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

Pages are as follows:

2 Statistical Analysis Plan
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285 Summary of amendment 3
286 Version 4 of protocol
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Laurence Klotz

Study: 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 (**PRECISE**)

Statistical Analysis Plan (SAP)

Version: Draft #1

Date: 26 February 2016

Author: Gregory R. Pond

OBJECTIVES

Overall aim

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

Hypotheses

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

Primary Objective

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

Secondary Objectives

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 (maximum cancer core length, CMCCL) 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.

Explanation for non-inferiority hypothesis

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

STUDY POPULATIONS

The per protocol population will consist of all subjects who satisfy all eligibility criteria and are randomized to the study, who undergo MPMRI-TB or systematic TRUS guided biopsy and have their primary outcome measured.

The intent-to-treat (ITT) population will consist of all subjects randomized to the study, regardless of any protocol violations or if they do not complete the study as defined in the protocol.

DEFINITIONS

Primary Outcome

The proportion of men in each arm with clinically significant cancer (Gleason $\geq$7) will be calculated based on histology results from biopsy procedures. The proportion within each arm will be calculated as the number of patients with clinically significant cancer divided by the number of evaluable patients.

Secondary Outcomes

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

STATISTICAL METHODS

Primary Analysis

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

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

Secondary Analyses

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

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

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

Treatment Allocation and Stratification

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

Stratification

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

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

(2) clinical centre.

Sample Size

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

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

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

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

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

To account 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.

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

Statistical Conventions

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

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

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

Missing Data

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

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

Interim Analyses

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

Timing of Final Analysis

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

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.

Short title: **PR**ostate **E**valuation for **C**linically **I**mportant disease: MRI vs **S**tandard **E**valuation procedures. (PRECISE)

Date: 27 September 2016

Version 1.0

Sponsor:
Ontario Institute for Cancer Research

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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 #: _____

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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	**Primary Objective** 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. **Secondary Objectives** 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 ≥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, CMCCL) 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)

	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, and semen 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, all inclusion criteria must be met. 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. ≥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	Men who meet the following criteria at the time of screening will be excluded: 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	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.** All subjects 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. All subjects in ARM A will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire

	following the MRI. Subjects in ARM A who do not receive a subsequent biopsy 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 (± I 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. Subjects in ARM A who do receive a MRI-targeted biopsy 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 (± I 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. All subjects in ARM B 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 (± I 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.
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 ≥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

Abbreviations:

ADC	Apparent diffusion coefficient
CI	Confidence interval
CRF	Case report form
DSMC	Data Safety and Monitoring Committee
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
ITT	Intention to treat
MCCL	Maximum cancer core length
MPMRI	Multi-parametric MRI, used interchangeably with MRI in this protocol.
MPMRI-TB	Multi-parametric magnetic resonance image-targeted biopsy of the prostate
MRI	Magnetic resonance imaging, used interchangeably with MPMRI in this protocol
MRS	Magnetic resonance spectroscopy
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PTC	Permission to Contact
PSA	Prostate specific antigen
REB	Research Ethics Board
STARD	Standards for the reporting of diagnostic studies
TRUS	Trans-rectal ultrasound
TSC	Trial Steering Committee
T2W	T2-weighted imaging

Definitions:

MP MRI-targeted biopsy	A biopsy technique where an MP MRI scan is used to determine the location of a suspicious target prior to biopsy.
Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure is not influenced by findings on MRI imaging. Currently this is the standard of care for prostate cancer in the province of Ontario.

5. Trial summary

5.1 Aim and Rationale

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

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

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

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

The potential implications of this trial include:

- 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

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 (± I week) after the procedure. EuroQOL 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 prostectomy) 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 be followed with serial PSA testing; PSA levels will increase if cancer is present. In addition to serial PSA testing, in this study men who had a negative MRI (defined as

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

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

5.3 Participating Sites

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

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

5.4 Study outcomes

5.4.1 Primary outcome

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

5.4.2 Secondary outcomes

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, CMCCL) 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.

6. Background

6.1 Prostate cancer diagnosis

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

6.2 Clinically significant versus clinically insignificant prostate cancer

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

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

6.3 Current standard of care: systematic TRUS guided biopsy

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

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

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

6.4.1 The role of imaging in prostate cancer diagnosis

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

6.4.2 Limitations of early MRI studies in prostate cancer

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

- **Poor reporting standards**. Many early studies failed to closely follow published guidelines for the standards of reporting of diagnostic studies (STARD) [23].
- **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.

6.4.3 Emerging role of MRI in the diagnosis of prostate cancer

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

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

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

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

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

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

6.4.3.1 MRI can influence the decision to perform a prostate biopsy

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

6.4.3.2 MRI can influence the biopsy technique

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

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

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

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

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

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

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

6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy

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

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

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

6.5 Novelty of PRECISE

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

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

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

7. Trial objectives

7.1 Overall aim

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

7.2 Hypotheses

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

7.3 Primary Objective

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

7.4 Secondary Objectives

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 ≥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. Maximal cancer core length of the most involved biopsy core (maximum cancer core length, MCCL) in each arm.
21. Total contiguous cancer core length of the most involved biopsy core (contiguous maximum cancer core length, CMCCL) excluding intervening normal regions.
22. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer by 2 years.
23. Proportion of men with post-biopsy adverse events
24. Health-related quality of life scores.
25. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
26. To determine the cost per diagnosis of cancer.

7.5 Explanation for non-inferiority hypothesis

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

7.6 Anticipated timeline of study progression

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

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

8. Study Population

8.1 Number of Subjects

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

8.2 Subject inclusion criteria

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

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. ≥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 within 3 months of randomization
4. Fit to undergo all procedures listed in protocol;
5. Able to provide written informed consent.

8.3 Subject exclusion criteria

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

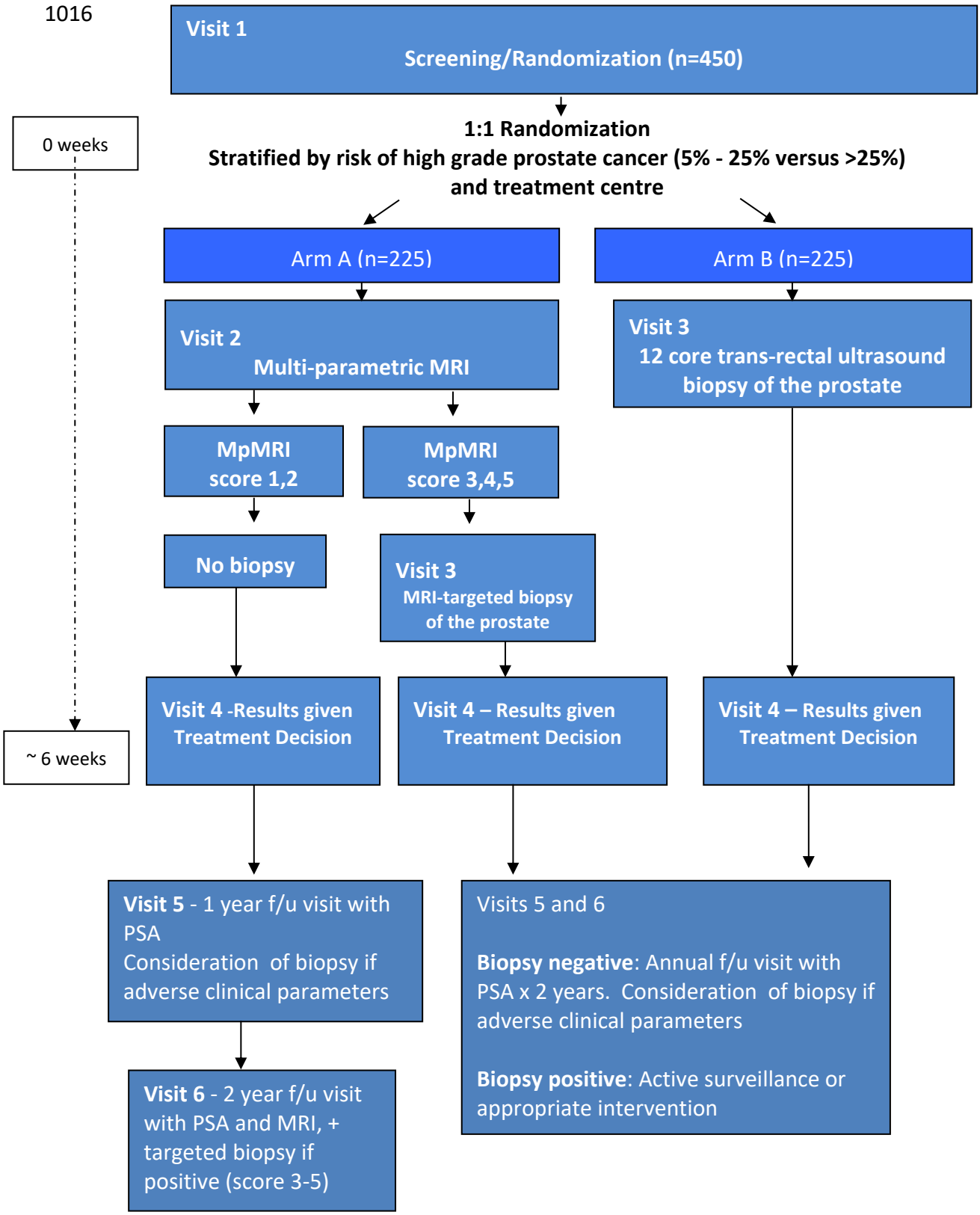
1. Prior prostate biopsy
2. Prior treatment for prostate cancer
3. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤ 50mls/min)
4. Contraindication to prostate biopsy
5. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip replacement surgery, metallic hip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

9. Study design

9.1 Study design

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

9.2 Study Trial Schema



9.3 Timeline of subject contact

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

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

	Contact with Subject * all study assessments should be conducted +/- 30 days of scheduled visits						
	Visit 0 Telephone consult	Visit 1 Screening/ Randomization	Visit 2 MRI	Visit 3	Visit 4 Post-Test	Visit 5 1 year follow up	Visit 6 2 year follow up
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						

[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.

[3] After treatment decision men revert to standard of care.

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 0 Telephone consult	Visit 1 Screening/Randomization	Visit 2 MRI	Visit 3 Biopsy	Visit 4 Post-test	Visit 5 1 year follow up	Visit 6 2 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 BiopsyQuestionnaire							
AE/SAE		Complete as required at any time following registration					
Withdrawal Form		Complete as required at any time following registration					

[1] Collected at baseline and annually.

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

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

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					

[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.

[3]The biopsy must be done within one month of randomization.
[4]After treatment decision men revert to standard of care and will be followed up at year 1 and year 2.

10. Trial Interventions and procedures

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

10.1 EQ-5D-5L Questionnaires

For all subjects enrolled in trial

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

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

10.2 Multiparametric MRI imaging procedure

For subjects in Arm A only

10.2.1 MRI Protocol

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

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

Within the specified PiRads-2 framework a common protocol will be formulated by a consensus of the radiologists involved in the trial at each site at a startup meeting. The highest agreed upon b-value image for DWI (at least 1400s/mm2) will be selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast media, injection rates and dynamic scanning temporal resolution will be matched for all sites. An optional multi b value DWI acquisition will be undertaken as well to allow for ancillary studies into non log linear apparent diffusion coefficient (ADC) models for tumor characterization.

10.2.2 MRI reporting

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

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

- 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)

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

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

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

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

10.3 Immediate post MRI/TRUS Fusion Biopsy questionnaire

For subjects in Arm A only

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

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

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

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

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

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

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

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

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

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

10.6 MRI-Targeted biopsy

For subjects in Arm A who do require a biopsy

10.6.1 MRI choice of targets for targeted biopsy

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

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

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

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

10.6.2 MRI Biopsy

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

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

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

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

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

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

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

10.7 Systematic TRUS guided biopsy

For all subjects in Arm B

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

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

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

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

10.8 Pathology

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

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

10.9 Post-procedural care

For all subjects in ARMS A and B receiving a biopsy

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

10.10 Immediate post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

10.11 30-day post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

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

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

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

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

10.13 Results and treatment decision (Visit 4)

The results of the biopsies and/or MRI will be explained to the patient by the clinical care team during this visit, which is approximately 2-3 weeks after the biopsy.
The research team should record the treatment decision in the patient file.
Possibilities for treatment decision include but are not limited to:

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

10.14 Follow up period

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

- time to cancer diagnosis
- Gleason score progression
- time to intervention on active surveillance
- time on active surveillance
- PSA

10.14.1 Indications for biopsies off protocol

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

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

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

1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.

2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase in PSA in 1 year.

3. Biopsy if a doubling of the risk of high grade cancer according to the NCI nomogram.

4.Biopsy if development of a suspicious nodule on DRE.

5. For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.

6. For men on the systematic biopsy arm which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these patients.

These are guidelines and should be interpreted with clinical judgment.

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

10.15 Additional tests for biomarker discovery - Optional

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

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

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

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

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

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

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

10.16 Long-term data linkage – Permission to Contact

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

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

10.17 End of Study

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

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

10.18 Risks and Benefits to Participants

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

10.18.1 Risks to subjects

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

10.18.1.1 Risk of Systematic TRUS guided biopsy

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

10.18.1.2 Risks of MPMRI

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. Patients 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 patients with impaired renal function, with an eGFR <30ml/min/1.73m2. These patients are ineligible for this study.

