. A panel of 56 miRNAs and snoRNAs, which have been
13448 demonstrated to be predictive of clinically significant prostate cancer, will be
13449 interrogated. The urine samples will be used to establish the sensitivity of the
13450 procedures and the precision of the analytic algorithms to identify those with
13451 significant prostate cancer. The long term goal of the project is to develop a non-
13452 invasive methodology that can be used to identify genetic alterations that identify a
13453 group of patients at high risk for clinically significant prostate cancer.

13454

13455

13456

13457

- Exosome Diagnostics, Inc.
13458 266 2 nd Ave.
13459 Waltham, MA 02451

13460

13461 This group will be interrogating non-coding RNAs extracted from urinary exosomes.
13462 They will assay exosomal RNA for three biomarkers known to be expressed in men
13463 with high-grade prostate cancer, using an algorithm that integrates this three-gene
13464 signature,

13465

13466

- MDNA Life Sciences, Inc.
13467 2054 Vista Parkway, Suite 400
13468 West Palm Beach, FL 33411

13469

13470 This group will evaluate the performance of the Prostate Mitomics test. This is a
13471 blood-based screening test which evaluates free plasma DNA for the presence of a
13472 mitochondrial DNA deletion. This deletion has been demonstrated to be associated
13473 with high grade prostate cancer. Nucleic acids will be extracted from each plasma

13474 sample using a commercially available reagent kit. The Prostate Mitomic Test is a
13475 quantitative real-time PCR test for a 3.4kb mitochondrial DNA deletion correlated
13476 with prostate cancer. Each sample will also be profiled for novel mitochondrial
13477 DNA mutations using standard laboratory techniques such as quantitative real-time
13478 PCR. Mutation frequency will be compared to clinical outcomes.

13479
13480

- 13481 • MDx Health, Inc
13482 15279 Alton Parkway, Suite 100
13483 Irvine, CA 926188

13484

13485 This group will perform the Select MDx assay, a two gene mRNA assay performed on
13486 urine, to evaluate its performance in predicting the presence of clinically significant
13487 prostate cancer.

13488

13489 **10.13 Long-term data linkage – Permission to Contact**

13490 The cohort of men who consent to participate in this study represent a uniquely
13491 characterized group. Their long-term outcomes will contribute to our understanding
13492 of the epidemiology of prostate cancer beyond the questions being addressed in this
13493 study.

13494

13495 Permission to Contact (PTC) is a feasible mechanism to engage subjects in research
13496 programs. This will allow researchers to contact study participants in the future to
13497 assess their willingness to respond to questionnaires. This potentially enables
13498 research that would complement the planned long-term follow up in terms of health
13499 status, for obtaining information about future biopsies not included in the study, and
13500 allow assessment of quality of life.

13501 **10.14 End of Study**

13502 The end of study assessment comprises an essential safety evaluation that should be
13503 completed prior to discharging any subject from the study.

- 13504 • Adverse events;
- 13505 • PSA measurement;
- 13506 • EQ-5D-5L questionnaire;
- 13507 • An MRI in those who did NOT have a biopsy;
- 13508 • Complete CRF.

13509 **10.15 Risks and Benefits to Participants**

13510 An important consideration of this study is that men are being randomized to one of
13511 two biopsy techniques when it is not known which will be more effective. Both
13512 diagnostic tests are currently used in clinical practice at the institutions involved in
13513 the trial. Though systematic TRUS guided biopsy could be considered standard of
13514 care, there is enough evidence to support the concept that MRI-targeted biopsy may
13515 be at least as effective as systematic TRUS guided biopsy[27].

13516 **10.15.1 Risks to subjects**

13517 The intervention proposed in this trial (MRI-biopsy) do not offer participants any
 13518 more risk than if they underwent standard of care (systematic TRUS guided biopsy)
 13519 for the diagnosis of prostate cancer.

13520 **10.15.1.1 Risk of Systematic TRUS guided biopsy**

13521 Systematic TRUS guided biopsy can be associated with discomfort, haematuria,
 13522 haemospermia and dysuria in a large proportion of subjects, which is self-resolving
 13523 (See Table 4). There is a 4% risk of systemic urosepsis[46].

13524 **10.15.1.2 Risks of MPMRI**

13525 MRI is associated with few risks. It is a safe procedure used in everyday clinical
 13526 practice (See Table 4). Small risks of allergic reactions are associated with the
 13527 intravenous administration of gadolinium, the contrast agent used in MRI scans. The
 13528 study uses a low molecular weight Gd chelate as a contrast agent (Gadovist, Bayer,
 13529 gadobutrol – generic). This contrast agent is used routinely for contrast enhanced
 13530 MRI and is approved by Health Canada. Subjects will be screened for any
 13531 contraindications to Gd injection or to MRI as per current clinical Dept of Medical
 13532 Imaging protocols at each institution. The commonest reported sides effects are of
 13533 limited duration and mild to moderate in intensity and include headache,
 13534 vasodilation, injection site pain, nausea, dizziness, rash, and dyspnea. The incidence
 13535 of these are <1%. Severe life threatening reactions such as severe anaphylaxis occur
 13536 very rarely, about 1:10,000-1: 100,000. These are treatable with epinephrine and
 13537 steroids. The risk of death is <1:100,000. There is a known risk of nephrogenic
 13538 systemic fibrosis, a potentially fatal condition in subjects with impaired renal
 13539 function, with an eGFR<30ml/min/1.73m2. These subjects are ineligible for this
 13540 study.

13541 **10.15.1.3 Risks of MRI-targeted biopsy**

13542 MRI-targeted biopsy is associated with similar risks to the standard of care
 13543 systematic TRUS guided biopsy. As fewer biopsy cores are being taken with MRI-
 13544 targeted biopsy, the theoretical risk of adverse events associated may be less than
 13545 that of systematic TRUS guided biopsy. In addition, as a proportion of men may not
 13546 require a biopsy (approximately 30%) on a group level there will be reduced number
 13547 of men experiencing these complications, which is one of the major advantages of an
 13548 MRI-based approach.

13549

13550 **Table 4: Adverse events associated with procedures**

13551

Side Effect \ Procedure	Systematic TRUS guided biopsy(Standard of care)	MRI	MRI-targeted biopsy
Pain / discomfort	Some have discomfort Some have pain	Intravenous cannulation (to allow contrast administration) can cause minimal discomfort	Similar / reduced compared to systematic TRUS guided biopsy

Dysuria	Majority have dysuria (self-resolving in 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematuria	Majority (self-resolving, 2-3 days)	No	Similar / reduced compared to systematic TRUS guided biopsy
Haematospermia	Majority (self-resolving, 1-2 weeks)	No	Similar / reduced compared to systematic TRUS guided biopsy
Erectile dysfunction	30% (self resolving after 1-2 months)	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary Tract infection	1-8 %	No	Similar / reduced compared to systematic TRUS guided biopsy
Systemic urosepsis	2-4%	No	Similar / reduced compared to systematic TRUS guided biopsy
Urinary retention	1%	No	Similar / reduced compared to systematic TRUS guided biopsy
Contrast allergy	N/A	Rare < 1 in 10000 – severe allergic reaction (breathing problems) < 1 in 2000 – moderate allergic reaction (nausea and vomiting) < 1 in 250 – mild allergic reaction (rash, itching)	N/A
Adverse effects of antibiotics	Rare <1%	N/A	Rare <1%

13552

13553

13554

13555 **10.15.2 Benefits to subjects**

13556 Subjects enrolled in this trial will benefit from the following:

- 13557 • Subjects in both arms may benefit from receiving a diagnostic test for suspected prostate cancer and will receive further treatment if required. The research team
- 13558 will also ensure streamlined diagnostic investigations to promptly conduct the
- 13559 diagnostic test and communicate the test outcome for the subject.
- 13560
- 13561 • Subjects enrolled in the trial will benefit from the dedicated research team
- 13562 involved in their care in addition to the clinical team normally involved in their
- 13563 care.
- 13564 • Subjects will benefit from additional discussions regarding the trial, which could
- 13565 increase their understanding of prostate cancer and help them to make a more
- 13566 informed decision about their health.

13567 • Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will
13568 remove any risk of post-biopsy infection. MRI-randomized subjects may also
13569 benefit from a reduced probability of having a clinically insignificant prostate
13570 cancer diagnosed. Clinically insignificant prostate cancer is often treated
13571 definitively per subject preference despite the lack of evidence supporting the
13572 need. All definitive local therapies for prostate cancer carry the risk of peri-
13573 operative complications as well as long-term risk of incontinence and erectile
13574 dysfunction.
13575

13576 **10.16 Concomitant medications**

13577 **10.16.1 Permitted Medications**

13578 All concomitant medications taken during the study will be recorded in the CRF with
13579 indication, dose information and dates of administration. The definition of which
13580 medication would be considered outside the routine medical practice is up to the
13581 discretion of the investigator. All dietary and herbal supplement usage will be
13582 recorded in the CRF.

13583 **10.16.2 Non-Drug Therapies**

13584 Any occurrence of prostate-related surgical and/or non-surgical (or minimally
13585 invasive) intervention during the conduct of the study will be recorded in the CRF.
13586

13587 **11. Schedule of Study Visits**

13588 **11.1 Visit 1 (Screening/Randomization): Screening, Consent,** 13589 **Randomization**

13590 **For all subjects enrolled in trial**

13591 Screening will occur any time following the referral of the subject. Ideally, this will be
13592 performed as soon as possible following receipt of referral.

13593 Subjects will be consented only after they have had time to consider the study. This
13594 may happen on the same visit as the screening visit.

13595 Randomization can happen immediately after the consent form is signed and
13596 eligibility is confirmed.

13597

13598 Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L
13599 questionnaire (Appendix 4), which is a validated 2-page questionnaire representing
13600 health related quality of life. It takes approximately 2 minutes to complete. This
13601 questionnaire should be completed at the screening visit before the subject leaves
13602 the clinic.

13603

13604 If a subject agrees to the optional informed consent, from randomization until any
13605 point prior to a biopsy, optional blood, urine semen and tissue samples will be
13606 collected for correlative studies.

13607

13608 If PSA testing was done greater than 3 months of randomization, this must be
13609 repeated at screening/Visit 1.

13610

13611 **11.2 Visit 2 (MRI): ARM A, for men randomized to MRI**

13612 This will occur approximately within one week of randomization. Men will receive an
13613 MRI (see Section 10.2.)

13614 **11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate**

13615 **For men randomized to ARM A, who have a lesion identified by MRI.** This
13616 appointment will follow approximately one-two weeks of MRI.

13617

13618 Depending on local Urology service structure, an appointment for a biopsy may need
13619 to be booked at the same time as the MRI is booked (i.e. immediately after
13620 randomization) in order for a biopsy to occur in timely fashion. If the results of the
13621 MRI show that a biopsy is not required, then the biopsy appointment can be used
13622 instead of Visit 4 for follow up of results and treatment decision.

13623

13624 Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy
13625 of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy
13626 Questionnaire (Appendix 7) ideally completed and returned immediately after a
13627 biopsy, before the subject leaves the department.