10.18.1.3 Risks of MRI-targeted biopsy

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.

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 biopsyy
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%

10.18.2 Benefits to subjects

Subjects enrolled in this trial will benefit from the following:

- 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 will also ensure streamlined diagnostic investigations to promptly conduct the diagnostic test and communicate the test outcome for the patient.
- Subjects enrolled in the trial will benefit from the dedicated research team involved in their care in addition to the clinical team normally involved in their care.
- Subjects will benefit from additional discussions regarding the trial, which could increase their understanding of prostate cancer and help them to make a more informed decision about their health.
- Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will remove any risk of post-biopsy infection. MRI-randomized subjects may also benefit from a reduced probability of having a clinically insignificant prostate cancer diagnosed. Clinically insignificant prostate cancer is often treated definitively per patient preference despite the lack of evidence supporting the need. All definitive local therapies for prostate cancer carry the risk of peri-operative complications as well as long-term risk of incontinence and erectile dysfunction.

10.19 Concomitant medications

10.19.1 Permitted Medications

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

10.19.2 Non-Drug Therapies

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

11. Schedule of Study Visits

11.1 Visit 0 (Telephone Consult): Telephone consult

For all subjects enrolled in trial

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

This will occur any time from referral letter being received to the first hospital visit. Ideally, this will be performed as soon as possible following receipt of referral. 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.

11.2 Visit 1 (Screening/Randomization): Screening, Consent, Randomization

For all subjects enrolled in trial

Screening will occur any time following the referral of the subject. Ideally, this will be performed as soon as possible following receipt of referral.
Subjects will be consented only after they have had time to consider the study. This may happen on the same visit as the screening visit.
Randomization will happen immediately after the consent form is signed.

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

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

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

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

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

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

For men randomized to ARM A, who have a lesion identified by MRI. This appointment will follow one-two weeks 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 biopsy to occur in timely fashion. If the results of the MRI show 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.

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

Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and complete as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however, the questionnaire should be completed as close as possible to 30 days post-biopsy.

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

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

For men randomized to ARM B only.

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

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

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

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

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

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

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

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

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

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

Possibilities for treatment decision include but are not limited to:

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

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

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

All subjects are planned to have a 52 week follow up visit.
Subjects will be followed to obtain the following information on an annual basis:

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

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6 (year 2).

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

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

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

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

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6.

12. Randomization

12.1 Randomization Procedure

Written informed consent will be obtained from all eligible subjects prior to commencing any study related procedures. The Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre, Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate

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

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

12.2 Stratification

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

12.3 Blinding and measures taken to avoid bias

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

Radiologists will not be blinded to patient information (e.g. PSA level) as international guidelines recommend that this should be available to them [48]. Radiologists will be aware that the patient is part of the trial. Radiology images are stored on the hospital database.

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

13. Data

Type of data to be collected:

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

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

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

14. Statistical Considerations

14.1 Sample Size Calculation

STATISTICAL methods

Primary Analysis

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

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

Secondary Analyses

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

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

Treatment Allocation and Stratification

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

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

Stratification

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

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

(2) clinical centre.

Sample Size

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

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

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

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

To account 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.

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

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

Statistical Conventions

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

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

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

Missing Data

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

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

14.2 Interim Analyses

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

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

Timing of Final Analysis

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

14.3 Populations:

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

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

14.4 Primary Outcome

14.4.1 Detection rate of clinically significant cancer

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 intention to treat population.

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

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

14.5 Secondary Outcomes

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

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

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

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

14.5.2 Proportion of men in each arm with Gleason ≥4+3 detected

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

14.5.3 Proportion of men in MPMRI arm who avoid biopsy.

14.5.4 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.

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

14.5.5 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)

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

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

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

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

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 haemotospermia.

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, 24-48 hours post intervention and at 30-days 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 patient-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

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

14.5.12.1 Data collection:

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

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

14.5.12.2 Sample consent form language:

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

14.5.12.3 Cost calculation

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

14.5.12.4 Primary Analysis

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

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

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

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

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

14.5.12.5 Secondary Cost Analyses

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

14.5.13 Missing Data

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

15. Participant compliance and withdrawal

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

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

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

15.1 Subject Withdrawal from Study

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

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

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

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

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

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

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

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

15.2 Study completion

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

16. Data Monitoring, Quality Control and Safety

16.1 Stopping / discontinuation rules

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

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

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

16.2 Monitoring, quality control and assurance

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

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

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

16.3 Assessment of safety

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

16.3.1 Definition of an Adverse Event (AE)

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

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

16.3.2 Definition of a Serious Adverse Event (SAE)

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

(a) results in death

(b) is life-threatening

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

(c) requires hospitalisation or prolongation of existing hospitalisation

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

(d) results in disability / incapacity

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

(e) is a congenital abnormality/birth defect.

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

16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

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

16.3.4 Lack of Efficacy

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

16.3.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

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

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

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

16.3.6 Recording/Reporting AEs and SAEs

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

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

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

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

Expected AEs includes the following:

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

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

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

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

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

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

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

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

16.3.7 Evaluating AEs and SAEs

16.3.7.1 Assessment of Intensity

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

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

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

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

16.3.7.2 Assessment of Causality

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

16.3.8 Follow-up of AEs and SAEs

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

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

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

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

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

16.3.9 Prompt Reporting of SAEs

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

16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI

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

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

Dr. Laurence Klotz
c/o Marlene Kebabdjian
Division of Urology
Sunnybrook Health Sciences Centre
2075 Bayview Avenue A304
Toronto, Ontario M4N 3M5 Canada
Phone: (416) 480-6100 ext 2890
E-mail: Laurence.Klotz@sunnybrook.ca
Marlene.kebabdjian@sunnybrook.ca

16.3.9.2 Completion and Transmission of the SAE Reports

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

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

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

16.3.10 Post-study AEs and SAEs

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

17. Study Administration

17.1 Regulatory and Ethical Considerations

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

17.1.1 Ethical Conduct of the Study and Ethics Approval

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

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

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

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

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

17.1.2 Informed Consent

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

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

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

17.1.3 Investigator Reporting Requirements

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

17.2 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

17.3 Quality Assurance

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

17.4 Study and Site Closure

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

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

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

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

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

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

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

17.5 Records Retention

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

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

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

17.6 Data Management

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

17.7 Publication

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

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

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

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

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

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

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Appendices

Appendix 1: Time windows for data collection

For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3
For details on time windows permitted for each trial intervention to be completed please see Table 5 below.

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

Contact and Purpose if not clear	Time window permitted
Visit 0 Telephone consult Purpose: give information on study. Send interested subjects the information sheet	Any time from referral letter being received to 1st visit in hospital. Ideally perform as soon as possible following receipt of referral. 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.
Visit 1 Screening (eligibility review)	Any time following referral of subject. Ideally perform as soon as possible following receipt of referral.
Visit 1 Consent Randomization EQ-5D-5L Questionnaire (baseline) Optional urine, semen and	 Complete only once subject has had 24 hours after receiving the patient information leaflet to fully consider the study. Ideally on same visit as screening. Immediately after consent form signed. Complete immediately after consent form is signed 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. Complete after additional informed consent

blood sample	signed, after randomization and up until any point prior to a biopsy.
Visit 2 MRI EQ-5D-5L Questionnaire (post MRI) Immediate post MRI/TRUS Fusion Biopsy Questionnaire	 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 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 30-day 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. To be given to subject to take home after biopsy and completed as instructed on day 30 post-

	biopsy. To be returned by post or at follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. 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.
Telephone reminder	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
Visit 3 EQ-5D-5L Questionnaire (post-biopsy)	Should be given to subject to take home after biopsy. To be completed 24-48 hours post-biopsy. Telephone call to remind to complete.
Visit 3 Post-MRI/TRUS Fusion Biopsy 30-day questionnaire	Only for subjects in the MRI arm who do not undergo biopsy. 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. To be returned at follow up appointment (Visit 4) or by post. 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60

	days post-MRI, it will be acceptable. Ideally the questionnaire should be completed as close as possible to 30 days post-MRI.
Telephone Reminder	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
Visit 4 Follow up for results And treatment Decision	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. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.
Visit 4 30-day post intervention EQ-5D-5L Questionnaire	To be completed at 30 days post-biopsy or 30-days post MRI if no biopsy occurs. 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. A telephone reminder from the research team to the subject can take place.
Visit 5 52 week follow up visit	The following information will be obtained on an annual basis: • 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

Visit 6 104 week follow up visit	The following information will be obtained on an annual basis: • time to cancer diagnosis; • Gleason score progression; • time to intervention on active surveillance; • time on active surveillance; • results of PSA tests. 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). 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

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.

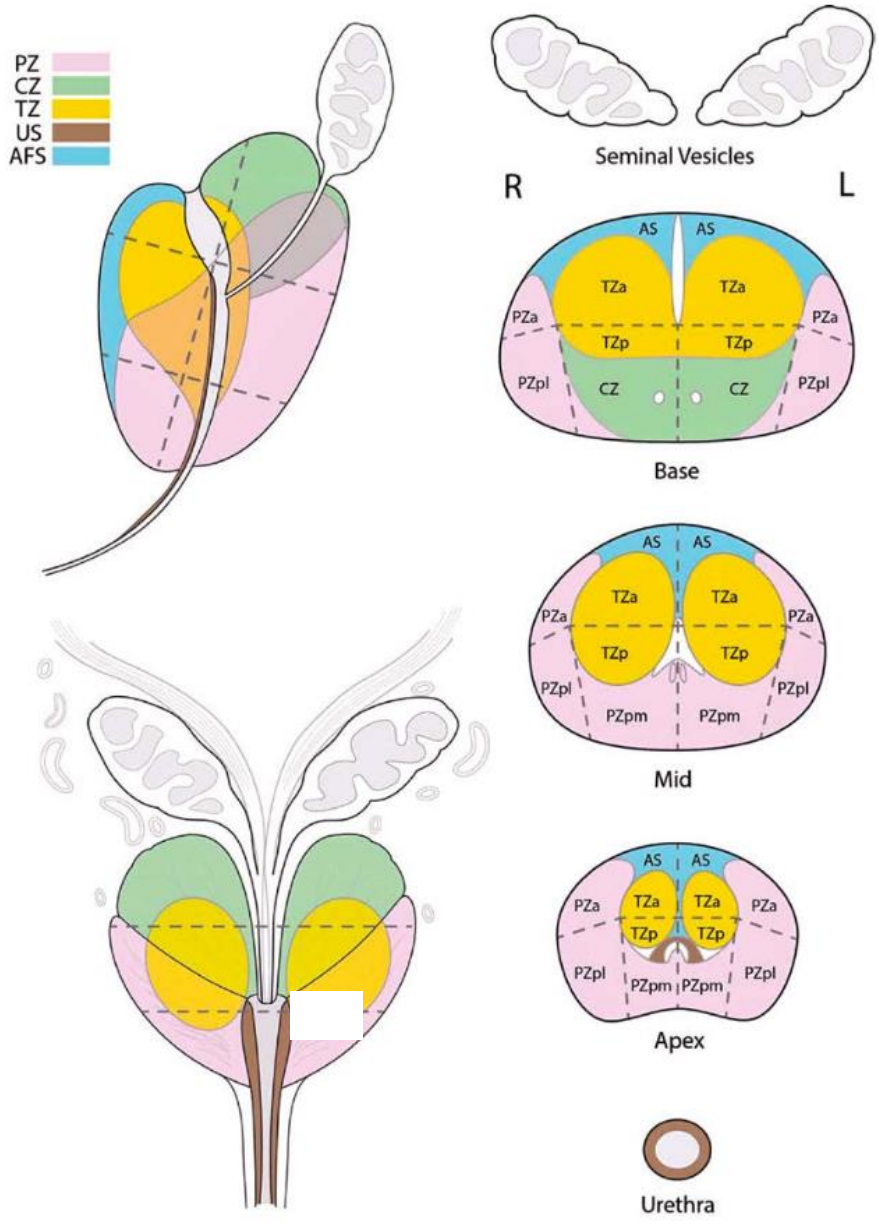


Image quality: Good, Minor image quality issues, acceptable for diagnosis, unacceptable

If image quality is not good please comment: _____

Findings (intermediate (PI-Rads 3), high (PI-Rads 4) or very high (PI-Rads 5))

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

Target 1:
Pi-Rads Score:
Size: x x mm
Location(s): (side)

Target 2:
Pi-Rads Score:
Size: x x mm
Location(s): (side)

Target 3:
Pi-Rads Score:
Size: x x mm
Location(s): (side)

There are more than 3 targets seen: Y/N

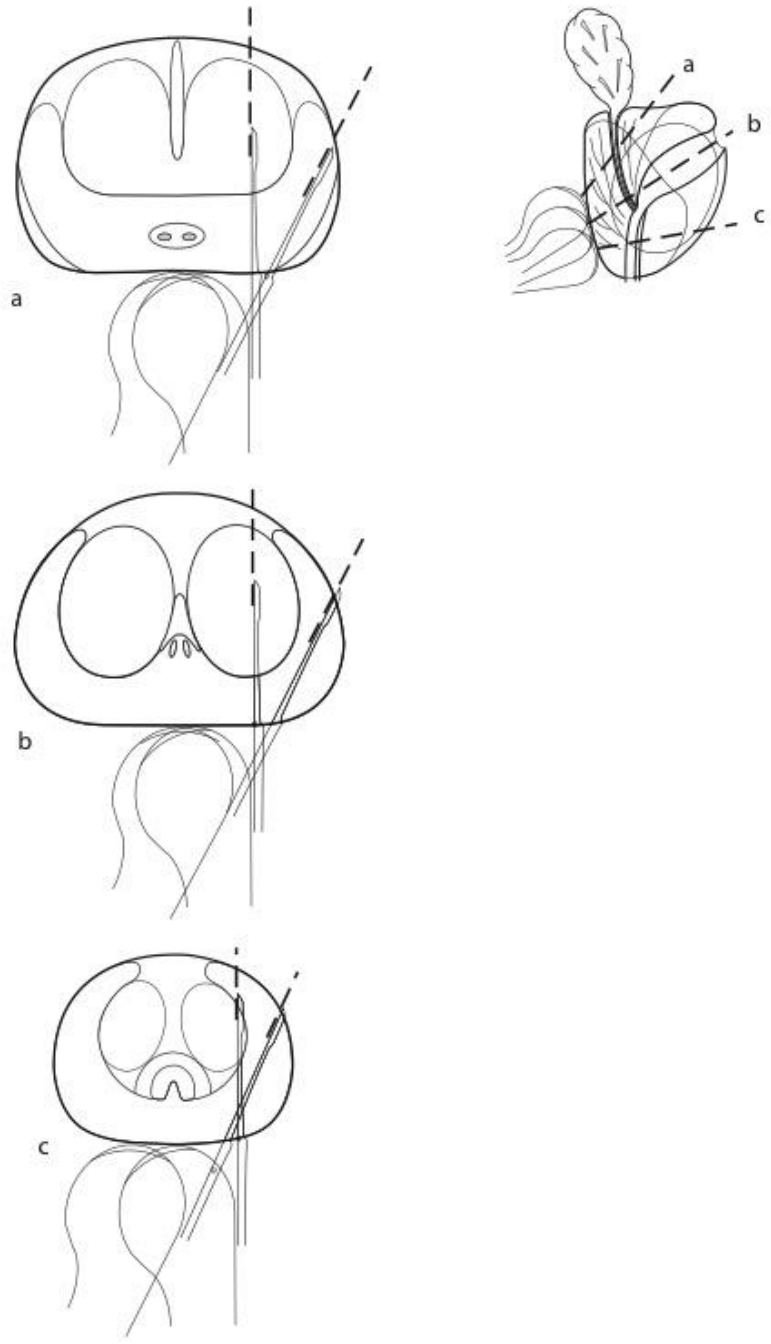
There is a multifocal pattern raising a concern for multifocal small volume cancer and a PSA Density >0.15 without a measurable focal lesion (3M pattern): Y/N

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

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

Appendix 3: Example of systematic TRUS guided biopsy schema

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



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

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

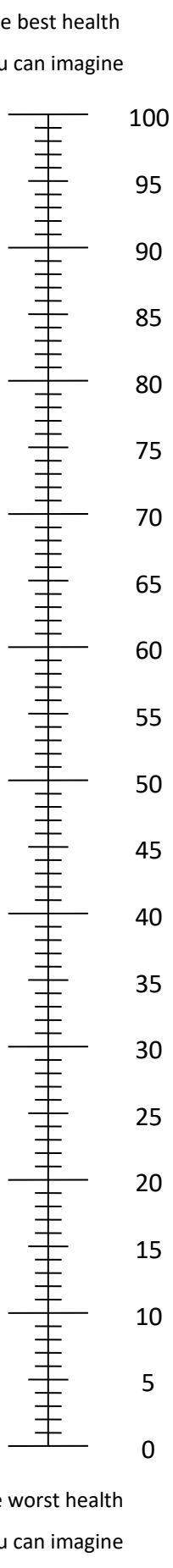
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



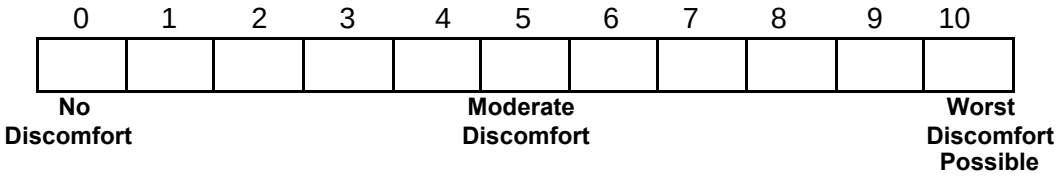
Appendix 5: Immediate Post MRI/TRUS Fusion Biopsy Questionnaire

Immediate post-MRI questionnaire

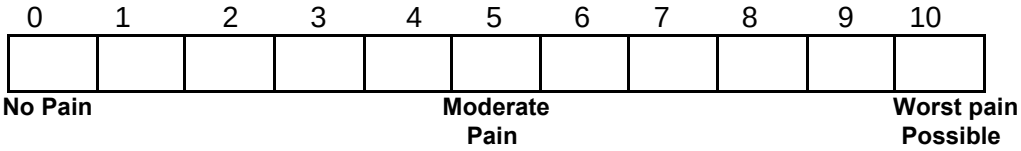
Please ask the patient to fill this out after the MRI

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 MRI cause you?



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



Please complete the next page of questions

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

3. Fevers

Yes	No
☐	☐
1	2

4. Blood in the urine

Yes	No
☐	☐
1	2

5. Blood in the semen

Yes	No
☐	☐
1	2

6. Blood in the stools or from the back passage

Yes	No
☐	☐
1	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	No
☐	☐
1	2

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

Yes	No
☐	☐
1	2

9. Urinary incontinence, meaning any undesired leakage of urine

Yes	No
☐	☐
1	2

10. Urinary tract infection diagnosed by a healthcare professional

Yes	No
☐	☐
1	2

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

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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
e.g. paracetamol	*1g*	*4*	*3*

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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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

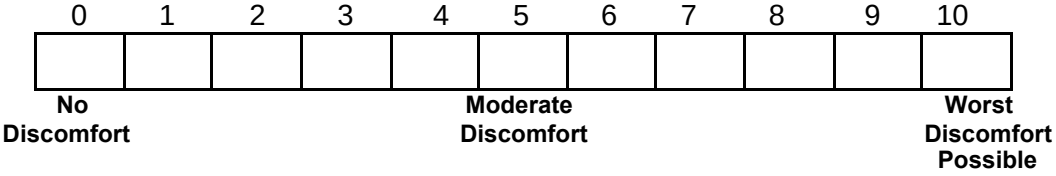
Appendix 7: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

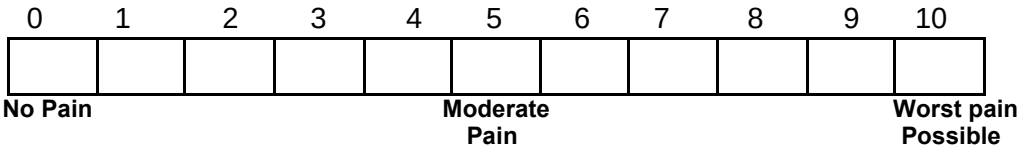
Please ask the patient to fill this out after the biopsy, before they leave the department.

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?



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



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

2911 # 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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

2912

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 ☐ 1 No ☐ 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
	☐ 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 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 ☐ 1 No ☐ 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
	☐ 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 biopsy procedure:

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

Yes ☐ 1 No ☐ 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
	☐ 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

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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
☐	☐	☐	☐

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
e.g. ciprofloxacin	*500mg*	*2*	*3*

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"):*

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	No
☐ 1	☐ 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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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.

PRECISE Protocol: *revision date:* 30 January 2017

Summary of Changes – Amendment 1

PROTOCOL CHANGES:

Protocol Version date change: 30January2017

Revisions to the protocol were necessary as a result of the protocol review by the investigators involved in the trial. The following changes have been made to the protocol as part of Amendment 1:

-Secondary Objectives: #7, #8 -page 3 -were omitted due to the challenges in obtaining this information due to site variablity in pathology reporting

-Secondary Objectives: addition of #12, #13 - page 4 -to determine impact Gd and reading of PI-rads by radiologist

-Subject Inclusion Criteria clarification of #2, page 21 - no changes to the criteria were made. Clarification was added to instructions on how to enter subjects into the risk calculator.

-Table 1, 2, 3 -Schedule of Assessment, page 24, 26, 28 - added 2 new visits (q6 mos), to obtain blood, and urine for correlative samples, if subject provided consent to optional sampling.

-Table 1, 2, 3, -Schedule of Assessment, page 24, 26, 28 -clarification of how samples are to be obtained, and their timelines

-Table 1, 2, 3 -Schedule of Assessment, page 24, 26, 28, -physical exam replaced with vital and DRE.

-MRI Reporting -page 31, 32- clarification, revision of how MRI is to be reported by the attending radiologist

-Pathology, page 34, removal of reporting of maximum cancer core length (MCCL) due to too much site variability on reporting.

-Section 10.15.1 Optional Sample collection, page 37, -revision on the amount of samples to be collected, more detailed information added

-removal of 2 questionnaires,- Appendix 5 and 6: 'Immediate post MRI questionnaire', and '30 Post MRI questionnaire

In addition to the above reference changes, minor administrative changes were made to revise typos, grammatical errors, and spacing.

INFORMED CONSENT CHANGES:

ICF date change change: 30January2017

-Arm A: - page 3, 'approximately' added to clarify estimated timelines.

-Non-Experimental Procedures, -page 3: physical exam replaced with vitals, DRE as per protocol change

-Questionnaires- page 3: ommitted, clarity added to the timelines requiring select questionnaires

OPTIONAL INFORMED CONSENT CHANGES:

Optional ICF date change: 30January2017

-Purpose, page 1 - revised wording, no content change

-Study Procedure: -page 2: -clarification/revision of sampe collection quantity, and timelines of collection.

-Confidentiality, page 3: -inclusion of study collaborators,

-Consent, page 5: order revised, no content change

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.

1. **Short title**: **Pr**ostate **E**valuation for **C**linically **I**mportant disease: MRI vs **S**tandard **E**valuation procedures. (PRECISE)

Date: 30 January 2017

Version 2.0

Sponsor:
Canadian Urology Research Consortium (CURC)

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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: _____

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3052 ## 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 vsStandard Evaluation procedures. (PRECISE)
Clinical study phase	Phase III
Study Objectives	**Primary Objective** 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. **Secondary Objectives** 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 ≥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 by2 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)

	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, all inclusion criteria must be met. 6. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy; 7. ≥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. 8. Serum PSA ≤ 20ng/ml; 9. Fit to undergo all procedures listed in protocol; 10. Able to provide written informed consent.
Exclusion Criteria	Men who meet the following criteria at the time of screening will be excluded: 7. Prior prostate biopsy; 8. Prior treatment for prostate cancer; 9. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min); 10. Contraindication to prostate biopsy; 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; 12. 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. All subjects 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.

	All subjects in ARM A will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI. Subjects in ARM A who do not receive a subsequent biopsy will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (± I 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. Subjects in ARM A who do receive a MRI-targeted biopsy 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 (± I 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. All subjects in ARM B 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 (± I 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.
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 ≥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

Abbreviations:

ADC	Apparent diffusion coefficient
CI	Confidence interval
CRF	Case report form
DSMC	Data Safety and Monitoring Committee
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
EDC	Electronic Data Capture
ITT	Intention to treat
MCCL	Maximum cancer core length
MPMRI	Multi-parametric MRI, used interchangeably with MRI in this protocol.
MPMRI-TB	Multi-parametric magnetic resonance image-targeted biopsy of the prostate
MRI	Magnetic resonance imaging, used interchangeably with MPMRI in this protocol
MRI-TB	Magnetic resonance imagining targeted biopsy
MRS	Magnetic resonance spectroscopy
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PTC	Permission to Contact
PSA	Prostate specific antigen
REB	Research Ethics Board
STARD	Standards for the reporting of diagnostic studies
TRUS	Trans-rectal ultrasound
TSC	Trial Steering Committee
T2W	T2-weighted imaging

Definitions:

MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is used to determine the location of a suspicious target prior to biopsy.
Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure is not influenced by findings on MRI imaging. Currently this is the standard of care for prostate cancer in the province of Ontario.

5. Trial summary

5.1 Aim and Rationale

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

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

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

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

The potential implications of this trial include:

- 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

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 (± I 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 for30-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 prostectomy) 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

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

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

5.3 Participating Sites

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

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

5.4 Study outcomes

5.4.1 Primary outcome

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

5.4.2 Secondary outcomes

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

6. Background

6.1 Prostate cancer diagnosis

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

6.2 Clinically significant versus clinically insignificant prostate cancer

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

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

6.3 Current standard of care: systematic TRUS guided biopsy

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

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

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

6.4.1 The role of imaging in prostate cancer diagnosis

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

6.4.2 Limitations of early MRI studies in prostate cancer

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

- **Poor reporting standards**. Many early studies failed to closely follow published guidelines for the standards of reporting of diagnostic studies (STARD) [23].
- **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.