13628

13629 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
13630 and complete as instructed on day 30 post-biopsy. This is to be returned by post or
13631 at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post
13632 biopsy then this questionnaire can be given to the research team when 30 days is
13633 finally complete. If Visit 4 is on or later than 30 days then this can be returned at the
13634 Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-
13635 biopsy, it will be acceptable, however, the questionnaire should be completed as
13636 close as possible to 30 days post-biopsy.

13637

13638 At the 30-days post biopsy interval, a member of the research team will call the
13639 subject to remind them to complete and return the 30-day questionnaires.

13640 **11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic**
13641 **TRUS-biopsy**

13642 **For men randomized to ARM B only.**

13643

13644 Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will
13645 complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed
13646 and returned immediately after the biopsy.

13647 Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy
13648 and it is to be completed as instructed on day 30 post-biopsy. This is to be returned
13649 by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30
13650 days post biopsy then this questionnaire can be given to the research team when 30
13651 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the
13652 Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-

13653 biopsy, it will be acceptable, however the questionnaire should be completed as
13654 close as possible to 30 days post-biopsy.

13655

13656 At 30-days post biopsy a member of the research team will call the subject to remind
13657 them to complete and return the 30-day questionnaires.

13658 **11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a**
13659 **biopsy**

13660 This appointment will include a follow up meeting with the investigator to discuss
13661 the results of the MRI as well as treatment decisions. This follow up should occur
13662 after the availability of the MRI report. At this visit the subject will also complete a
13663 30-day post intervention EQ-5D-5L Questionnaire.

13664

13665 Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8), which has been
13666 posted to them by the research team. If Visit 4 is earlier than 30 days post MRI then
13667 this questionnaire can be given to the research team when 30-days is finally
13668 complete. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4
13669 appointment. As long as the questionnaire is completed at 30-60 days post-MRI, it
13670 will be acceptable, however the questionnaire should be completed as close as
13671 possible to 30 days post-MRI.

13672

13673 At 30-days post MRI, a member of the research team will call the subject to remind
13674 them to complete the 30-day questionnaires.

13675 **11.6 Visit 4 (Post-test follow up): For all men who received a biopsy**

13676 This appointment will include a follow up meeting with the investigator to discuss
13677 the results of the biopsy as well as treatment decisions. This should be completed as
13678 soon as possible following the availability of any pathology results. The follow up
13679 appointment should be within 1 month of the biopsy. Depending on local Urology
13680 service structure, these results may need to be discussed at an MDT meeting to
13681 inform treatment decision.

13682

13683 The research team should record the treatment decision in the subject file.

13684

13685 Possibilities for treatment decision include but are not limited to:

- 13686 • Further diagnostic test (e.g. PSA, biopsy, MRI)
- 13687 • Active Surveillance
- 13688 • Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- 13689 • Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- 13690 • Hormone therapy

13691

13692 At this visit the subject will also receive a 30-day post intervention EQ-5D-5L
13693 Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy
13694 questionnaire (Appendix 8), which has been posted to them by the research team.
13695 The questionnaire needs to be completed on the 30th day post-intervention (i.e. post
13696 biopsy). However it will be accepted if completed up to 72 hours prior to or after the

13697 30th day. A telephone reminder from the research team to the subject can take
13698 place.
13699

13700 **11.7 Visit 5 (6 month follow up):26 week follow up**

13701 All subjects will have a 26 week visit

13702 Subjects will have the following:

- 13703 • Vitals, DRE (not required, at discretion of PI)
- 13704 • PSA
- 13705 • Optional sample collection (blood)

13706 **11.8 Visit 6 (1 year follow up): 52 week follow up**

13707 All subjects are planned to have a 52 week follow up visit.

13708 Subjects will be followed to obtain the following information on an annual basis:

- 13709 • Vitals, DRE
- 13710 • time to cancer diagnosis;
- 13711 • Gleason score progression;
- 13712 • time to intervention on active surveillance;
- 13713 • time on active surveillance;
- 13714 • results of PSA tests.
- 13715 • Time to follow up biopsy and/or mpMRI if performed (see follow up
13716 guidelines)
- 13717 • Indication for follow up biopsy
- 13718 • Was MRI performed prior to follow up biopsy
- 13719 • Was the biopsy systematic, targeted only or both systematic + targets, not
13720 done because of negative MRI
- 13721 • Optional sample collection (blood, urine)

13722

13723 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
13724 will have an additional MRI at Visit 6 (year 2).

13725 **11.9 Visit 7 (18 month follow up): 78 week follow up**

13726 All subjects will have a 78 week visit

13727 Subjects will have the following:

- 13728 • Vitals, DRE (not required, at discretion of PI)
- 13729 • PSA
- 13730 • Optional sample collection (blood)

13731

13732 **11.10 Visit 8 (2 year follow up): End of study**

13733 All study participants will be followed for up to two years or until they undergo
13734 radical treatment

13735 Subjects will be followed to obtain the following information on an annual basis:

- 13736 • Vitals, DRE
- 13737 • time to cancer diagnosis;
- 13738 • Gleason score progression;

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- 13751
- time to intervention on active surveillance;
 - time on active surveillance;
 - results of PSA tests.
 - Optional sample collection (blood, urine)
 - Time to follow up biopsy and/or mpMRI if performed (see follow up guidelines)
 - Indication for follow up biopsy
 - Was MRI performed prior to follow up biopsy
 - Was the biopsy systematic, targets only or both systematic + targets, not done because of negative mpMRI

13752 Follow-up will cease once treatment beyond active surveillance is undertaken
13753 (prostatectomy, radiation therapy, focal therapy, etc.).

13754

13755 Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy
13756 will have an additional MRI at Visit 8.

13757

13758 **12. Randomization**

13759 **12.1 Randomization Procedure**

13760 Written informed consent will be obtained from all eligible subjects prior to
13761 commencing any study related procedures. The Ontario Clinical Oncology Group
13762 (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre,
13763 Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate
13764 subject randomization. Subjects will be allocated to the two treatment arms in an
13765 approximate 1:1 ratio by use of a dynamic allocation scheme[47].

13766

13767 After documentation of written informed consent and confirmation of subject
13768 eligibility, clinical centres will randomize the subject by accessing the CMC's web-
13769 based Interactive Registration/Randomization System (IRIS). Prior to randomization
13770 and treatment allocation, the subjects' individualized risk of high-grade prostate
13771 cancer, obtained using the PCPTRC 2.0 calculator found at
13772 <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp> must be determined.

13773 **12.2 Stratification**

13774 Eligible, consenting subjects will be stratified by: (1) individualized risk of high-grade
13775 prostate cancer (5% to 25%, >25%); and (2) clinical centre

13776 **12.3 Blinding and measures taken to avoid bias**

13777 This study is unblinded, and all subjects will be aware of the treatment that they are
13778 receiving. As the MRI scan is unique to one of the arms it will not be possible to blind
13779 the participants or investigators as to what intervention is being received. Therefore,
13780 participants will be informed which arm they have been allocated to. Where
13781 possible, the data will be coded so as to blind individuals analyzing the data from
13782 which of the groups the data was from. Summary details of randomized allocation

13783 and outcomes will not be made available (unless specifically authorized by the Trial
13784 Steering Committee and/or Data Monitoring Committee) in order to maintain the
13785 overall blind of the trial.

13786

13787 Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be
13788 aware that the subject is part of the trial.

13789 Pathologists will be blinded to the cohort allocation. Concealment may be
13790 challenging due to the different number of cores in the two groups, but this is
13791 unavoidable. This is unlikely to represent a significant source of bias.

13792

13793

13794 **13. Data**

13795

13796 Type of data to be collected:

- 13797 • EQ-5D–5L questionnaires. These will measure quality of life and which will be
13798 measured at specific times throughout the trial.
- 13799 • Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and
13800 continuous data
- 13801 • MRI – diagram representing MRI; categorical data for areas and scores of
13802 suspicion (e.g. Sector 1p, score of suspicion 4/5)
- 13803 • MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and
13804 continuous data
- 13805 • Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers
13806 yes/no)
- 13807 • Treatment decisions – categorical data (e.g. radical treatment)
- 13808 • PSA – continuous data (e.g. value of PSA in ng/ml)

13809

13810 Please see **Appendix1** for the time window for data collection.

13811

13812 **14. Statistical Considerations**

13813 **14.1 Sample Size Calculation**

13814 **STATISTICAL methods**

13815 **Primary Analysis**

13816 Absolute differences in the proportion of clinically significant cancer detected
13817 between arms will be calculated and compared using the Clopper-Pearson method.
13818 If the lower boundary of an one-sided, 97.5% confidence interval for the difference
13819 in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less
13820 than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower
13821 bound is greater than zero, superiority can be claimed.

13822

13823 A supportive analysis will be performed by using a logistic regression model,
13824 evaluating the odds ratio for detecting high grade cancers, adjusted for stratification
13825 factors. MRI-guided biopsy would be considered non-inferior if the lower bound of
13826 the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower

13827 bound was calculated to approximate an absolute 5% difference of interest (NOTE:
13828 the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).
13829

13830 **Secondary Analyses**

13831 For each secondary outcome, where appropriate, a difference in proportions with
13832 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.
13833 Differences in the 1-year and 2-year rates along with 95% CI will be calculated for
13834 time-to-event outcomes.

13835
13836 χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for
13837 differences between allocation arms in secondary outcomes. Logistic regression and
13838 Cox proportional hazards regression will be used to examine the effect of allocation
13839 arm on outcomes, adjusted for stratification factors. All secondary outcomes will be
13840 two-sided and statistical significance will be set at the $\alpha=0.05$ level. No statistical
13841 adjustments will be made due to multiple testing, however, results for secondary
13842 outcomes will be interpreted cautiously, acknowledging that tests were performed
13843 on secondary outcomes and numerous secondary tests were performed. Figures and
13844 tables will be used to illustrate results of interest.

13845

13846 **Treatment Allocation and Stratification**

13847 Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by
13848 use of a dynamic allocation scheme. Specifically, the first 20 subjects will be
13849 randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a
13850 biased coin method will be used, whereby the number of subjects within each
13851 stratum will be calculated, and the next eligible subject will be allocated (with
13852 probability $p=0.8$) to the arm which reduces the imbalance. If no imbalance exists,
13853 allocation to each arm will occur with probability $p=0.5$.

13854

13855 Stratification

13856 For treatment allocation, the subjects' individualized risk of high-grade prostate
13857 cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator,
13858 found at <http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp>. Eligible, consenting
13859 subjects will be stratified by:

13860 (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);

13861 (2) clinical centre.

13862

13863 **Sample Size**

13864 Rates of clinically significant cancer (Gleason ≥ 7) detection from targeted-alone
13865 biopsy in a population with no prior biopsy have been shown to be 42% [37] and
13866 50% from another study [36].

13867

13868 Rates of clinically significant cancer detection from one the largest studies of
13869 systematic TRUS guided biopsy in men without prior biopsy are shown to be 27%
13870 [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will
13871 detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than
13872 systematic TRUS guided biopsy.

13873

13874 For this study, it will be conservatively hypothesized that systematic TRUS guided
13875 biopsy will detect clinically significant cancer in 30% of men, and targeted biopsy will
13876 detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic
13877 TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5%
13878 one sided-alpha, assuming a targeted biopsy detection rate of clinically significant
13879 cancer of 40%, and a detection rate for systematic TRUS guided biopsy of 30% and
13880 using a margin of clinical unimportance of 5%, 211 men per arm will be required. The
13881 choice of 5% as the margin of non-inferiority represents a difference that would be
13882 considered clinically important.