6.4.3 Emerging role of MRI in the diagnosis of prostate cancer

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

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

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

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

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

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

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

6.4.3.1 MRI can influence the decision to perform a prostate biopsy

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

6.4.3.2 MRI can influence the biopsy technique

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

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

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

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

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

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

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

6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy

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

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

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

6.5 Novelty of PRECISE

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

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

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

7. Trial objectives

7.1 Overall aim

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

7.2 Hypotheses

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

7.3 Primary Objective

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

7.4 Secondary Objectives

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.
28. Proportion of men in each arm with clinically insignificant cancer detected.
29. Proportion of men in each arm with Gleason ≥4+3 detected.
30. Proportion of men in MRI arm who avoid biopsy.
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.
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).
33. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer by 2 years.
34. Proportion of men with post-biopsy adverse events
35. Health-related quality of life scores.
36. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
37. To determine the cost per diagnosis of cancer.
38. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield
39. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone

7.5 Explanation for non-inferiority hypothesis

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

7.6 Anticipated timeline of study progression

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

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

8.Study Population

8.1 Number of Subjects

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

8.2 Subject inclusion criteria

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

7. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;
8. ≥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.
9. Serum PSA ≤ 20ng/ml within 3 months of randomization
10. Fit to undergo all procedures listed in protocol;
11. Able to provide written informed consent.

8.3 Subject exclusion criteria

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

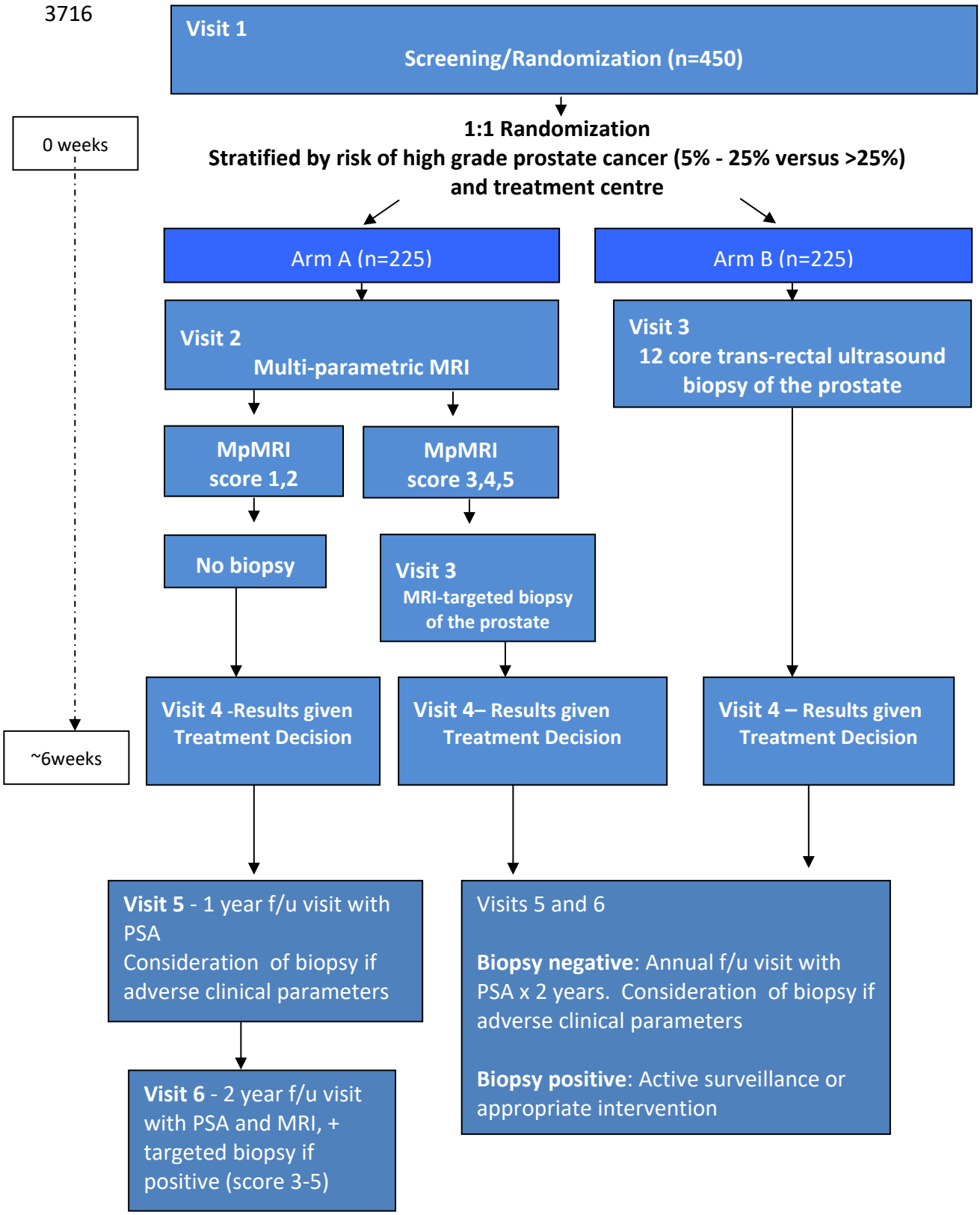
7. Prior prostate biopsy
8. Prior treatment for prostate cancer
9. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min)
10. Contraindication to prostate biopsy
11. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip replacement surgery, metallic hip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

9. Study design

9.1 Study design

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

9.2 Study Trial Schema



9.3 Timeline of subject contact

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

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

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4]PSA will have been done prior to visit 1 as part of screening.

[5] If MRI indicates a target, biopsy must be done

[6]After treatment decision men revert to standard of care.

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							

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4] tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[5]PSA 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.[7]After treatment decision men revert to standard of care.

3787 **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 follow 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							

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[2]Urine 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.
[3]Collected at baseline, and annually.
[4]PSA will have been done prior to visit 1 as part of screening.
[5] If MRI indicates a target, biopsy must be done, and tissue must be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.[6]After treatment decision men revert to standard of care.

10. Trial Interventions and procedures

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

10.1 EQ-5D-5L Questionnaires

For all subjects enrolled in trial

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

- All subjects should complete the baseline questionnaire at the screening visit before leaving the department.
- Subjects will be given the questionnaire before they leave the department and the subject should take this home. Subjects can return the completed questionnaire to the investigator by post in a pre-addressed envelope provided by the investigator. It cannot be filled out immediately after the procedure in the department as it assesses domains such as washing, dressing and carrying out usual activities, which cannot be established immediately after the biopsy. Subjects will be reminded by the biopsy operator to complete the questionnaire at home and may be given a phone call by the research team to remind them to complete the questionnaire.
- Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date that the subject should fill out the questionnaires should be written on top of the questionnaire. (This can also be done at Visit 4).
- All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up visit.

10.2 Multiparametric MRI imaging procedure

For subjects in Arm A only

10.2.1 MRI Protocol

A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic phased array coil and an automated injector system with the subject in the supine position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS v2.

Within the specified PiRads-2 framework a common protocol will be formulated by a consensus of the radiologists involved in the trial at each site at a startup meeting. The highest agreed upon b-value image for DWI (at least 1400s/mm2) will be selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast media, injection rates and dynamic scanning temporal resolution will be matched for all sites. An optional multi b value DWI acquisition will be undertaken as well to allow for ancillary studies into non log linear apparent diffusion coefficient (ADC) models for tumor characterization. This is summarized in an MRI Operations Manual

Subjects will be asked to follow their local standard of care MRI examination preparation instructions for the MRI procedure.

10.2.2 MRI reporting

The MRI will be reported by an experienced radiologist using the MRI Reporting Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5 pointLikert score for purposes of comparison. . Biopsy decisions will be based on the PiRads scores.

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

- 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)

The location of the suspicious areas in the prostate should be marked on a diagram of the prostate (see Appendix2) and the sector numbers containing each suspicious area should be recorded in the case report form.

Radiologists will be blinded to the PSA.

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

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

10.3 No target identified on MPMRI (PiRads 1 or 2)

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

Men who have MRIs that do not identify any suspicious lesion will not receive a biopsy. These subjects will benefit from being part of the trial as a result of not having to undergo an invasive biopsy procedure, avoiding the discomfort associated with the procedure, the risk of being diagnosed with clinically insignificant cancer and the risk of sepsis associated with the biopsy procedure. Studies suggest that if the MRI does not identify areas suspicious for cancer there is an85-95% chance that clinically significant cancer is not present[28, 34, 35].

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

10.4 MRI-Targeted biopsy

For subjects in Arm A who do require a biopsy

10.4.1 MRI choice of targets for targeted biopsy

Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in MRI-targeted biopsy. Operator experience (number of targeted biopsies performed to date) will be recorded before each procedure. The number of biopsy operators should be kept to the minimum number possible.

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

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

10.4.2 MRI Biopsy

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

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

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

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

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

Biopsy cores from different suspicious areas will be aliquoted separately. The vials will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there are) which should match the assignment of suspicious areas by the radiologist on the MRI report. The order of lettering a-d should match the order in which the biopsies were performed in each region. The first biopsy should be at the center of the target and the remaining fanning out from the center. Each core from the same suspicious area must be submitted separately. Alternative methods of storing cores that allow identification of the order of score samples from each target are acceptable.

10.5 Systematic TRUS guided biopsy

For all subjects in Arm B

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

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

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

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

10.6 Pathology

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

For men undergoing MRI-targeted biopsy it is required that pathology reported per suspicious area targeted and per targeted core. For systematic TRUS guided biopsy, each core will be reported and graded.

10.7 Post-procedural care

For all subjects in ARMS A and B receiving a biopsy

After a biopsy procedure the subject can be discharged. within 2-3 weeks for results of the histopathology and treatment options to be discussed.

10.8 Immediate post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

10.9 30-day post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

Subjects should be reminded at 30 days to complete this questionnaire.

10.10 Results and treatment decision (Visit 4)

The results of the biopsies and/or MRI will be explained to the subject by the clinical care team during this visit, which is approximately 2-3 weeks after the biopsy. The research team should record the treatment decision in the subject file. Possibilities for treatment decision include but are not limited to:

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

10.11 Follow up period

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

- time to cancer diagnosis
- Gleason score progression
- time to intervention on active surveillance
- time on active surveillance
- PSA

10.11.1 Indications for biopsies off protocol

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

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

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

1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.

2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase in PSA in 1 year.

3. Biopsy if a doubling of the risk of high grade cancer according to the NCI nomogram.

4. Biopsy if development of a suspicious nodule on DRE.

5.For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.

12. For men on the systematic biopsy arm which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these subjects.

These are guidelines and should be interpreted with clinical judgment.

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

10.12 Additional tests for biomarker discovery - Optional

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

We propose two initial biomarker analyses for men recruited to the PRECISE study. First we propose testing the utility of existing validated tests, these potentially include the Genomic Prostate Score (OncotypeDx) [44] and a recently developed multiple Kallikrein biomarker test[45]. We will test the hypothesis that alongside conventional PSA measurements, the multiple Kallikrein test or other serum biomarker test, may identify subjects whose MRI was initially negative for prostate cancer, but who are at high risk of harboring clinically significant disease as detected by the secondary MRI at 2 years. We will also test the association between serum biomarkers and clinically significant or clinically insignificant prostate cancer detected during the PRECISE study. We will also explore the potential for the

Genomic Prostate Score to provide additional information over and above Gleason grade. These studies will be separately funded from PRECISE.

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

10.12.1 Samples to be collected for future biomarker discovery work (Optional)

Participants will be asked to consent to provide a blood, urine,semen, and tissue sample after the consent and screen visit and subsequent visits for storage and use in future biomarker studies. This will involve a separate consent form.

Samples include:

- Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- Urine – 75 mls urine
- Semen-1-5 cc (single ejaculate)
- Tissue-unstained biopsy sections -15 unstained slides from cancer, and
  -15 unstained slide from non-cancer cores (if possible)

10.13 Long-term data linkage – Permission to Contact

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

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

10.14 End of Study

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

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

10.15 Risks and Benefits to Participants

An important consideration of this study is that men are being randomized to one of two biopsy techniques when it is not known which will be more effective. Both diagnostic tests are currently used in clinical practice at the institutions involved in

the trial. Though systematic TRUS guided biopsy could be considered standard of care, there is enough evidence to support the concept that MRI-targeted biopsy may be at least as effective as systematic TRUS guided biopsy[27].

10.15.1 Risks to subjects

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

10.15.1.1 Risk of Systematic TRUS guided biopsy

Systematic TRUS guided biopsy can be associated with discomfort, haematuria, haematospermia and dysuria in a large proportion of subjects, which is self-resolving (See Table 4). There is a 4% risk of systemic urosepsis[46].

10.15.1.2 Risks of MPMRI

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.

10.15.1.3 Risks of MRI-targeted biopsy

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.

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
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%

10.15.2 Benefits to subjects

Subjects enrolled in this trial will benefit from the following:

- 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 will also ensure streamlined diagnostic investigations to promptly conduct the diagnostic test and communicate the test outcome for the subject.
- Subjects enrolled in the trial will benefit from the dedicated research team involved in their care in addition to the clinical team normally involved in their care.
- Subjects will benefit from additional discussions regarding the trial, which could increase their understanding of prostate cancer and help them to make a more informed decision about their health.
- Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will remove any risk of post-biopsy infection. MRI-randomized subjects may also benefit from a reduced probability of having a clinically insignificant prostate cancer diagnosed. Clinically insignificant prostate cancer is often treated definitively per subject preference despite the lack of evidence supporting the need. All definitive local therapies for prostate cancer carry the risk of peri-operative complications as well as long-term risk of incontinence and erectile dysfunction.

10.16 Concomitant medications

10.16.1 Permitted Medications

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

10.16.2 Non-Drug Therapies

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

11. Schedule of Study Visits

11.1 Visit 1 (Screening/Randomization): Screening, Consent, Randomization

For all subjects enrolled in trial

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

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

Randomization can happen immediately after the consent form is signed and eligibility is confirmed.

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

If a subject agrees to the optional informed consent, from randomization until any point prior to a biopsy, optional blood, urine,semenand tissue samples will be collected for correlative studies.

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

11.2 Visit 2 (MRI): ARM A, for men randomized to MRI

This will occur approximately within one week of randomization. Men will receive an MRI (see Section 10.2.)

11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate

For men randomized to ARM A, who have a lesion identified by MRI. This appointment will follow approximately one-two weeks 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 biopsy to occur in timely fashion. If the results of the MRI show 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.

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

Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and complete as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however, the questionnaire should be completed as close as possible to 30 days post-biopsy.

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

11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic TRUS-biopsy

For men randomized to ARM B only.

Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after the biopsy.
Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and completed as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-biopsy.

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

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

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

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

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

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

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

The research team should record the treatment decision in the subject file.

Possibilities for treatment decision include but are not limited to:

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

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

11.7 Visit 5 (6 month follow up):26 week follow up

All subjects will have a 26 week visit
Subjects will have the following:

- PSA
- Optional sample collection (blood, urine)

11.8 Visit 6(1 year follow up): 52 week follow up

All subjects are planned to have a 52 week follow up visit.
Subjects will be followed to obtain the following information on an annual basis:

- time to cancer diagnosis;
- Gleason score progression;
- time to intervention on active surveillance;
- time on active surveillance;
- results of PSA tests.
- 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, targeted only or both systematic + targets, not done because of negative MRI
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6 (year 2).

11.9 Visit 7 (18 month follow up): 78 week follow up

All subjects will have a 78 week visit
Subjects will have the following:

- PSA
- Optional sample collection (blood, urine)

11.10 Visit 8 (2 year follow up): End of study

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

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

- 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)

- 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

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 8.

12. Randomization

12.1 Randomization Procedure

Written informed consent will be obtained from all eligible subjects prior to commencing any study related procedures. The Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre, Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate subject randomization. Subjects will be allocated to the two treatment arms in an approximate 1:1 ratio by use of a dynamic allocation scheme[47].

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

12.2 Stratification

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

12.3 Blinding and measures taken to avoid bias

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

Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be aware that the subject is part of the trial.
Pathologists will be blinded to the cohort allocation. Concealment may be challenging due to the different number of cores in the two groups, but this is unavoidable. This is unlikely to represent a significant source of bias.

13. Data

Type of data to be collected:

- EQ-5D–5L questionnaires. These will measure quality of life and will be measured continuously throughout the trial.
- Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and continuous data (e.g. maximum cancer core length)
- MRI – diagram representing MRI; categorical data for areas and scores of suspicion (e.g. Sector 1p, score of suspicion 4/5)
- MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and continuous data (e.g. maximum cancer core length)
- Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers yes/no)
- Treatment decisions – categorical data (e.g. radical treatment)
- PSA – continuous data (e.g. value of PSA in ng/ml)

Please see **Appendix1** for the time window for data collection.

14. Statistical Considerations

14.1 Sample Size Calculation

STATISTICAL methods

Primary Analysis

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

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

Secondary Analyses

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

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

Treatment Allocation and Stratification

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

<u>Stratification</u>

For treatment allocation, the subjects' individualized risk of high-grade prostate

cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp. Eligible, consenting subjects will be stratified by:
(1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);
(2) clinical centre.

Sample Size

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

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

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

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

To account 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.

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

Statistical Conventions

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

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

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

Missing Data

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

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

14.2 Interim Analyses

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. Unless otherwise specified by one of these bodies, a futility analysis will be performed after approximately 200 subjects are enrolled and have their primary outcome ascertained. Simulation will be used to estimate the conditional probability of futility assuming the study was to continue to completion, and assuming the clinically significant cancer detection rate is 30% in both arms. If the conditional probability is 0.95 or higher that continuation of the study will result in a negative result, the DSMC will recommend a suspension of recruitment to the trial, and initiation of a quality assurance review. A decision to permanently close the study or continue with

accrual will be determined by the Steering Committee, based on the results of the quality assurance review, and the recommendation of the DSMC.

Timing of Final Analysis

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

14.3 Populations:

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

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

14.4 Primary Outcome

14.4.1 Detection rate of clinically significant cancer

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 intention to treat population.

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

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

14.5 Secondary Outcomes

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

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

The proportion of men in each arm with clinically insignificant cancer (Gleason <7) will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.2 Proportion of men in each arm with Gleason ≥4+3 detected

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

14.5.3 Proportion of men in MPMRI arm who avoid biopsy.

14.5.4 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.

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

14.5.5 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)

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 haemotospermia.

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, 24-48 hours post intervention and at 30-days 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

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

14.5.12.1 Data collection:

As part of the informed consent process, participants in Ontario will also consent to having their Ontario Health Insurance Number recorded, to be later transferred to the Institute for Clinical Evaluative Sciences (ICES) where it will be linked to a number of administrative claims databases recording health system resource utilization such as physician billing [Ontario Health Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity Level Reporting (ALR)];clinic and emergency department visits [National Ambulatory Care Reporting System (NACRS),Emergency Department visits); radiation (ALR); homecare (Home Care databases) and a few additional ones as determined necessary (e.g., Long-term care, Mental Health, Diabetes.The overall, number and proportion of health system resources will be determined.In this way we can capture comprehensive resource utilization related to on-trial management including any adverse events.

14.5.12.2 Health Insurance number handling and security

As the economic implications of this study are of prime importance to some of the funders, the request for data linkage will be part of the main consent form. If a participant indicates to the study team that they decline or

withdraw consent, the OHIP number will be recorded as 9999-999-999-XX. The OHIP numbers will stay with the participating institution until after accrual is complete, and then they will all be transferred at one time under data sharing agreements between ICES and each institution. Data will be transferred using a secure electronic file transfer system established by ICES and managed by authorized ICES personnel responsible for receiving data. The file transfer system uses security safeguards including encryption and authentication.

ICES is a Prescribed Entity under the Personal Health Information Protection Act (PHIPA), and can receive and use personal health information for purposes of analysis and compiling statistical information and other research. Its policies and procedures for privacy protection and data security have been approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-monitored and requiring passkeys to access private offices and computers. ICES has extensive experience in the protection of confidentiality when using such data. It has a UNIX-based network that cannot be accessed externally. ICES data facilities are fully 'moated' (no connections to other computers). At ICES, routine procedures for data backup are instituted by a data management team. The data is burned onto a CD or placed on an external hard drive and placed in a locked vault. All ICES staff and scientific affiliates are required to sign agreements of confidentiality annually. Internal audits are conducted to monitor compliance with ICES policies, standards and procedures.

> Study data with direct personal identifiers such as OHIP numbers will reside on a dedicated and secure server at ICES and will only be accessible by a named Data Covenantor. The Covenantor will encode the OHIP number, replacing it with an ICES key number (IKN) (a code) and transferring it to a "moated" server for the study project. (The Data Covenantor is an ICES person named in our data sharing agreements and identified to the Office of the Information and Privacy Commissioner, who can access personal health information at ICES for the purposes of receiving, coding, transferring or destroying personal health information.) The coded study data will only be made available to the Principal Investigator and project staff directly responsible for data analysis (under the supervision of the investigator). No subject, physician or institution will be identified in the reporting of results

14.5.12.3 Cost calculation

Once the utilization of health services is determined from those cases linked to administrative databases, publicly available costs (2016$CAN) will be applied to health services. Costs for physician and laboratory services will be determined by applying that year's fee code. Costs for hospital care will be estimated using the Canadian Institute for Health Information (CIHI) Resource Intensity Weight method for the most recently available year. Outpatient

prescription drug costs for participants not covered by ODB (those under age 65 and not on social assistance) will be considered to be the same as the trial arm-specific average for those with coverage. Costs will then be inflated using the healthcare-specific Consumer Price Index reported by Statistics Canada into constant Canadian dollars for the year the study ends. Due to the short time horizon, discounting will not be applied.

14.5.12.4 Primary Analysis

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

Should the clinical trial find a difference between the two arms on the primary endpoint, an incremental cost-benefit analysis will be calculated by deriving the additional cost per case of clinically significant cancer diagnosed, according to the following equation:

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

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

14.5.12.5 Secondary Cost Analyses

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

14.5.13 Missing Data

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

15. Participant compliance and withdrawal

The study will be completed when at least422subjects have been randomized, have undergone a diagnostic test and completed follow up. Compliance to randomized treatment will be assessed by monitoring the completed forms, e.g. the systematic TRUS guided biopsy form or the MRI-targeted biopsy form.

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

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

15.1 Subject Withdrawal from Study

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

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

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

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

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

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

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

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

15.2 Study completion

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

16. Data Monitoring, Quality Control and Safety

16.1 Stopping / discontinuation rules

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

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

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

16.2 Monitoring, quality control and assurance

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

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

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

16.3 Assessment of safety

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

16.3.1 Definition of an Adverse Event (AE)

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

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

16.3.2 Definition of a Serious Adverse Event (SAE)

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

(a) results in death

(b) is life-threatening

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

(c) requires hospitalisation or prolongation of existing hospitalisation

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

(d) results in disability / incapacity

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

(e) is a congenital abnormality/birth defect.

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

16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

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

16.3.4 Lack of Efficacy

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

16.3.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

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

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

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

16.3.6 Recording/Reporting AEs and SAEs

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

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

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

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

Expected AEs includes the following:

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

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

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

The Trial Coordinator, Principle Investigator or Chief Investigator should be informed of any SAE within 24 hours.
All SAE report forms must be completed and the SAE logs updated. All SAEs must be followed up until a resolution is reached (i.e. recovered, recovering, recovered with sequelae, fatal, not recovered or unknown).

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

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

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

16.3.7 Evaluating AEs and SAEs

16.3.7.1 Assessment of Intensity

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

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

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

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

16.3.7.2 Assessment of Causality

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

16.3.8 Follow-up of AEs and SAEs

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

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

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

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

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

16.3.9 Prompt Reporting of SAEs

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

16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI

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

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

Dr. Laurence Klotz
c/o Marlene Kebabdjian
Sunnybrook Health Sciences Centre
2075 Bayview Avenue A304
Toronto, Ontario M4N 3M5 Canada
Phone: (416) 480-6100 ext 2890
E-mail:Laurence.Klotz@sunnybrook.ca
Marlene.kebabdjian@sunnybrook.ca

16.3.9.2 Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to the PI within 24 hours. The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the PI within the designated time frames. If the investigator does not have all information regarding as SAE, he/she will not wait to receive additional information before notifying the PI of the event and completing the form. The form will be updated when additional information is received.

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

16.3.10 Post-study AEs and SAEs

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

17. Study Administration

17.1 Regulatory and Ethical Considerations

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

17.1.1 Ethical Conduct of the Study and Ethics Approval

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

Participating sites from Ontario will use the Ontario Cancer Research Ethics Board (OCREB) as their Board of Record.
This study will be conducted in accordance with 'good clinical practice' (GCP) and all applicable regulatory requirements, including where applicable, the 2013 version of the Declaration of Helsinki.

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

If the protocol, the informed consent form or any other information that the REB has approved for presentation to potential subjects is amended during the study, the site investigator(s) is responsible for ensuring the REB reviews and approves, where applicable, these amended documents. The site investigator(s) must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining the REB approval of the amended form before new subjects consent to take part in the study suing this version of the form. Copies of the REB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the PI promptly.

17.1.2 Informed Consent

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

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

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

17.1.3 Investigator Reporting Requirements

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

17.2 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

17.3 Quality Assurance

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

time and the time of his/her staff to the auditory/inspector to discuss findings and any relevant issues.

17.4 Study and Site Closure

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

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

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

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

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

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

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

17.5 Records Retention

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

The site investigator(s) will retain study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study as dictated by any institutional

requirements or local laws or regulations of Health Canada standards/procedures; otherwise, the retention period will default to 25 years.

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

17.6 Data Management

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

17.7 Publication

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

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

5. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
6. Drafting the work or revising it critically for important intellectual content; AND
7. Final approval of the version to be published; AND
8. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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

Trial funding agencies (OICR, PCC and collaborators as appropriate) will be acknowledged in all publications.

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

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Appendices

Appendix 1: Time windows for data collection

For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3
For details on time windows permitted for each trial intervention to be completed please see Table 5 below.