13883
13884 Thus total men required in study = **422**.

13885
13886 To account for potential withdrawal / loss to follow up and the effect of
13887 stratification, the sample size will be inflated by 5%, and a target of **450 men** will be
13888 recruited.

13889
13890 Note that the rate of clinically significant cancers is very dependent on the
13891 population registered for this study. It is possible that fewer (or more) subjects will
13892 have clinically significant cancers than what is initially hypothesized. However, if the
13893 population rate of clinically significant cancers is less (i.e. the systematic TRUS guided
13894 biopsy detection rate is <30%) and other statistical assumptions remain as stated
13895 previously, the statistical power will increase. The minimum statistical power would
13896 be obtained if the clinically significant cancer detection rate was 45% for systematic
13897 TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84%
13898 power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the
13899 rate of clinically significant cancer in the population is miss-specified, assuming an
13900 absolute difference of 10% between targeted and systematic TRUS guided
13901 biopsy detection rates, and a 5% margin of non-inferiority.

13902
13903 **Statistical Conventions**

13904 For categorical data, tables will be presented showing the n and percentage
13905 (n/N*100%) of subjects. Analyses will be presented by study allocation arm
13906 separately.

13907
13908 Duration of time will be described in either years, months or weeks, and calculated
13909 using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or
13910 X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date –
13911 date of birth + 1)/365.25.

13912
13913 Transformations of the data in order to meet statistical assumptions may be
13914 considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to
13915 assess any of the model fittings. All the statistical analysis will be carried out using
13916 SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-
13917 project.org) or higher.

13918
13919 **Missing Data**

13920 Missing values for the primary endpoint will be examined closely. Sources and
13921 reasons for the absence of data incurred as a result of subjects lost-to-follow up,

13922 dropouts, and intermittent missing values will be described and explored by various
13923 summary statistics as well as graphical displays between the two allocation arms.
13924 Subjects' lost-to-follow up or dropouts will be explored and the characteristics of
13925 those subjects will be described by allocation arm and tested using Fisher's exact
13926 tests or Wilcoxon rank sum tests.

13927
13928 Missing data for secondary endpoints will be described. The methods for evaluating
13929 missing data of the primary endpoint may be employed for endpoints of interest. For
13930 summarization of baseline data, the following conventions will be used for partial
13931 missing date information occurring prior to randomization (e.g. for medical history
13932 or prior treatment). If year is missing, the date will be set at missing. If year is
13933 available, but month and date is missing, the month and date will be set to July 1st of
13934 the respective year. If date is missing, but year and month available, the day will be
13935 set to the 15th of the respective month.

13936 **14.2 Interim Analyses**

13937
13938 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
13939 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
13940 conduct if there are concerns about subject safety or futility. Unless otherwise
13941 specified by one of these bodies, a futility analysis will be performed after
13942 approximately 200 subjects are enrolled and have their primary outcome
13943 ascertained. Simulation will be used to estimate the conditional probability of futility
13944 assuming the study was to continue to completion, and assuming the clinically
13945 significant cancer detection rate is 30% in both arms. If the conditional probability is
13946 0.95 or higher that continuation of the study will result in a negative result, the
13947 DSMC will recommend a suspension of recruitment to the trial, and initiation of a
13948 quality assurance review. A decision to permanently close the study or continue with
13949 accrual will be determined by the Steering Committee, based on the results of the
13950 quality assurance review, and the recommendation of the DSMC.

13951 13952 **Timing of Final Analysis**

13953 A single, final, analysis will occur after all subjects have undergone their initial biopsy
13954 and all data related to the initial biopsy is documented and validated. Follow-up
13955 analyses will be conducted after all subjects have completed two years of follow-up.

13956 **14.3 Populations:**

13957 The per protocol, study population will consist of all subjects who satisfy all eligibility
13958 criteria and are randomized to the study, who undergo MPMRI-TB or systematic
13959 TRUS guided biopsy and have their primary outcome measured. This population will
13960 be used for the primary analysis of non-inferiority.

13961 The intent-to-treat (ITT) population will consist of all subjects randomized to the
13962 study, regardless of any protocol violations or if they do not complete the study as
13963 defined in the protocol. The ITT population will be used as a supportive analysis of
13964 the primary analysis, for all safety analyses, and for any analysis investigating
13965 superiority.

13966 **14.4 Primary Outcome**

13967 **14.4.1 Detection rate of clinically significant cancer**

13968 The proportion of men in each arm with clinically significant cancer (Gleason ≥ 7) will
13969 be calculated based on histology results from biopsy procedures. Analysis will be on
13970 the intention to treat population.

13971

13972 Absolute differences in proportion of clinically significant cancer detected between
13973 arms will be calculated and compared. If the lower boundary of the 97.5%
13974 confidence interval for the difference in detection rates of MPMRI-TB compared to
13975 systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-
13976 inferior. In the event that the lower bound is greater than zero, superiority can be
13977 claimed.

13978

13979 The primary analysis will be conducted once all subjects have completed visit 4,
13980 when the results of the biopsy or MRI are given to the subject.

13981

13982 **14.5 Secondary Outcomes**

13983 For each secondary outcome, where appropriate, a difference in proportions with
13984 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

13985

13986 **14.5.1 Proportion of men in each arm with clinically insignificant
13987 cancer detected**

13988 The proportion of men in each arm with clinically insignificant cancer (Gleason < 7)
13989 will be calculated based on histology results from biopsy procedures. In addition, the
13990 numbers with clinically insignificant cancer identified by MRI alone will also be
13991 included.

13992

13993 **14.5.2 Proportion of men in each arm with Gleason $\geq 4 + 3$ detected**

13994 The proportion of men in each arm with Gleason $\geq 4 + 3$ will be calculated based on
13995 histology results from biopsy procedures. In addition, the numbers with clinically
13996 insignificant cancer identified by MRI alone will also be included.

13997

13998 **14.5.3 Proportion of men in MPMRI arm who avoid biopsy.**

13999

14000 **14.5.4 Proportion of men in the MRI arm whom the PI-RADS score for
14001 suspicion of clinically significant cancer was 3, 4 or 5 but no clinically
14002 significant cancer was detected.**

14003 The proportion of men in each arm whom the PI-RADS score for suspicion of
14004 clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was
14005 detected, will be calculated based on histology results from biopsy procedures.

14006

14007 **14.5.5 Proportion of men in each arm who go on to definitive local
14008 treatment (e.g. radical prostatectomy, radiotherapy, brachytherapy) or
14009 systemic treatment (e.g. hormone therapy, chemotherapy)**

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14.5.8 Proportion of men with a negative MRI who progress within 24 months after their study MRI, or who are upgraded within 24 months

Men with a negative MRI who do not undergo a biopsy will have a follow-up MRI 2 years after their study MRI. We will determine the proportion of men whose subsequent MRI shows a PI-RADS 3 or greater lesion. The results of targeted biopsy of those lesions will be recorded and analyzed. The number of men who are upgraded to Gleason ≥ 7 due to an off-protocol biopsy will also be recorded.

14.5.9 Proportion of men with post-biopsy adverse events

Immediate post-biopsy discomfort and pain will be characterized by intensity using the numerical analogue score. Scores for each arm will be compared. 30-day biopsy specific complications and adverse events will be characterized according to their presence, absence, duration and how much of a problem the symptoms caused the subject. Whether the subject had contact with health care providers/system will also be recorded. The proportion of individuals experiencing each symptom, proportion in whom that symptom caused a problem and proportion who had contact with healthcare providers/system will be calculated and compared qualitatively between arms utilizing classification systems validated in previous studies [39]. The biopsy specific complications that will be compared include pain, urinary retention, fever, pain, erectile dysfunction, urinary incontinence, haematuria, haematochezia and haematospermia.

Any post-biopsy complications up to 30-days post biopsy procedure will be tabulated and listed by duration and management.

14.5.10 Health related quality of life

EQ-5D-5L descriptive domain summary indices and visual analogue scores will be assessed at baseline, at 2 years and changes will be compared between arms.

EQ-5D was selected as a simple, low burden quality of life instrument that will provide validated information on symptoms, particularly anxiety, that could be compared across disease states and studies. Other subject-reported outcomes directly linked to the interventions will be captured in the post-biopsy surveys. Since it provides utilities, these will be incorporated into a secondary economic analysis if the results permit.

14.5.11 Proportion Gleason score upgrading in men undergoing radical prostatectomy

Of the men who undergo radical prostatectomy, the proportion who have cancer upgraded from the biopsy histopathology to the radical prostatectomy histopathology in each arm will be calculated and compared.

14.5.12 Cost Outcomes

14056 As the study design for clinical outcomes is one of non-inferiority, the primary
14057 economic analysis will be **cost minimization analysis**. The perspective of the
14058 economic analysis will be that of the public payer. The primary goal of the analysis
14059 will be to support arguments for public funding. Thus the costs of participant
14060 burden, logistical challenges, and expense of obtaining societal costs, will not be
14061 evaluated.

14062

14063 **14.5.12.1 Data collection:**

14064 As part of the informed consent process, participants in Ontario will also
14065 consent to having their Ontario Health Insurance Number recorded, to be
14066 later transferred to the Institute for Clinical Evaluative Sciences (ICES) where
14067 it will be linked to a number of administrative claims databases recording
14068 health system resource utilization such as physician billing [Ontario Health
14069 Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization
14070 and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug
14071 Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity
14072 Level Reporting (ALR)]; clinic and emergency department visits [National
14073 Ambulatory Care Reporting System (NACRS), Emergency Department visits];
14074 radiation (ALR); homecare (Home Care databases) and a few additional ones
14075 as determined necessary (e.g., Long-term care, Mental Health, Diabetes. The
14076 overall, number and proportion of health system resources will be
14077 determined. In this way we can capture comprehensive resource utilization
14078 related to on-trial management including any adverse events.

14079 **14.5.12.2 Health Insurance number handling and security**

14080 As the economic implications of this study are of prime importance to some
14081 of the funders, the request for data linkage will be part of the main consent
14082 form. If a participant indicates to the study team that they decline or
14083 withdraw consent, the OHIP number will be recorded as 9999-999-999-XX.
14084 The OHIP numbers will stay with the participating institution until after
14085 accrual is complete, and then they will all be transferred at one time under
14086 data sharing agreements between ICES and each institution. Data will be
14087 transferred using a secure electronic file transfer system established by ICES
14088 and managed by authorized ICES personnel responsible for receiving
14089 data. The file transfer system uses security safeguards including encryption
14090 and authentication.

14091

14092 ICES is a Prescribed Entity under the Personal Health Information Protection
14093 Act (PHIPA), and can receive and use personal health information for
14094 purposes of analysis and compiling statistical information and other research.
14095 Its policies and procedures for privacy protection and data security have been
14096 approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-
14097 monitored and requiring passkeys to access private offices and
14098 computers. ICES has extensive experience in the protection of confidentiality
14099 when using such data. It has a UNIX-based network that cannot be accessed
14100 externally. ICES data facilities are fully 'moated' (no connections to other
14101 computers). At ICES, routine procedures for data backup are instituted by a
14102 data management team. The data is burned onto a CD or placed on an

14103 external hard drive and placed in a locked vault. All ICES staff and scientific
14104 affiliates are required to sign agreements of confidentiality annually. Internal
14105 audits are conducted to monitor compliance with ICES policies, standards and
14106 procedures.