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

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

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 30-day 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. To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy. To be returned by post or at follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60

Telephone reminder	days post-biopsy, it will be acceptable. Ideally the questionnaire should be completed as close as possible to 30 days post-biopsy. 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
Visit 4 Follow up for results And treatment Decision	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. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.
Visit 5 **26 week follow up**	• DRE • PSA • Optional blood, urine
Visit6 1 year follow up 52 week follow up visit	The following information will be obtained on an annual basis: • 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)
Visit 7 **78 week follow up**	• DRE • PSA • Optional blood, urine

Visit 8 104 week follow up visit	The following information will be obtained on an annual basis: • 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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5499

Appendix 2: MPMRI Reporting Proforma

Date of MRI scan: | | | | | | | | | |
day month year

Date of Report: | | | | | | | | | |
day month year

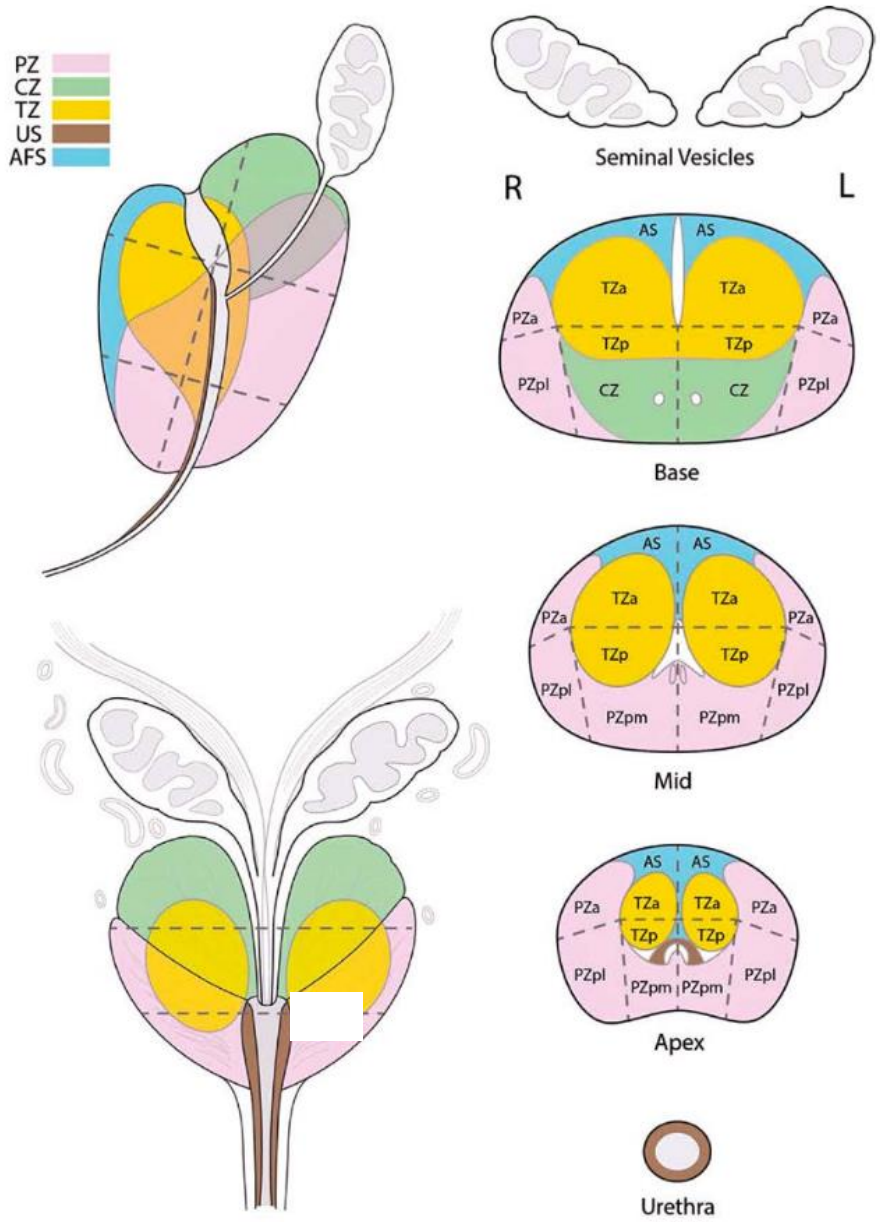
Reporting Radiologist:

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.

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…)



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**

If image quality is not good please comment:

_____

_____

_____

How to record locations

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

Number of candidate tumor sites:_____

Target 1 (Highest Pi-Rads score and then largest):

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:_____ mm^2/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): _____

Target 2:

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:_____ mm^2/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): _____

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:_____ mm^2/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:

_____

_____

_____

_____

_____ cm	(SI) x	_____ cm	(AP) x	_____ cm	(LR)	**Volume:**	_____	cc

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: _____

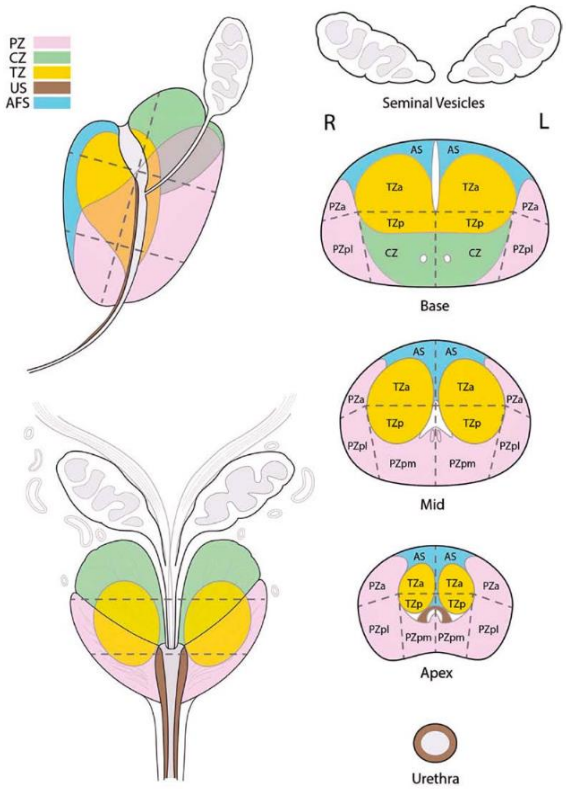
There was a change in lesions number or rank when adding DCE sequence **(Y/N):_____**

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___

If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2…)



Target 1:

Present (Y/N):_____

Change from Part 1 (Y/N):_____,

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:_____ mm^2/s $x10^{-6}$

Size: ___x___ x ___mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____,_____,_____,_____

_____,_____,_____,_____

Extraprostatic extension (Y/N/E-equivocal): _____

Target 2:

Present (Y/N):_____

Change from Part 1 (Y/N):_____

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:_____ mm^2/s $x10^{-6}$
Size: ___x___ x ___mm (Ax1 > Ax2 x SI)
Location(s) (largest to smallest area involved):
_____,_____,_____,_____
_____,_____,_____,_____
Extraprostatic extension (Y/N/E-equivocal): _____

Target 3:
Present (Y/N):____
Change from Part 1 (Y/N):____
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:_____ mm^2/s $x10^{-6}$
Size: ___x___ x ___mm (Ax1 > Ax2 x SI)
Location(s) (largest to smallest area involved):
_____,_____,_____,_____
_____,_____,_____,_____
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:
_____
_____
_____
_____

Safety:
Was there an immediate reaction to Gd contrast injection (Y/N):____

If yes, please give details:

_____

_____

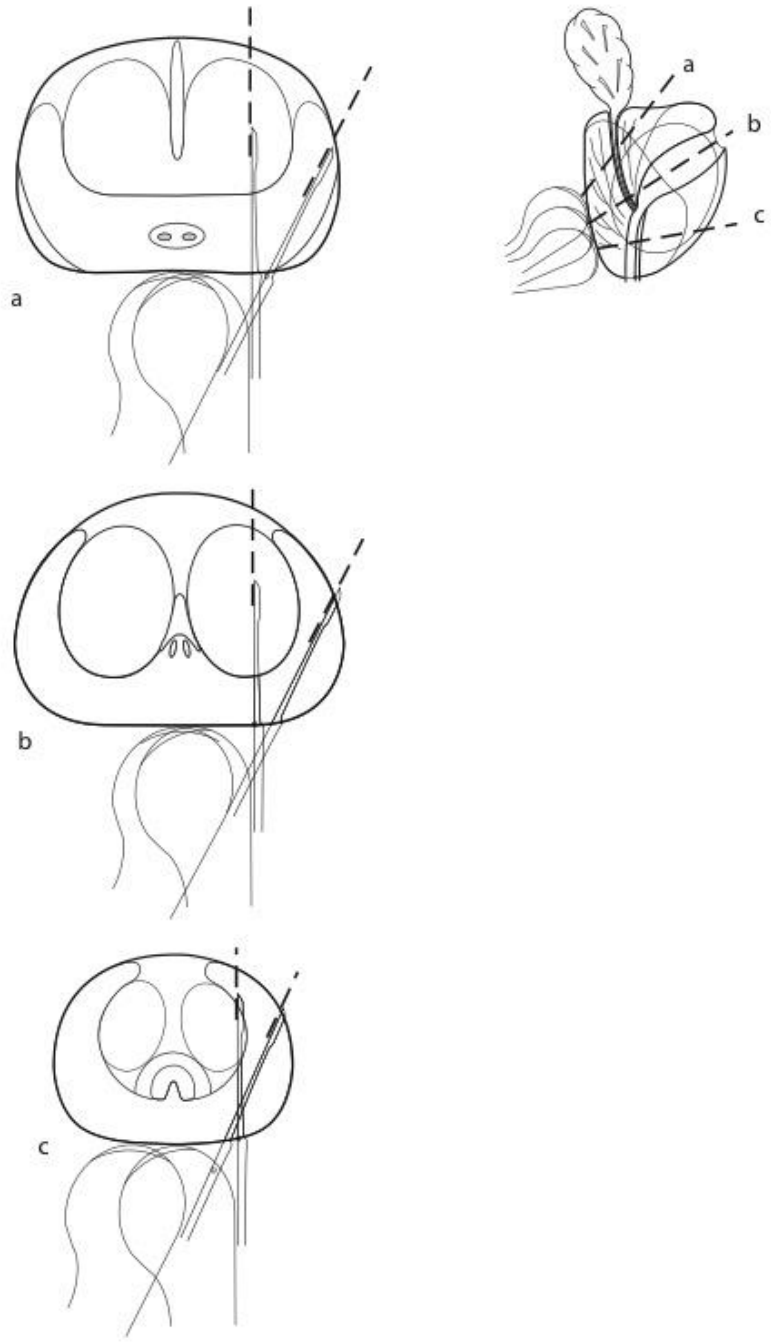
Will subject require an TRUS/MRI-fused biopsy (Pi-Rads >=3)? ❑**No** ❑**Yes**

Please send this form and a DVD with the images AND completed MRI Report to:

Marlene Kebabdjian
Sunnybrook Health Sciences Center
Urology Research, A304
2075 Bayview Avenue
Toronto, Ontario M4N 3M5

Appendix 3: Example of systematic TRUS guided biopsyschema

Figure depicting 12-core systematic TRUS guided biopsyschema that sites are recommended to follow. Axial/coronal sections of a prostate gland (left) showing biopsy courses of the 12 biopsies performed under ultrasound guidance with an end fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c, apex.F romHaffner*et al*[37].



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

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

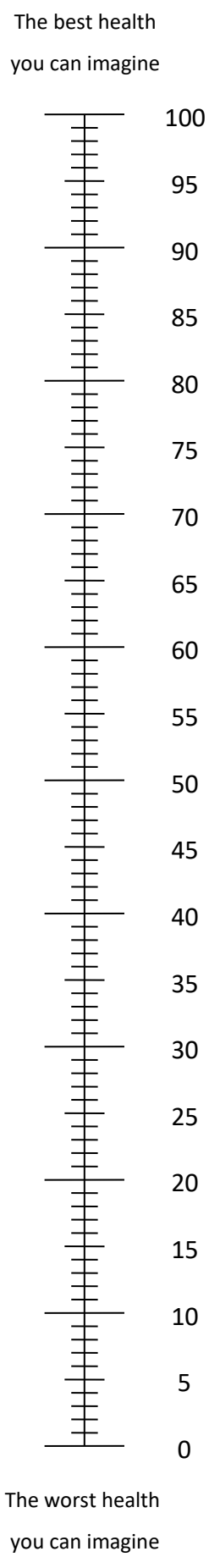
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐



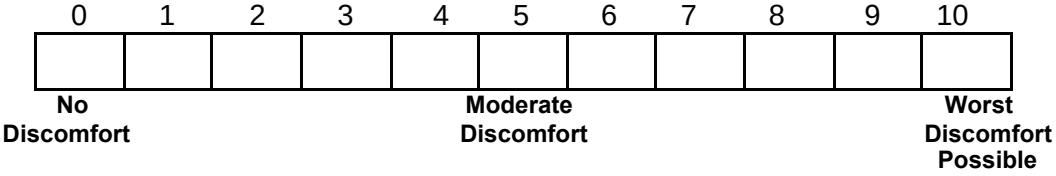
Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

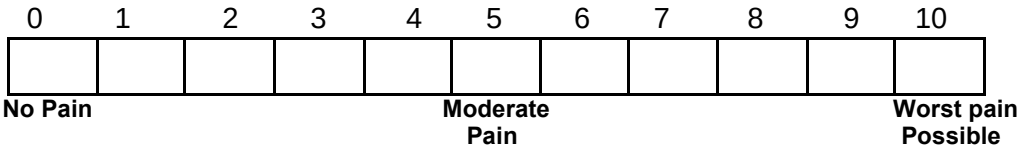
Please ask the patient to fill this out after the biopsy, before they leave the department.

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?



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



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.

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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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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
	☐ 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 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 ☐ 1 No ☐ 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
	☐ 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 biopsy procedure:

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

Yes ☐ 1 No ☐ 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
	☐ 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

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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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
☐	☐	☐	☐

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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
e.g. ciprofloxacin	*500mg*	*2*	*3*

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"):*

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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"):*

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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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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.

PRECISE Trial: Amendment 2

Summary of Changes

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'

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**: **Pr**ostate **E**valuation for **C**linically **I**mportant disease: MRI vs **S**tandard **E**valuation procedures. (PRECISE)

Date: 13 March 2017

Version 3.0

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Confidential

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: 13 March 2017
Version 3.0

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

Signature: _____

Name: _____

Title: _____

Date: _____

Site name: _____

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6040 ## 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	**Primary Objective** 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. **Secondary Objectives** 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. 28. Proportion of men in each arm with clinically insignificant cancer detected. 29. Proportion of men in each arm with Gleason ≥4+3 detected. 30. Proportion of men in MRI arm who avoid biopsy. 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. 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). 33. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason ≥7 cancer by2 years. 34. Proportion of men with post-biopsy adverse events 35. Health-related quality of life scores. 36. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy. 37. To determine the cost per diagnosis of cancer. 38. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield 39. 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)

	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, all inclusion criteria must be met. 11. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy; 12. ≥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. 13. Serum PSA ≤ 20ng/ml; 14. Fit to undergo all procedures listed in protocol; 15. Able to provide written informed consent.
Exclusion Criteria	Men who meet the following criteria at the time of screening will be excluded: 13. Prior prostate biopsy; 14. Prior treatment for prostate cancer; 15. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min); 16. Contraindication to prostate biopsy; 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; 18. 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. All subjects 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.

	All subjects in ARM A will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI. Subjects in ARM A who do not receive a subsequent biopsy will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (± I 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. Subjects in ARM A who do receive a MRI-targeted biopsy 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 (± I 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. All subjects in ARM B 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 (± I 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.
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 ≥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

Abbreviations:

ADC	Apparent diffusion coefficient
CI	Confidence interval
CRF	Case report form
DSMC	Data Safety and Monitoring Committee
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
EDC	Electronic Data Capture
ITT	Intention to treat
MCCL	Maximum cancer core length
MPMRI	Multi-parametric MRI, used interchangeably with MRI in this protocol.
MPMRI-TB	Multi-parametric magnetic resonance image-targeted biopsy of the prostate
MRI	Magnetic resonance imaging, used interchangeably with MPMRI in this protocol
MRI-TB	Magnetic resonance imaging targeted biopsy
MRS	Magnetic resonance spectroscopy
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PTC	Permission to Contact
PSA	Prostate specific antigen
REB	Research Ethics Board
STARD	Standards for the reporting of diagnostic studies
TRUS	Trans-rectal ultrasound
TSC	Trial Steering Committee
T2W	T2-weighted imaging

Definitions:

MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is used to determine the location of a suspicious target prior to biopsy.
Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure is not influenced by findings on MRI imaging. Currently this is the standard of care for prostate cancer in the province of Ontario.

5. Trial summary

5.1 Aim and Rationale

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

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

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

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

The potential implications of this trial include:

- 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

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 (+ I 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 for30-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 prostectomy) 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

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

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

5.3 Participating Sites

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

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

5.4 Study outcomes

5.4.1 Primary outcome

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

5.4.2 Secondary outcomes

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.
28. Proportion of men in each arm with clinically insignificant cancer detected.
29. Proportion of men in each arm with Gleason $\geq$4+3 detected.
30. Proportion of men in MRI arm who avoid biopsy.
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.
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).
33. Proportion of men with a negative MRI who develop a positive MRI and/ or Gleason **≥** 7 cancer by 2 years.
34. Proportion of men with post-biopsy adverse events
35. Health-related quality of life scores.
36. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
37. To determine the cost per diagnosis of cancer.

38. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield
39. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone

6. Background

6.1 Prostate cancer diagnosis

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

6.2 Clinically significant versus clinically insignificant prostate cancer

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

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

6.3 Current standard of care: systematic TRUS guided biopsy

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

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

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

6.4.1 The role of imaging in prostate cancer diagnosis

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

6.4.2 Limitations of early MRI studies in prostate cancer

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

- **Poor reporting standards**. Many early studies failed to closely follow published guidelines for the standards of reporting of diagnostic studies (STARD) [23].
- **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.

6.4.3 Emerging role of MRI in the diagnosis of prostate cancer

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

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

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

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

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

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

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

6.4.3.1 MRI can influence the decision to perform a prostate biopsy

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

6.4.3.2 MRI can influence the biopsy technique

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

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

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

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

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

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

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

6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy

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

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

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

6.5 Novelty of PRECISE

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

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

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

7. Trial objectives

7.1 Overall aim

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

7.2 Hypotheses

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

7.3 Primary Objective

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

7.4 Secondary Objectives

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 ≥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 with a negative MRI who develop a positive MRI and/ or Gleason ≥ 7 cancer 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 alone

7.5 Explanation for non-inferiority hypothesis

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

7.6 Anticipated timeline of study progression

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

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

8.Study Population

8.1 Number of Subjects

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

8.2 Subject inclusion criteria

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

13. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;
14. ≥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.
15. Serum PSA ≤ 20ng/ml within 3 months of randomization
16. Fit to undergo all procedures listed in protocol;
17. Able to provide written informed consent.

8.3 Subject exclusion criteria

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

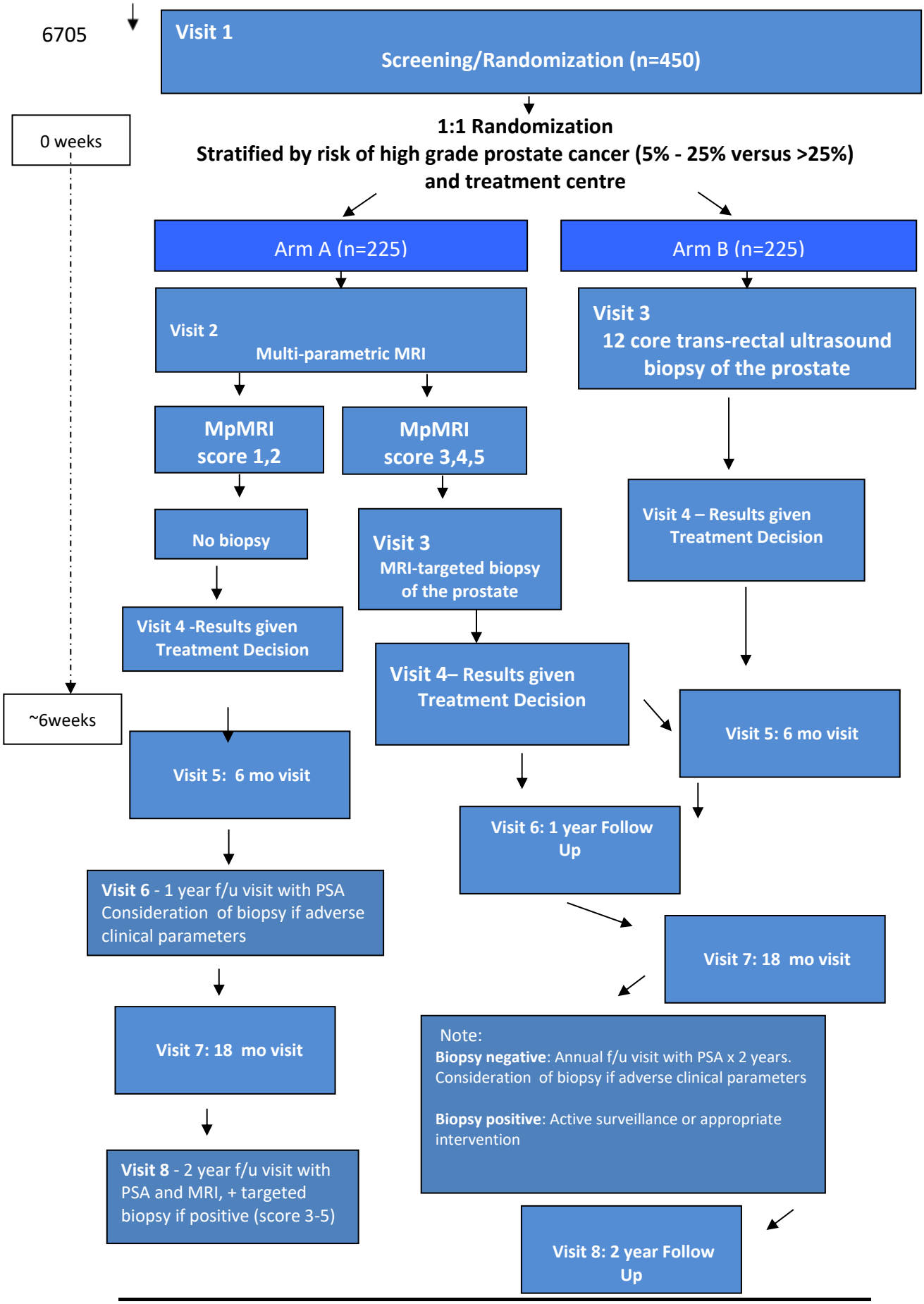
13. Prior prostate biopsy
14. Prior treatment for prostate cancer
15. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min)
16. Contraindication to prostate biopsy
17. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work
18. Unfit to undergo any procedures listed in protocol.

9. Study design

9.1 Study design

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

9.2 Study Trial Schema



9.3 Timeline of subject contact

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

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

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4]PSA will have been done prior to visit 1 as part of screening.

[5] If MRI indicates a target, biopsy must be done

[6]After treatment decision men revert to standard of care.

6723 **Table 2: ARM A: Men randomized to MRI arm who have a lesion on MRI and require a**
6724 **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							

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4] tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[5]PSA will have been done prior to visit 1 as part of screening.

[6]See 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.

[7]After treatment decision men revert to standard of care.

6776
6777
6778 **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 follow 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				

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[2]Urine 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.
[3]Collected at baseline, and annually.
[4]PSA will have been done prior to visit 1 as part of screening.
[5] See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue must be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[6]After treatment decision men revert to standard of care.

10. Trial Interventions and procedures

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

10.1 EQ-5D-5L Questionnaires

For all subjects enrolled in trial

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

- All subjects should complete the baseline questionnaire at the screening visit before leaving the department.
- Subjects who have a normal MRI and do not require a biopsy will complete an EQ-5D-5L questionnaire at Visit 4.
- Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date that the subject should fill out the questionnaires should be written on top of the questionnaire. (This can also be done at Visit 4).
- All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up visit.

10.2 Multiparametric MRI imaging procedure

For subjects in Arm A only

10.2.1 MRI Protocol

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

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

Within the specified PiRads-2 framework a common protocol will be formulated by a consensus of the radiologists involved in the trial at each site at a startup meeting. The highest agreed upon b-value image for DWI (at least 1400s/mm2) will be selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast media, injection rates and dynamic scanning temporal resolution will be matched for all sites. An optional multi b value DWI acquisition will be undertaken as well to allow for ancillary studies into non log linear apparent diffusion coefficient (ADC) models for tumor characterization. This is summarized in an MRI Operations Manual

Subjects will be asked to follow their local standard of care MRI examination preparation instructions for the MRI procedure.

10.2.2 MRI reporting

The MRI will be reported by an experienced radiologist using the MRI Reporting Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5 pointLikert score for purposes of comparison. Biopsy decisions will be based on the PiRads scores.

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

- 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)

The location of the suspicious areas in the prostate should be marked on a diagram of the prostate (see Appendix2) and the sector numbers containing each suspicious area should be recorded in the case report form.

Radiologists will be blinded to the PSA.

Imaging interpretation will be carried out at each site, however ensuring consistency and quality of imaging interpretation is crucial. A central imaging site will be designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site will perform the interpretation of all images for that site. The designated radiologist must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A startup meeting involving all radiologists will be held prior to start of accrual where each site will bring 5 MRI cases performed at their site for consensus review, scoring

and discussion. This will provide a commonality of approach to interpretation among the radiologists before the study begins. After this startup meeting each site will send one set of MRI images and its interpretation for central review for site qualification.

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

10.3 No target identified on MPMRI (PiRads 1 or 2)

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

Men who have MRIs that do not identify any suspicious lesion will not receive a biopsy. These subjects will benefit from being part of the trial as a result of not having to undergo an invasive biopsy procedure, avoiding the discomfort associated with the procedure, the risk of being diagnosed with clinically insignificant cancer and the risk of sepsis associated with the biopsy procedure. Studies suggest that if the MRI does not identify areas suspicious for cancer there is an85-95% chance that clinically significant cancer is not present[28, 34, 35].

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

10.4 MRI-Targeted biopsy

For subjects in Arm A who do require a biopsy

10.4.1 MRI choice of targets for targeted biopsy

Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in MRI-targeted biopsy. Operator experience (number of targeted biopsies performed to date) will be recorded before each procedure. The number of biopsy operators should be kept to the minimum number possible.

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

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

10.4.2 MRI Biopsy

The procedure will be performed in the outpatient departments of sites possessing the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI

fusion system at their institution before they are qualified to participate as an operator in the study.

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

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

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

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

Biopsy cores from different suspicious areas will be aliquoted separately. The vials will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there are) which should match the assignment of suspicious areas by the radiologist on the MRI report. The order of lettering a-d should match the order in which the biopsies were performed in each region. The first biopsy should be at the center of the target and the remaining fanning out from the center. Each core from the same suspicious area must be submitted separately. Alternative methods of storing cores that allow identification of the order of score samples from each target are acceptable.