14107
14108 Study data with direct personal identifiers such as OHIP numbers will
14109 reside on a dedicated and secure server at ICES and will only be
14110 accessible by a named Data Covenantor. The Covenantor will encode
14111 the OHIP number, replacing it with an ICES key number (IKN) (a code)
14112 and transferring it to a “moated” server for the study project. (The
14113 Data Covenantor is an ICES person named in our data sharing
14114 agreements and identified to the Office of the Information and
14115 Privacy Commissioner, who can access personal health information at
14116 ICES for the purposes of receiving, coding, transferring or destroying
14117 personal health information.) The coded study data will only be made
14118 available to the Principal Investigator and project staff directly
14119 responsible for data analysis (under the supervision of the
14120 investigator). No subject, physician or institution will be identified in
14121 the reporting of results
14122

14123 **14.5.12.3 Cost calculation**

14124 Once the utilization of health services is determined from those cases linked
14125 to administrative databases, publicly available costs (2016\$CAN) will be
14126 applied to health services. Costs for physician and laboratory services will be
14127 determined by applying that year’s fee code. Costs for hospital care will be
14128 estimated using the Canadian Institute for Health Information (CIHI) Resource
14129 Intensity Weight method for the most recently available year. Outpatient
14130 prescription drug costs for participants not covered by ODB (those under age
14131 65 and not on social assistance) will be considered to be the same as the trial
14132 arm-specific average for those with coverage. Costs will then be inflated
14133 using the healthcare-specific Consumer Price Index reported by Statistics
14134 Canada into constant Canadian dollars for the year the study ends. Due to the
14135 short time horizon, discounting will not be applied.

14136 **14.5.12.4 Primary Analysis**

14137 A within-trial analysis will be conducted to calculate the total cost for each
14138 arm and mean cost per subject for each arm. Frequency distributions and
14139 measures of central tendency (e.g. means and medians) will be determined
14140 for each resource category (e.g. hospitalizations)for each arm of the study.
14141 Confidence intervals for the difference in costs and resource utilization
14142 between the strategies overall and for each resource category will also be
14143 calculated. Univariate comparisons between the groups will be made
14144 primarily using nonparametric tests, such as Wilcoxon rank-sum test. In the
14145 primary analysis, assuming equivalence in the primary outcome, an arm with
14146 significantly lower mean costs will be considered the economically most
14147 attractive approach.
14148

14149 Should the clinical trial find a difference between the two arms on the
14150 primary endpoint, an incremental cost-benefit analysis will be calculated by
14151 deriving the additional cost per case of clinically significant cancer diagnosed,
14152 according to the following equation:

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\text{Diagnoses}_{(\text{Arm A})} - \text{Diagnoses}_{(\text{Arm B})}}$$

14153 The cost of avoiding each additional case of clinically insignificant cancer
14154 diagnosed may also be similarly calculated. Consideration will be given to
14155 extending this analysis using economic modeling with incorporation of utility
14156 values from the EQ-5D to allow a lifetime perspective to be taken and the
14157 estimation of quality adjusted life years (QALYs).

14158 **14.5.12.5 Secondary Cost Analyses**

14159 One and multi-way sensitivity analyses will be carried out around major cost
14160 drivers by varying the costs over their observed ranges and conducting
14161 threshold analyses where appropriate. Sensitivity analyses will also be
14162 performed to evaluate potential limitations in the data, such as ODB costs as
14163 described above (though the proportion without ODB coverage should be
14164 similar in the two arms, and it is not expected to be a major cost-driver).

14165
14166
14167

14168 **14.5.13 Missing Data**

14169 The impact of missing data will be explored in all analyses; sensitivity
14170 analyses/multiple imputation will be performed as appropriate.

14171

14172 **15. Participant compliance and withdrawal**

14173

14174 The study will be completed when at least 422 subjects have been randomized, have
14175 undergone a diagnostic test and completed follow up. Compliance to randomized
14176 treatment will be assessed by monitoring the completed forms, e.g. the systematic
14177 TRUS guided biopsy form or the MRI-targeted biopsy form.

14178

14179 In consenting to the study, subjects are consenting to study monitoring, imaging and
14180 biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to
14181 withdraw consent at any stage and their care will not be affected in any way. All
14182 communication surrounding the withdrawal and its reasons should be noted in the
14183 subject's record. Such cases should be reported to the PRECISE Study Operations
14184 Office. Data up to the time of withdrawal can be included in the study.

14185

14186 As the study diagnostic tests are for suspected cancer it is not anticipated that there
14187 will be significant loss to follow up.

14188

14189 **15.1 Subject Withdrawal from Study**

14190 A subject may discontinue participation in this study at any time at the investigator's
14191 discretion or at the request of the subject.

14192

14193 If a subject discontinues at or before Visit 1 (randomization), he is not required to
14194 complete end of study assessments.

14195

14196 If a subject discontinues after Visit 1 (randomization) for any reason, the investigator
14197 should make every effort to complete the activities bulleted below.

14198

14199 • End of study assessments as outlined in **Section 10.14**.

14200 • Any occurrence of death, prostatic surgical intervention, non-surgical treatment
14201 for prostate cancer after study withdrawal should be documented in the CRF and
14202 source documents.

14203

14204 Subjects who are discontinued from the study after randomization will not be
14205 replaced. Subjects withdrawn from the study retain their subject number if already
14206 given. New subjects will be allocated a new subject number.

14207

14208 In the event that a subject is prematurely discontinued from the study at any time
14209 due to an AE, the procedures describe in **Section 16.3** must be followed.

14210

14211 Subjects should be withdrawn from the study for any of the following criteria:

14212 • Non-compliance with the requirements of the study.

14213 • Request to discontinue treatment. This request can be made by either the
14214 subject or the investigator.

14215 • Develops progressive disease.

14216

14217 **15.2 Study completion**

14218 The primary end point will be reached when the last subject entered has their
14219 systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be
14220 followed for up to 2 years following study entry or until they have radical treatment.

14221 Subjects who are found to have significant prostate cancer and are treated will not
14222 be included in follow up for this period. This includes subjects diagnosed as part of
14223 study protocol, and subjects diagnosed during the follow up period by standard-of-
14224 care procedures. However, post MRI/biopsy questionnaires will not be required
14225 following non-protocol based procedures.

14226

14227 **16. Data Monitoring, Quality Control and Safety**

14228 **16.1 Stopping / discontinuation rules**

14229 The study will be completed when 450 participants have been randomized,
14230 undergone a diagnostic test and completed follow up.

14231

14232 The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC)
14233 or Trial PI may recommend cessation of the trial or suggestion modifications to trial
14234 conduct if there are concerns about subject safety or futility. See Section 14.2.1 for
14235 further details on the interim analysis. Appropriate documentation as per the PI's
14236 requirement will be completed if stopping the trial is necessary and the ethics
14237 committee will be informed.

14238

14239 As the study is unblinded there will be no need for randomization code breaks.

14240

14241 **16.2 Monitoring, quality control and assurance**

14242

14243 Members of the trial team will be Good Clinical Practice (or equivalent) trained.

14244

14245 An independent DSMC will be appointed to monitor subject safety and the rate of
14246 recruitment of subjects in the study. They will meet at least once a year whilst the
14247 trial is ongoing for routine review of safety data and trial progression. They have the
14248 power to call additional meetings and review data at any point in the trial should
14249 they wish to do so.

14250

14251 The PI may also arrange an independent trial monitor to review the study data.

14252 **16.3 Assessment of safety**

14253 The investigator is responsible for the detection and documentation of events
14254 meeting the criteria and definition of an AE or SAE as provided in this protocol.

14255 During this study, when there is a safety evaluation, the investigator or site staff will
14256 be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

14257 **16.3.1 Definition of an Adverse Event (AE)**

14258 Adverse events (AE) will be defined as "any untoward medical occurrence in a
14259 clinical trial subject undergoing any intervention in the trial, which does not
14260 necessarily have a causal relationship with this treatment".

14261

14262 Only adverse events specific to biopsy-related complications including pain, fever,
14263 hematuria, hematochezia, hematospermia, urinary retention and urinary
14264 incontinence will be recorded. Any other adverse events will not be recorded. Please
14265 refer to section 16.3.6 of the protocol.

14266 **16.3.2 Definition of a Serious Adverse Event (SAE)**

14267 Serious adverse events (SAE) will be defined as "any untoward medical occurrence as
14268 a result of any intervention in the trial that:

14269 **(a) results in death**

14270 **(b) is life-threatening**

14271 The term 'life-threatening' in the definition of 'serious' refers to an event in which
14272 the subject was at risk of death at the time of the event. It does not refer to an
14273 event, which hypothetically might have caused death, if it were more severe.

14274 **(c) requires hospitalisation or prolongation of existing hospitalisation**

14275 In general, hospitalization signifies that the subject has been detained (usually
14276 involving at least an overnight stay) at a hospital or emergency ward for observation
14277 and/or treatment that would not have been appropriate in the physicians' office or
14278 outpatient setting. Complications that occur during hospitalization are AEs. If a
14279 complication prolongs hospitalization or fulfils any other serious criteria, the event is
14280 serious. When in doubt as to whether 'hospitalization'; occurred or was necessary,
14281 the AE should be considered serious. Hospitalization for elective treatment of a pre-
14282 existing condition that did not worsen form baseline is not considered an AE.

14283 **(d) results in disability / incapacity**

14284 The term disability means substantial disruption of a person's ability to conduct
14285 normal life functions. This definition is not intended to include experiences of
14286 relatively minor medical significance such as uncomplicated headache, nausea,
14287 vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may
14288 interfere or prevent everyday life functions but do not constitute a substantial
14289 disruption.

14290 **(e) is a congenital abnormality/birth defect.**

14291 Medical or scientific judgement should be exercised in deciding whether reporting is
14292 appropriate in other situations, such as important medical events that may not be
14293 immediately life threatening or result in death or hospitalization but may jeopardise
14294 the subject or may require medical or surgical intervention to prevent one of the
14295 outcomes listed in the above definition. These should also be considered serious.
14296 Examples of such events are invasive or malignant cancers, intensive treatment in an
14297 emergency room or at home for allergic bronchospasm, blood dyscrasias or
14298 convulsions that do not result in hospitalization, or development of drug
14299 dependence or drug abuse.

14300 **16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs**

14301 An event which is part of the natural course of the disease under study (i.e., disease
14302 progression) does not need to be reported as a serious adverse event. Progression of
14303 the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death
14304 due to progressive disease is to be recorded on 'Record of Death' CRF page and not
14305 as an SAE. However, if the progression of the underlying disease is greater than that
14306 which would normally be expected for the subject, or if the investigator considers
14307 that there was a causal relationship between treatment with study medication or
14308 protocol design/procedures and the disease progression, then this must be reported
14309 as an SAE. Any new primary cancer must be reported as an SAE.

14310 **16.3.4 Lack of Efficacy**

14311 "Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical
14312 sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE
14313 definition (including clarifications).

14314 **16.3.5 Clinical Laboratory Abnormalities and Other Abnormal
14315 Assessments as AEs and SAEs**

14316 Abnormal laboratory findings or other abnormal assessments that are judged by the
14317 investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet
14318 the definition of an AE or SAE. Clinically significant abnormal laboratory findings or

14319 other abnormal assessments that are detected during the study or are present at
14320 baseline and significantly worsen following the start of the study will be reported as
14321 AEs or SAEs. However, clinically significant abnormal findings or other abnormal
14322 assessments that are associated with the disease being studied, unless judged by the
14323 investigator as more severe than expected for the subject's condition or that are
14324 present or detected at the start of the study and do not worsen, will not be reported
14325 as AEs or SAEs.

14326

14327 The trial interventions are routinely carried out in clinical practice for investigation of
14328 suspected cancer and the risks of the interventions are therefore not any greater
14329 than if a man was not part of the trial. The risks of the procedures are relatively low,
14330 as detailed in Section 11.

14331

14332 The investigator will exercise his or her medical and scientific judgment in deciding
14333 whether an abnormal laboratory finding or other abnormal assessment is clinically
14334 significant.

14335 **16.3.6 Recording/Reporting AEs and SAEs**

14336 The AE reporting period for this study begins at randomization and
14337 will be recorded until 30-days post-biopsy. In the event that the subject does not
14338 undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

14339

14340 Only adverse events specific to biopsy-related complications including pain, fever,
14341 hematuria, hematochezia, hematospermia, urinary retention and urinary
14342 incontinence will be recorded. Any other adverse events will not be recorded.

14343

14344 AEs will be recorded by a member of the research team or clinical team on an AE
14345 report form. All SAEs must be recorded on a SAE report form. SAE report forms
14346 should be sent to the CTG who will keep a log of AEs and SAEs. AE and SAE logs will
14347 be reviewed by the DSMC.

14348

14349 For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or
14350 DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria
14351 as a SAE, will be collected and reported.

14352

14353 Expected AEs includes the following:

14354

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

14355

14356

14357

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14360

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14362

14363 In addition, small risks of allergic reactions are associated with the intravenous
14364 administration of gadolinium, the contrast agent used in MRI scans, as described in

14365 section 10.18.1.2. This contrast agent is used consistently in MRI scanning and is not
14366 limited to this trial.
14367
14368 If any of these symptoms are accompanied by events consistent with the definition
14369 of an SAE as specified above, then the event will be considered an SAE.
14370
14371 The Trial Coordinator, Principal Investigator or Chief Investigator should be informed
14372 of any SAE within 24 hours.
14373 All SAE report forms must be completed and the SAE logs updated. All SAEs must be
14374 followed up until a resolution is reached (i.e. recovered, recovering, recovered with
14375 sequelae, fatal, not recovered or unknown).
14376
14377 Local sites may have specific institutional protocols for reporting SAEs, which should
14378 be followed in addition.
14379
14380 When an AE/SAE occurs, it is the responsibility of the investigator to review all
14381 documentation relative to the event. The investigator will then record all relevant
14382 information regarding an AE/SAE on the CRF.
14383
14384 The investigator will attempt to establish a diagnosis of the event based on signs,
14385 symptoms and/or other clinical information. In such cases, the diagnosis should be
14386 documented as the AE/SAE and not the individual signs/symptoms.

14387 **16.3.7 Evaluating AEs and SAEs**

14388 **16.3.7.1 Assessment of Intensity**

14389
14390 The investigator will make an assessment of intensity for each AE and SAE reported
14391 during the study. Degree of severity and change in severity will be recorded by
14392 means of National Cancer Institute, Common Terminology Criteria for Adverse
14393 Events (NCI CTCAE), version 4.03.
14394
14395 If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on
14396 the investigator's clinical judgment. The intensity of each AE and SAE recorded in the
14397 CRF should be assigned to one of the following categories:
14398
14399 **Mild:** An event that is easily tolerated by the subject, causing minimal discomfort
14400 and not interfering with everyday activities.
14401 **Moderate:** An event that is sufficiently discomforting to interfere with normal
14402 everyday activities.
14403 **Severe:** An event that prevents normal everyday activities.
14404
14405 An event that is classified as severe should not be confused with a SAE. Severity is a
14406 category utilized for rating the intensity of an event; both AEs and SAEs can be
14407 assessed as severe.

14408 **16.3.7.2 Assessment of Causality**

14409 The investigator is obligated to assess the relationship between investigational
14410 product and the occurrence of each AE/SAE. The investigator will use clinical
14411 judgment to determine the relationship. Alternative causes and the temporal
14412 relationship of the event to the investigational product will be considered and
14413 investigated. The investigator will also consult the CIB and or Product Information,
14414 for marketed products, in the determination of his/her assessment.

14415 **16.3.8 Follow-up of AEs and SAEs**

14416 After the initial AE/SAE report, the investigator is required to proactively follow each
14417 subject and provide further information to the PI of the study, on the subject's
14418 condition.

14419
14420 All AEs and SAEs documented at a previous visit/contact and are ongoing, will be
14421 reviewed at subsequent visits/contacts.

14422
14423 All AEs and SAEs will be followed until resolution, until the condition stabilizes, until
14424 the event is otherwise explained or until the subject is lost to follow-up. Once
14425 resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will
14426 ensure that follow-up includes any supplemental investigations as may be indicated
14427 to elucidate the nature and/or causality of the AE or SAE.

14428
14429 The PI may request that the investigator perform or arrange for the conduct of
14430 supplemental measurements and/or evaluations to elucidate as fully as possible the
14431 nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a
14432 subject dies during participation in the study or during a recognized follow-up
14433 period, the PI will be provided with any post-mortem findings.

14434
14435 New or updated information will be recorded on the originally completed SAE CRF,
14436 with all changes signed and dated by the investigator or designate. The updated SAE
14437 CRF should be resent to the PI.

14438 **16.3.9 Prompt Reporting of SAEs**

14439 Once the investigator determines that an event meets the protocol definition of an
14440 SAE, the SAE will be reported to the PI (CURC) within 24 hours.

14441

14442 **16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI**

14443 The Site Investigator must immediately inform the PI (CURC) of all SAEs (within 24
14444 hours) at the following fax number: 1-416-480-6121.

14445

14446 The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing
14447 addresses is as follows:

14448 Dr. Laurence Klotz

14449 c/o Marlene Kebabdjian

14450 Sunnybrook Health Sciences Centre

14451 2075 Bayview Avenue A304

14452 Toronto, Ontario M4N 3M5 Canada
14453 Phone: (416) 480-6100 ext 2890
14454 E-mail: Laurence.Klotz@sunnybrook.ca
14455 Marlene.kebabdjian@sunnybrook.ca

14456 **16.3.9.2 Completion and Transmission of the SAE Reports**

14457 Once an investigator becomes aware that an SAE has occurred in a study subject,
14458 she/he will report the information to the PI within 24 hours. The SAE CRF will always
14459 be completed as thoroughly as possible with all available details of the event, signed
14460 by the investigator (or designee), and forwarded to the PI within the designated time
14461 frames. If the investigator does not have all information regarding as SAE, he/she will
14462 not wait to receive additional information before notifying the PI of the event and
14463 completing the form. The form will be updated when additional information is
14464 received.

14465
14466 The investigator will always provide an assessment of causality at the time of the
14467 initial report as described in Section 16.3.6.2.

14468 **16.3.10 Post-study AEs and SAEs**

14469 If the investigator learns of any SAE at any time after a subject has been discharged
14470 from the study, and such event(s) is (are) reasonably related to the study
14471 intervention, the investigator should promptly notify the PI (CURC).
14472

14473 **17. Study Administration**

14474 **17.1 Regulatory and Ethical Considerations**

14475 An important consideration is that men are being randomized to one of two biopsy
14476 techniques when it is not known which will be more effective in diagnosing clinically
14477 significant prostate cancer. Both diagnostic tests are currently used in everyday
14478 clinical practice at the institutions involved in the trial. Though systematic TRUS
14479 guided biopsy could be considered standard of care, there is enough evidence to
14480 support the concept that MPMRI-targeted biopsy may be as effective, if not more so,
14481 than systematic TRUS guided biopsy[27]. This study aims to confirm this.

14482 **17.1.1 Ethical Conduct of the Study and Ethics Approval**

14483 The PI and each participating site will obtain approval to conduct the study from the
14484 Research Ethics Board (REB) prior to initiating the study.

14485
14486 Participating sites from Ontario will use the Ontario Cancer Research Ethics Board
14487 (OCREB) as their Board of Record.

14488 This study will be conducted in accordance with 'good clinical practice' (GCP) and all
14489 applicable regulatory requirements, including where applicable, the 2013 version of
14490 the Declaration of Helsinki.

14491
14492 The investigator is responsible for ensuring that this protocol, the site's informed
14493 consent form and any other information that will be present to potential subjects
14494 are reviewed and approved by the appropriate REB. The investigator agrees to allow

14495 the REB direct access to all relevant regulatory documents. The PI will provide the
14496 site investigator(s) with relevant document(s)/data that are needed for REB review
14497 and approval of the study. Before CRFs can be shipped to the site, the PI must
14498 receive copies of the REB approval, the approved informed consent form and any
14499 other information that the REB has approved for presentation to potential subjects.

14500
14501 If the protocol, the informed consent form or any other information that the REB has
14502 approved for presentation to potential subjects is amended during the study, the
14503 site investigator(s) is responsible for ensuring the REB reviews and approves, where
14504 applicable, these amended documents. The site investigator(s) must follow all
14505 applicable regulatory requirements pertaining to the use of an amended informed
14506 consent form including obtaining the REB approval of the amended form before new
14507 subjects consent to take part in the study using this version of the form. Copies of
14508 the REB approval of the amended informed consent form/other information and the
14509 approved amended informed consent form/other information must be forwarded to
14510 the PI promptly.

14511 **17.1.2 Informed Consent**

14512 Informed consent will be obtained before the subject can participate in the study.
14513 The contents and process of obtaining informed consent will be in accordance with
14514 all applicable regulatory requirements.

14515
14516 The subject's consent to participate in the study should be obtained after a full
14517 explanation has been provided of the procedures to be given. Subjects should be
14518 given sufficient time (at least 24 hours) after being given the study subject
14519 information sheet to consider and discuss participation in the study with family and
14520 friends.

14521
14522 A contact number will be given to the subject should he wish to discuss any aspect of
14523 the study. Following this, the clinician will determine that the subject is fully
14524 informed of the study and their participation, in accordance with Good Clinical
14525 Practice Guidelines. Subjects will always be asked to sign a consent form. One copy
14526 will be given to the subject, one copy will be kept with subject's hospital notes and
14527 one copy should be kept in the local investigator's file.

14528 **17.1.3 Investigator Reporting Requirements**

14529 The investigator is responsible for reporting SAEs to the REB in accordance with all
14530 applicable regulations. Furthermore, the investigator may be required to provide
14531 periodic safety updates on the conduct of the study at his or her site and notification
14532 of study closure to the REB.

14533 **17.2 Study Monitoring**

14534 This study will be monitored by a CRA. The CRA will contact the sites by telephone
14535 on a predetermined basis and would conduct a monitoring visits based on the data
14536 entered in the EDC and queries.

14537
14538 During these contacts, the monitor will:

-
- 14539 • Check the progress of the study
 - 14540 • Review study data collected
 - 14541 • Conduct source document verification
 - 14542 • Identify any issues and address their resolution

14543

14544 This will be done in order to verify that the:

- 14545 • Data are authentic, accurate and complete
- 14546 • Safety and rights of subjects are being protected
- 14547 • Study is conducted in accordance with the currently approved protocol (and
- 14548 any amendments), GCP and all applicable regulatory requirements

14549

14550 The investigator agrees to allow CRA personnel direct access to all relevant
14551 documents and to allocate his/her time and the time of his/her staff to CRA
14552 personnel to discuss findings and any relevant issues.

14553 **17.3 Quality Assurance**

14554 To ensure compliance with GCP and all applicable regulatory requirements,
14555 regulatory agencies may conduct a regulatory inspection of the study. Such
14556 audits/inspections can occur at any time during or after completion of the study. If
14557 an audit or inspection occurs, the investigator and institution agree to allow the
14558 auditor/inspector direct access to all relevant documents and to allocate his/her
14559 time and the time of his/her staff to the auditor/inspector to discuss findings and
14560 any relevant issues.

14561 **17.4 Study and Site Closure**

14562 Upon completion of the study, the site investigator(s) will conduct the following
14563 activities:

- 14564 • Return of all study data to the Sponsor (CURC)
- 14565 • Submission of all study data and data queries to OCOG
- 14566 • Review of site study records for completeness

14567

14568 In addition, the Principal Investigator has the right to temporarily suspend or
14569 prematurely discontinue this study either at a single site or at all sites at any time for
14570 reasons including but not limited to, safety or ethical issues or severe non-
14571 compliance. If the PI determines such action is needed, the PI will discuss this with
14572 the site investigator (including the reasons for taking such action) at that time. When
14573 feasible, the PI will provide advance notification to the site investigator of the
14574 impending action prior to it taking effect.

14575

14576 Individual site Investigators may also terminate their participation in the study at any
14577 time. If the investigator determines such action is needed, the investigator will
14578 discuss this with the PI(including the reasons for taking such action) at that time.
14579 When feasible, the investigator will provide advance notification to the Plof the
14580 impending action prior to it taking effect.

14581

14582 The PI will promptly inform all other investigators and/or institutions conducting the
14583 study if the study is suspended or terminated for safety reasons and will also inform

14584 the regulatory authorities of the suspension or termination of the study and the
14585 reason(s) for the action. If required by applicable regulations, the investigator must
14586 inform the REB promptly and provide the reason for the suspension or termination.

14587

14588 If the study is prematurely discontinued, all study data must be returned to the PI. In
14589 addition, the investigator has the responsibility to return any used/unused clinical
14590 supplies.

14591

14592 Financial compensation to investigators and/or institutions will be in accordance
14593 with the agreement established between the investigator and the PI.

14594 **17.5 Records Retention**

14595 Following closure of the study, the site investigator(s) must maintain all site study
14596 records in a safe and secure location. The records must be maintained to allow easy
14597 and timely retrieval when needed and whenever feasible, to allow any subsequent
14598 review of data in conjunction with assessment of the facility, supporting systems and
14599 staff.

14600

14601 The site investigator(s) will retain study records to comply with all applicable
14602 regulatory requirements. The minimum retention time will meet the strictest
14603 standard applicable to that site for the study as dictated by any institutional
14604 requirements or local laws or regulations of Health Canada standards/procedures;
14605 otherwise, the retention period will default to 25 years.

14606

14607 The site investigator(s) must inform the PI of any changes in the archival
14608 arrangements, including but not limited to the following: archival at an off-site
14609 facility, transfer of ownership of the records in the event the investigator leaves the
14610 site. The PI should be informed of this change if it affects their access to the
14611 information in case of an audit.

14612 **17.6 Data Management**

14613 Subject data are collected by the investigator or designee using the CRF within an
14614 Electronic Data Capture (EDC) system. Subject data necessary for analysis and
14615 reporting will be entered/transmitted into a validated database. Clinical data
14616 management will be performed in accordance with applicable standards and data
14617 cleaning procedures. Database lock will occur when data management quality
14618 control procedures are completed.

14619 **17.7 Publication**

14620 The results from the study will be analyzed and published as soon as possible and is
14621 appropriate. All study-related communications can only be presented or published
14622 after approval from all relevant members involved in the trial.

14623

14624 All publications shall include appropriate indication named authors as agreed on by
14625 the members involved in the trial. For the main study reports, senior and first
14626 authorship will be determined by agreement of the Chief Investigator, the Principal
14627 Investigator at time of manuscript drafting. Authorship will be based on

14628 recommendations of the International Committee of Medical Journal Editors
14629 (www.ICMJE.org) where all authors meet the following for criteria:
14630
14631 17. Substantial contributions to the conception or design of the work; or the
14632 acquisition, analysis, or interpretation of data for the work; AND
14633 18. Drafting the work or revising it critically for important intellectual content;
14634 AND
14635 19. Final approval of the version to be published; AND
14636 20. Agreement to be accountable for all aspects of the work in ensuring that
14637 questions related to the accuracy or integrity of any part of the work are
14638 appropriately investigated and resolved.
14639
14640 If there are no named authors (i.e. group authorship) then a writing committee will
14641 be identified that would usually include these people. The clinical trials.gov
14642 registration number that will be allocated to this trial will be attached to any
14643 publications resulting from this trial.
14644
14645 Trial funding agencies (OICR, PCC and collaborators as appropriate) will be
14646 acknowledged in all publications.
14647
14648 The members of the trial steering committee will be listed with their affiliations in
14649 the acknowledgements/appendix of the main publication.
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Appendices

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Appendix 1: Time windows for data collection

14861

14862 For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3

14863 For details on time windows permitted for each trial intervention to be completed

14864 please see Table 5 below.

14865

14866 Table 5: Details of time windows permitted for all trial interventions.

14867

Contact and Purpose if not clear	Time window permitted +/-30 days of scheduled visit
Visit 1 Screening (eligibility review, med hx,)	Any time following referral of subject. Ideally perform as soon as possible following receipt of referral.
Visit 1 Consent Vitals, DRE Randomization EQ-5D-5L Questionnaire (baseline) Optional blood, urine semen and tissue sample	Complete only once subject has had 24 hours after receiving the patient information to fully consider the study. Ideally on same visit as screening. Complete at screening Immediately after consent form signed and eligibility is confirmed. Complete immediately after consent form is signed Complete after additional informed consent signed, after randomization and up until any point prior to a biopsy.
Visit 2 MRI	Only for men randomized to this arm. Any time following randomization. Ideally within 1 week of randomization.

<p>Visit 3</p> <p>MRI-Targeted Biopsy of Prostate</p>	<p>Only for men randomized to this arm who have a lesion on MRI that needs a biopsy.</p> <p>Any time following the MRI being reported, ideally within 1 week of MRI.</p> <p>Depending on local Urology service structure, an appointment for a biopsy may need to be booked at the same time as the MRI is booked (i.e. immediately after randomization) in order for a slot to be secured for a biopsy to occur in timely fashion.</p> <p>If it is determined from the MRI that a biopsy is not required then the biopsy appointment can be used instead of Visit 4 for follow up of results and treatment decision.</p>
<p>Visit 3</p> <p>Systematic TRUS guided biopsy</p>	<p>Only for men randomized to this arm.</p> <p>Any time following randomization. Ideally within 4 weeks of randomization.</p>
<p>Visit 3</p> <p>Immediate post-biopsy questionnaire</p> <p>30-day post-biopsy questionnaire</p>	<p>Should be completed and returned immediately after a biopsy, before the subject leaves the department. As long as questionnaire completed within 24 hours it will be acceptable.</p> <p>To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy.</p> <p>To be returned by post or at follow up appointment (Visit 4).</p> <p>If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is finally complete.</p> <p>If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment.</p> <p>As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as</p>

Telephone reminder	<p>possible to 30 days post-biopsy.</p> <p>At 30-days post biopsy a member of the research team will phone the subject to remind them to fill out the 30-day questionnaires</p>
<p>Visit 4</p> <p>Follow up for results And treatment Decision</p> <p>EQ-5D-5L Questionnaire</p>	<p>Should be completed as soon as possible following the availability of any pathology results. Alternatively, if a man is in the MRI arm and the MRI is negative, this follow up should occur after the availability of the MRI report. Ideally the follow up appointment should be within 6 weeks of randomization.</p> <p>Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.</p> <p>To be completed</p>
<p>Visit 5</p> <p>26 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood
<p>Visit 6</p> <p>1 year follow up 52 week follow up visit</p>	<p>The following information will be obtained on an annual basis:</p> <ul style="list-style-type: none"> • Vitals, DRE • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
<p>Visit 7</p> <p>78 week follow up</p>	<ul style="list-style-type: none"> • Vitals, DRE • PSA • Optional blood

Visit 8

104 week follow up visit

The following information will be obtained on an annual basis:

- Vitals, DRE
- time to cancer diagnosis;
- Gleason score progression;
- time to intervention on active surveillance;
- time on active surveillance;
- results of PSA tests.
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MPMRI-targeted biopsy will have an additional MPMRI at Visit 8. This will be followed by a targeted-biopsy if results of MRI are positive (PI-RADS 3-5).

All patients in both Arm A and B who have remained undiagnosed or untreated (on active surveillance) will have a follow up MRI 2 years after study entry.

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

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Appendix 2: MPMRI Reporting Proforma

Date of MRI scan:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
day		month			year		

Date of Report:

<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
day		month			year		

Reporting Radiologist:

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Form Completion Instructions:

14878 Radiologists should annotate this diagram with up to 3 suspicious areas
14879 scoring 3 or greater on the PI-RADS v2 scale of suspicion. The three most
14880 suspicious areas should be annotated, each with the score clearly marked.

14881
14882 "T1" should be the area with the greatest degree of suspicion. If
14883 applicable, "T2" should be the area with the next greatest degree of
14884 suspicion and finally if applicable, "T3" should be the area with the next
14885 greatest degree of suspicion.

14886
14887 For each suspicious area, triaxial measurements should be recorded with
14888 all 3 measurements in orthogonal planes provided whenever possible. In
14889 the PZ, lesions should be measured on ADC. In the TZ, lesions should be
14890 measured on T2W.

14891
14892 If lesion measurement is difficult or compromised on ADC (for PZ) or T2W
14893 (for TZ), measurement should be made on the sequence that show the
14894 lesion best. For example, coronal measurements may be best performed
14895 in the peripheral zone on T2 images.

14896
14897

IMPORTANT SUBMISSION INSTRUCTIONS:

14898

14900 **Please send this completed case report form and a DVD with the images AND**
14901 **completed MRI Report to:**

14902

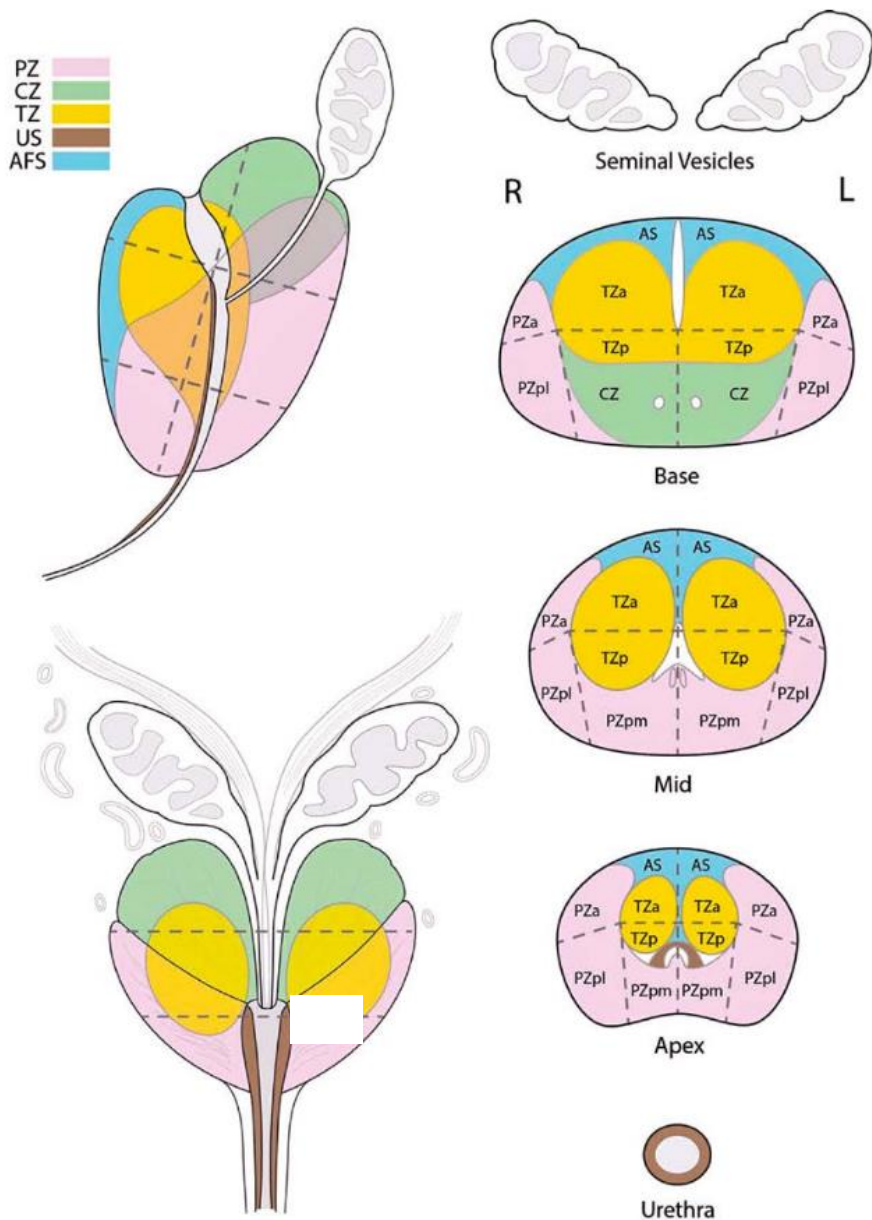
14903 Marlene Kebabdjian
14904 Sunnybrook Health Sciences Centre
14905 Urology Research, A304
14906 2075 Bayview Avenue, A304
14907 Toronto, Ontario, M4N 3M5

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NO DCE (Part 1 or 2) – T2/DWI/ADC
DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE PSA

Draw lesions on diagram below annotating each with the T index (i.e T1; T2...)



14960
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NO DCE (Part 1 or 2) – T2/DWI/ADC
**DO NOT VIEW DCE – YOU SHOULD NOT KNOW THE
PSA**

Image quality: Good
(DWI + T2) Minor image quality issues (still acceptable)
 Unacceptable but some lesions seen warranting biopsy
 Unacceptable, can't interpret at all

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If image quality is not good please comment:

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How to record locations

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14978

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

14979

Number of candidate tumor sites: _____

14980

If none, please proceed to Section B

14981

14982

Section A:

14983

Target 1 (*Highest Pi-Rads score and then largest*):

14984

Present (Y/N): _____

14985

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

14986

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

14987

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

14988

x10⁻⁶

14989

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

14990

Location(s) (largest to smallest area involved):

14991

_____, _____, _____, _____

14992

_____, _____, _____, _____ (as per location code

14993

format above)

14994

14995

Extraprostatic extension: No Yes Equivocal _____

14996

14997

Target 2:

14998

Present (Y/N): _____

15000

Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____

15001

Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____

15002

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s

15003

x10⁻⁶

15004

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

15005 Location(s) (largest to smallest area involved):
 15006 _____/_____/_____/_____
 15007 _____/_____/_____/_____ (as per location code
 15008 format above)
 15009 Extraprostatic extension: No Yes Equivocal
 15010
 15011

15012 **Target 3:**

15013 Present (Y/N): _____
 15014 Overall Pi-Rads Score(1-5): _____ Your Likert Score(1-5): _____
 15015 Pi-Rads Score (T2) (1-5) : _____ Pi-Rads Score (DWI) (1-5): _____
 15016 Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
 15017 x10⁻⁶
 15018 Size: _____x_____x_____mm (Ax1 > Ax2 x SI)
 15019 Location(s) (largest to smallest area involved):

15020 _____/_____/_____/_____
 15021 _____/_____/_____/_____ (as per location code
 15022 format above)
 15023
 15024 Extraprostatic extension: No Yes Equivocal
 15025

15026 There are more than 3 targets seen (Y/N): _____
 15027 If yes give describe:

15028 _____
 15029 _____
 15030 _____

15031 **Section B:**

LSV invasion: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal	RSV invasion: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal
Adenopathy: <input type="checkbox"/> No <input type="checkbox"/> Yes <input type="checkbox"/> Equivocal	Worst PI-RADS Score: _____

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Other Findings:

_____	(SI)	_____	(AP)	_____	(LR)	Volume:	_____	cc
cm	x	cm	x	cm				

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DCE (Part 2 or 2) – T2/DWI/ADC/DCE
VIEW DCE – YOU SHOULD NOT KNOW THE PSA

**Image quality
of DCE + DWI +
T2:**

- Good**
- Minor image quality issues (still acceptable)**
- Unacceptable but some lesions seen warranting biopsy**
- Unacceptable, can't interpret at all**

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If image quality is not good please comment:

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Number of candidate tumor sites: _____
If none, please proceed to Section C

15068
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There was a change in lesions number or rank when adding DCE sequence: No Yes

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If Yes, please give the correspondence between Target numbers with and without DCE (i.e. Target 1 without DCE = Target x with DCE) and **fill in all fields below to avoid confusion. Also draw lesions on diagram below again**

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Also draw lesions on diagram on next page again.

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15078

Correspondence:

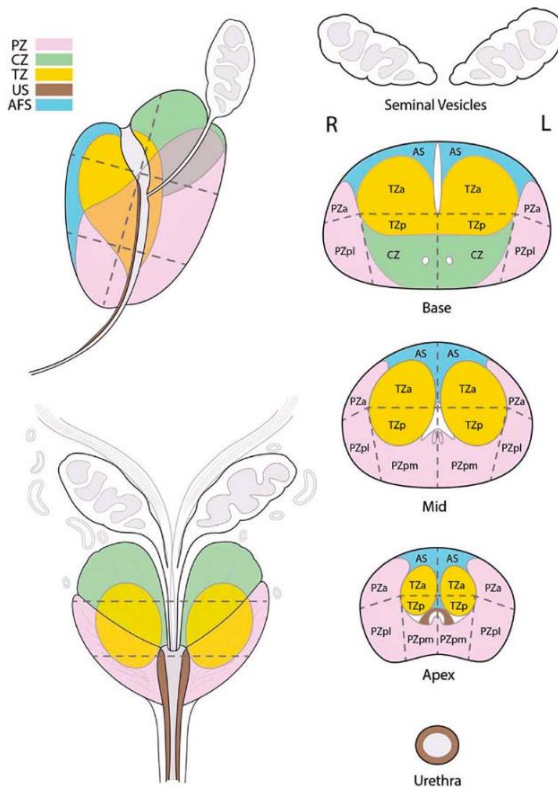
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Old T1 = New T____ Old T2 = New T____ Old T3 = New
T____

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If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2...)



15104

Target 1:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

15114

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
 x10⁻⁶

Size: _____ x _____ x _____ mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____ / _____ / _____ / _____

_____ / _____ / _____ / _____

Extraprostatic extension: No Yes Equivocal

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Target 2:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
x10⁻⁶

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____ / _____ / _____ / _____

_____ / _____ / _____ / _____

Extraprostatic extension: No Yes Equivocal

Target 3:

Present: No Yes

Change from Part 1: No Yes

If YES, complete ALL sections below

If NO change in scores, ONLY complete DCE PiRads score below.

All other entries are assumed = to Part 1

Overall Pi-Rads Score: _____ Your Likert Score: _____

Pi-Rads Score (T2) : _____ Pi-Rads Score (DWI): _____

Pi-Rads Score (DCE, 0,1): _____

Mean ADC: _____ Min ADC – single voxel: _____ mm²/s
x10⁻⁶

Size: _____x_____ x _____mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____ / _____ / _____ / _____

_____ / _____ / _____ / _____

Extraprostatic extension: No Yes

There are more than 3 targets seen (Y/N): _____

If yes give describe:

Section C:

LSV invasion: No Yes Equivocal

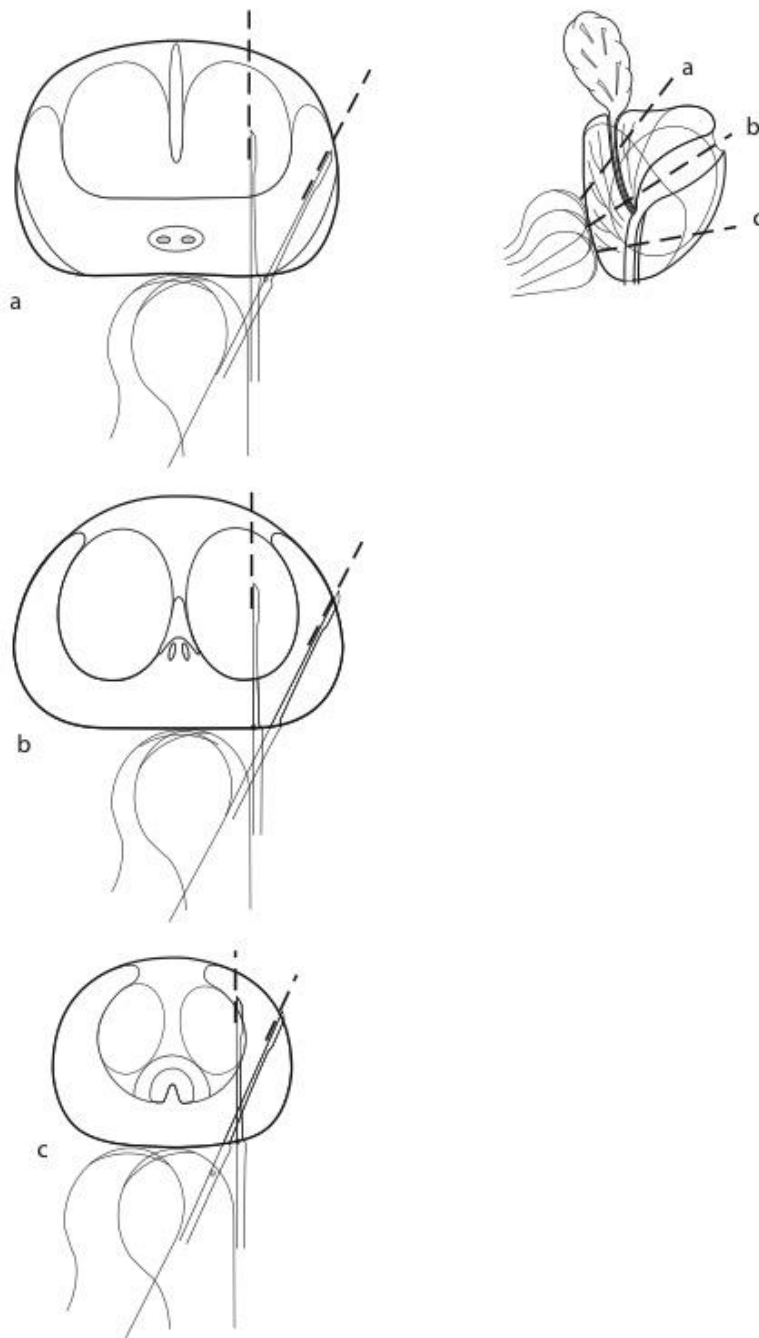
RSV invasion: No Yes
Equivocal

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15227

15228 **Appendix 3: Example of systematic TRUS guided biopsy schema**

15229

15230 Figure depicting 12-core systematic TRUS guided biopsyschema that sites are
15231 recommended to follow. Axial/coronal sections of a prostate gland (left) showing
15232 biopsy courses of the 12 biopsies performed under ultrasound guidance with an end
15233 fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,



15235

15236 **Appendix 4: 2-page EQ-5D-5L Questionnaire**

15237 Under each heading, please tick the ONE box that best describes your health TODAY

15238

15239 **MOBILITY**

15240 I have no problems in walking about

15241 I have slight problems in walking about

-
- 15242 I have moderate problems in walking about
- 15243 I have severe problems in walking about
- 15244 I am unable to walk about
- 15245
- 15246 **SELF-CARE**
- 15247 I have no problems washing or dressing myself
- 15248 I have slight problems washing or dressing myself
- 15249 I have moderate problems washing or dressing myself
- 15250 I have severe problems washing or dressing myself
- 15251 I am unable to wash or dress myself
- 15252
- 15253 **USUAL ACTIVITIES** (*e.g. work, study, housework,*
15254 *family or leisure activities*)
- 15255 I have no problems doing my usual activities
- 15256 I have slight problems doing my usual activities
- 15257 I have moderate problems doing my usual activities
- 15258 I have severe problems doing my usual activities
- 15259 I am unable to do my usual activities
- 15260
- 15261 **PAIN / DISCOMFORT**
- 15262 I have no pain or discomfort
- 15263 I have slight pain or discomfort
- 15264 I have moderate pain or discomfort
- 15265 I have severe pain or discomfort
- 15266 I have extreme pain or discomfort
- 15267
- 15268 **ANXIETY / DEPRESSION**
- 15269 I am not anxious or depressed
- 15270 I am slightly anxious or depressed
- 15271 I am moderately anxious or depressed
- 15272 I am severely anxious or depressed
- 15273 I am extremely anxious or depressed
- 15274
- 15275 © 1990 EuroQol Group. EQ-5D™ is a trade mark of the EuroQol Group

15276

15277 • We would like to know how good or bad your health
15278 is TODAY.

The best health
you can imagine

15279 • This scale is numbered from 0 to 100.

15280 • 100 means the best health you can imagine.

15281 0 means the worst health you can imagine.

15282 • Mark an X on the scale to indicate how your health is
15283 TODAY.

15284 • Now, please write the number you marked on the
15285 scale in the box below.

15286

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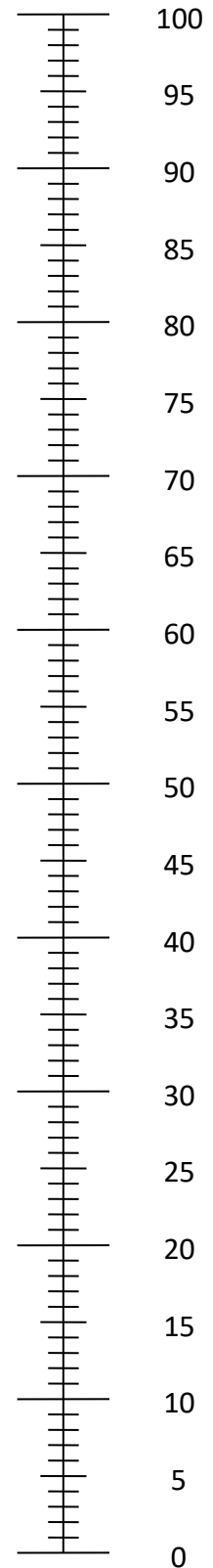
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YOUR HEALTH TODAY=



The worst health
you can imagine

Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

Please ask the patient to fill this out after the biopsy, before they leave the department.

Please tick the box corresponding to the number, which describes how you felt immediately after the biopsy procedure:

1. Overall, how much discomfort did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Discomfort			Moderate Discomfort					Worst Discomfort Possible		

2. Overall, how much pain did the biopsy procedure cause you?

0	1	2	3	4	5	6	7	8	9	10
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
No Pain			Moderate Pain					Worst pain Possible		

-
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Please complete the next page of questions

Did you experience any of the following in the month **before** your biopsy procedure.
For each question, tick the box that applies:

3. Fevers

Yes

1

No

2

4. Blood in the urine

Yes

1

No

2

5. Blood in the semen

Yes

1

No

2

6. Blood in the stools or from the back passage

Yes

1

No

2

7. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes

1

No

2

8. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes

1

No

2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes

1

No

2

10. Urinary tract infection diagnosed by a healthcare professional

Yes

1

No

2

11. Pain at the site where the biopsies were taken from

Yes

1

No

2

Thank you for completing the questionnaire. Please hand this to a member of staff before you leave. Please ensure you are given the 30-day questionnaire for completion at 30 days following the biopsy.

15295

Appendix 6: 30-day post biopsy questionnaire

30-day post biopsy questionnaire

30-days after the biopsy procedure, the patient should complete this questionnaire:

Did you experience the following problem in the 30-days after the biopsy procedure:

1. Fevers

Yes No

1 2

2. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

3. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

4. Blood in the urine

Yes No

1 2

5. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

6. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

7. Blood in the semen

Yes No

1 2

8. If you answered yes, specify on which days after the biopsy you had this? (*tick as many boxes as are applicable*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

1	2	3	4	5	6

9. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

10. Blood in the stools or from the back passage

Yes No
1 2

11. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

12. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

13. Acute urinary retention, meaning the painful inability to pass urine which was relieved by passing a catheter into the bladder through the penis

Yes No
1 2

14. If you answered yes, how long after the biopsy did this occur? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

15. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

Did you experience the following problem in the 30-days after the biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes No
1 2

17. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

18. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4

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Did you experience the following problem in the 30-days after the biopsy procedure:

19. Urinary incontinence, meaning any undesired leakage of urine

Yes No
1 2

20. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

21. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

22. Urinary tract infection diagnosed by a healthcare professional

Yes No
1 2

23. If you answered yes, how long after the biopsy did this occur after? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

24. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

Did you experience the following problem in the 30-days after the biopsy procedure:

25. Pain at the site where the biopsies were taken from

Yes No
1 2

26. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2 3-5 6-10 11-15 16-20 21-30

<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

27. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem at all Minor Problem Moderate Problem Major Problem

1 2 3 4

15299

28. Please list any **new** medications that you have taken **since the biopsy**. Do not list your regular medications but do list any **new** medications started related to the biopsy. Think especially about any painkillers or antibiotics that you may have taken. Only list the medications if you have taken them. An example is given in the first box:

Name of medication	Dosage	Number of doses per day	Number of days
<i>e.g. ciprofloxacin</i>	<i>500mg</i>	<i>2</i>	<i>3</i>

29. Since the biopsy, have you had contacts with hospital services for reasons related to the biopsy, which were unplanned and not part of the routine study visits?

Please answer yes if you have had any unplanned contact with any healthcare staff e.g. doctor, nurse, other. Please also answer yes if you have had any unplanned consultations with healthcare staff over the phone

Yes

1

No

2

30. If yes, please answer describe:

(i) who the contact was with (*e.g. nurse/doctor/other*)

(ii) reason for contact (*e.g. concern over fevers*)

(iii) manner of contact (*e.g. telephone/attendance at outpatient clinic/attendance in accident and emergency*)

(iv) any treatment you received (please be as specific as possible *e.g. "I was admitted to the ward and treated for an infection of the blood stream for 5 days of intravenous antibiotics with 1.2g co-amoxiclav three times a day and I had 2 days of painkillers with intravenous paracetamol 1g four times a day"*):

15300

31. How many times, if any, have you attended the accident and emergency department?

32. How many nights, if any, have you been admitted to hospital as an inpatient?

33. How many days, if any, have you been admitted to a day ward in hospital without staying the night?

34. How many days, if any, have you been admitted to an intensive care unit for?

35. Since the biopsy, have you had contact with the community healthcare team for reasons related to the biopsy?

Please answer yes if you have had any contact with any healthcare staff in the community e.g. GP, practice nurse, community nurse, other. Please also answer yes if you have had any consultations with community healthcare staff over the phone

Yes

1

No

2

36. If yes, please answer describe:

(i) who the contact was with (e.g. nurse/doctor/other)

(ii) reason for contact (e.g. concern over fevers)

(iii) manner of contact (e.g. telephone/attendance at GP surgery/home visit)

(iv) any treatment you received (please be as specific as possible e.g. "I received 5 days of oral antibiotics for a urinary tract infection- 625mg co-amoxiclav three times a day and I had 2 days of painkillers with paracetamol 1g four times a day"):

15301

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37. Have you felt unwell in any other way that we have not asked that you feel is due to the biopsy?

Yes

1

No

2

38. If you answered yes, please describe:

39. If you answered yes, how long after the biopsy did you have this for? (*tick one*)

Days: 0-2	3-5	6-10	11-15	16-20	21-30
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
1	2	3	4	5	6

40. If you answered yes, how much of a problem was this for you? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

41. If **another biopsy** in the future was medically necessary, how much of a problem would it be for you to undergo the same procedure? (*tick one box*)

Not a problem

at all

1

Minor Problem

2

Moderate Problem

3

Major Problem

4

?

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Thank you for completing the questionnaire. Please post the questionnaire in the pre-paid self-addressed envelope or give to the research team at your next visit. Please contact us if you have any queries.

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