10.5 Systematic TRUS guided biopsy

For all subjects in Arm B

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

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

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy

and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

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

10.6 Pathology

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

For men undergoing MRI-targeted biopsy it is required that pathology reported per suspicious area targeted and per targeted core. For systematic TRUS guided biopsy, each core will be reported and graded.

10.7 Post-procedural care

For all subjects in ARMS A and B receiving a biopsy

After a biopsy procedure the subject can be discharged within 2-3 weeks for results of the histopathology and treatment options to be discussed.

10.8 Immediate post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

10.9 30-day post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

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

Subjects should be reminded at 30 days to complete this questionnaire.

10.10 Results and treatment decision (Visit 4)

The results of the biopsies and/or MRI will be explained to the subject by the clinical care team during this visit, which is approximately 2-3 weeks after the biopsy. The research team should record the treatment decision in the subject file. Possibilities for treatment decision include but are not limited to:

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

10.11 Follow up period

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

- time to cancer diagnosis
- Gleason score progression
- time to intervention on active surveillance
- time on active surveillance
- PSA

10.11.1 Indications for biopsies off protocol

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

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

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

1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.

2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase in PSA in 1 year.

3. Biopsy if a doubling of the risk of high grade cancer according to the NCI nomogram.

4. Biopsy if development of a suspicious nodule on DRE.

5. For men with a positive study MRI (especially PI-rads 4 or 5) and a targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.

18. For men on the systematic biopsy arm which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these subjects.

These are guidelines and should be interpreted with clinical judgment.

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

10.12 Additional tests for biomarker discovery - Optional

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

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

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

10.12.1 Samples to be collected for future biomarker discovery work (Optional)

Participants will be asked to consent to provide a blood, urine,semen, and tissue sample after the consent and screen visit and subsequent visits for storage and use in future biomarker studies. This will involve a separate consent form.

Samples include:

- Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- Urine – 75 mls urine
- Semen-1-5 cc (single ejaculate)
- Tissue-unstained biopsy sections -15 unstained slides from cancer, and
  -15 unstained slide from non-cancer cores
  (if possible)

10.13 Long-term data linkage – Permission to Contact

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

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

10.14 End of Study

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

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

10.15 Risks and Benefits to Participants

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

10.15.1 Risks to subjects

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

10.15.1.1 Risk of Systematic TRUS guided biopsy

Systematic TRUS guided biopsy can be associated with discomfort, haematuria, haematospermia and dysuria in a large proportion of subjects, which is self-resolving (See Table 4). There is a 4% risk of systemic urosepsis[46].

10.15.1.2 Risks of MPMRI

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.

10.15.1.3 Risks of MRI-targeted biopsy

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.

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
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%

10.15.2 Benefits to subjects

Subjects enrolled in this trial will benefit from the following:

- 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 will also ensure streamlined diagnostic investigations to promptly conduct the diagnostic test and communicate the test outcome for the subject.
- Subjects enrolled in the trial will benefit from the dedicated research team involved in their care in addition to the clinical team normally involved in their care.
- Subjects will benefit from additional discussions regarding the trial, which could increase their understanding of prostate cancer and help them to make a more informed decision about their health.
- Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will remove any risk of post-biopsy infection. MRI-randomized subjects may also benefit from a reduced probability of having a clinically insignificant prostate cancer diagnosed. Clinically insignificant prostate cancer is often treated definitively per subject preference despite the lack of evidence supporting the need. All definitive local therapies for prostate cancer carry the risk of peri-operative complications as well as long-term risk of incontinence and erectile dysfunction.

10.16 Concomitant medications

10.16.1 Permitted Medications

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

10.16.2 Non-Drug Therapies

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

11. Schedule of Study Visits

11.1 Visit 1 (Screening/Randomization): Screening, Consent, Randomization

For all subjects enrolled in trial

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

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

Randomization can happen immediately after the consent form is signed and eligibility is confirmed.

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

If a subject agrees to the optional informed consent, from randomization until any point prior to a biopsy, optional blood, urine,semenand tissue samples will be collected for correlative studies.

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

11.2 Visit 2 (MRI): ARM A, for men randomized to MRI

This will occur approximately within one week of randomization. Men will receive an MRI (see Section 10.2.)

11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate

For men randomized to ARM A, who have a lesion identified by MRI. This appointment will follow approximately one-two weeks 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 biopsy to occur in timely fashion. If the results of the MRI show 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.

Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after a biopsy, before the subject leaves the department.

Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and complete as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however, the questionnaire should be completed as close as possible to 30 days post-biopsy.

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

11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic TRUS-biopsy

For men randomized to ARM B only.

Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after the biopsy.
Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and completed as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-biopsy.

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

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

This appointment will include a follow up meeting with the investigator to discuss the results of the MRI as well as treatment decisions. This follow up should occur

after the availability of the MRI report. At this visit the subject will also complete a 30-day post intervention EQ-5D-5L Questionnaire.

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

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

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

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

The research team should record the treatment decision in the subject file.

Possibilities for treatment decision include but are not limited to:

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

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

11.7 Visit 5 (6 month follow up):26 week follow up

All subjects will have a 26 week visit

Subjects will have the following:

- Vitals, DRE
- PSA
- Optional sample collection (blood, urine)

11.8 Visit 6(1 year follow up): 52 week follow up

All subjects are planned to have a 52 week follow up visit.
Subjects will be followed to obtain the following information 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.
- 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, targeted only or both systematic + targets, not done because of negative MRI
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6 (year 2).

11.9 Visit 7 (18 month follow up): 78 week follow up

All subjects will have a 78 week visit
Subjects will have the following:

- Vitals, DRE
- PSA
- Optional sample collection (blood, urine)

11.10 Visit 8 (2 year follow up): End of study

All study participants will be followed for up to two years or until they undergo radical treatment
Subjects will be followed to obtain the following information 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)

- 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

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 8.

12. Randomization

12.1 Randomization Procedure

Written informed consent will be obtained from all eligible subjects prior to commencing any study related procedures. The Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre, Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate subject randomization. Subjects will be allocated to the two treatment arms in an approximate 1:1 ratio by use of a dynamic allocation scheme[47].

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

12.2 Stratification

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

12.3 Blinding and measures taken to avoid bias

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

Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be aware that the subject is part of the trial.
Pathologists will be blinded to the cohort allocation. Concealment may be challenging due to the different number of cores in the two groups, but this is unavoidable. This is unlikely to represent a significant source of bias.

13. Data

Type of data to be collected:

- EQ-5D–5L questionnaires. These will measure quality of life and will be measured at specific times throughout the trial.
- Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and continuous data
- MRI – diagram representing MRI; categorical data for areas and scores of suspicion (e.g. Sector 1p, score of suspicion 4/5)
- MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and continuous data
- Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers yes/no)
- Treatment decisions – categorical data (e.g. radical treatment)
- PSA – continuous data (e.g. value of PSA in ng/ml)

Please see **Appendix1** for the time window for data collection.

14. Statistical Considerations

14.1 Sample Size Calculation

STATISTICAL methods

Primary Analysis

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

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

Secondary Analyses

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

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

Treatment Allocation and Stratification

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

Stratification

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

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

(2) clinical centre.

Sample Size

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

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

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

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

To account 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.

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

Statistical Conventions

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

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

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

Missing Data

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

Missing data for secondary endpoints will be described. The methods for evaluating missing data of the primary endpoint may be employed for endpoints of interest. For summarization of baseline data, the following conventions will be used for partial missing date information occurring prior to randomization (e.g. for medical history or prior treatment). If year is missing, the date will be set at missing. If year is

available, but month and date is missing, the month and date will be set to July 1st of the respective year. If date is missing, but year and month available, the day will be set to the 15th of the respective month.

14.2 Interim Analyses

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. Unless otherwise specified by one of these bodies, a futility analysis will be performed after approximately 200 subjects are enrolled and have their primary outcome ascertained. Simulation will be used to estimate the conditional probability of futility assuming the study was to continue to completion, and assuming the clinically significant cancer detection rate is 30% in both arms. If the conditional probability is 0.95 or higher that continuation of the study will result in a negative result, the DSMC will recommend a suspension of recruitment to the trial, and initiation of a quality assurance review. A decision to permanently close the study or continue with accrual will be determined by the Steering Committee, based on the results of the quality assurance review, and the recommendation of the DSMC.

Timing of Final Analysis

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

14.3 Populations:

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

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

14.4 Primary Outcome

14.4.1 Detection rate of clinically significant cancer

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 intention to treat population.

Absolute differences in proportion of clinically significant cancer detected between arms will be calculated and compared. If the lower boundary of the 97.5% confidence interval for the difference in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-

inferior. In the event that the lower bound is greater than zero, superiority can be claimed.

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

14.5 Secondary Outcomes

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

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

The proportion of men in each arm with clinically insignificant cancer (Gleason <7) will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.2 Proportion of men in each arm with Gleason ≥4+3 detected

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

14.5.3 Proportion of men in MPMRI arm who avoid biopsy.

14.5.4 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.

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

14.5.5 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)

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 haemotospermia.

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

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

14.5.12.1 Data collection:

As part of the informed consent process, participants in Ontario will also consent to having their Ontario Health Insurance Number recorded, to be later transferred to the Institute for Clinical Evaluative Sciences (ICES) where

it will be linked to a number of administrative claims databases recording health system resource utilization such as physician billing [Ontario Health Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity Level Reporting (ALR)];clinic and emergency department visits [National Ambulatory Care Reporting System (NACRS),Emergency Department visits); radiation (ALR); homecare (Home Care databases) and a few additional ones as determined necessary (e.g., Long-term care, Mental Health, Diabetes.The overall, number and proportion of health system resources will be determined.In this way we can capture comprehensive resource utilization related to on-trial management including any adverse events.

14.5.12.2 Health Insurance number handling and security

As the economic implications of this study are of prime importance to some of the funders, the request for data linkage will be part of the main consent form. If a participant indicates to the study team that they decline or withdraw consent, the OHIP number will be recorded as 9999-999-999-XX. The OHIP numbers will stay with the participating institution until after accrual is complete, and then they will all be transferred at one time under data sharing agreements between ICES and each institution. Data will be transferred using a secure electronic file transfer system established by ICES and managed by authorized ICES personnel responsible for receiving data. The file transfer system uses security safeguards including encryption and authentication.

ICES is a Prescribed Entity under the Personal Health Information Protection Act (PHIPA), and can receive and use personal health information for purposes of analysis and compiling statistical information and other research. Its policies and procedures for privacy protection and data security have been approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-monitored and requiring passkeys to access private offices and computers. ICES has extensive experience in the protection of confidentiality when using such data. It has a UNIX-based network that cannot be accessed externally. ICES data facilities are fully 'moated' (no connections to other computers). At ICES, routine procedures for data backup are instituted by a data management team. The data is burned onto a CD or placed on an external hard drive and placed in a locked vault. All ICES staff and scientific affiliates are required to sign agreements of confidentiality annually. Internal audits are conducted to monitor compliance with ICES policies, standards and procedures.

> Study data with direct personal identifiers such as OHIP numbers will reside on a dedicated and secure server at ICES and will only be accessible by a named Data Covenantor. The Covenantor will encode the OHIP number, replacing it with an ICES key number (IKN) (a code) and transferring it to a "moated" server for the study project. (The Data Covenantor is an ICES person named in our data sharing

agreements and identified to the Office of the Information and Privacy Commissioner, who can access personal health information at ICES for the purposes of receiving, coding, transferring or destroying personal health information.) The coded study data will only be made available to the Principal Investigator and project staff directly responsible for data analysis (under the supervision of the investigator). No subject, physician or institution will be identified in the reporting of results

14.5.12.3 Cost calculation

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

14.5.12.4 Primary Analysis

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

Should the clinical trial find a difference between the two arms on the primary endpoint, an incremental cost-benefit analysis will be calculated by deriving the additional cost per case of clinically significant cancer diagnosed, according to the following equation:

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

The cost of avoiding each additional case of clinically insignificant cancer diagnosed may also be similarly calculated. Consideration will be given to

extending this analysis using economic modeling with incorporation of utility values from the EQ-5D to allow a lifetime perspective to be taken and the estimation of quality adjusted life years (QALYs).

14.5.12.5 Secondary Cost Analyses

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

14.5.13 Missing Data

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

15. Participant compliance and withdrawal

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

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

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

15.1 Subject Withdrawal from Study

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

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

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

- End of study assessments as outlined in **Section 10.17.**

- Any occurrence of death, prostatic surgical intervention, non-surgical treatment for prostate cancer after study withdrawal should be documented in the CRF and source documents.

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

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

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

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

15.2 Study completion

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

16. Data Monitoring, Quality Control and Safety

16.1 Stopping / discontinuation rules

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

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

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

16.2 Monitoring, quality control and assurance

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

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

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

16.3 Assessment of safety

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

16.3.1 Definition of an Adverse Event (AE)

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

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

16.3.2 Definition of a Serious Adverse Event (SAE)

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

(a) results in death

(b) is life-threatening

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

(c) requires hospitalisation or prolongation of existing hospitalisation

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

(d) results in disability / incapacity

The term disability means substantial disruption of a person’s ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may

interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital abnormality/birth defect.

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

16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

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

16.3.4 Lack of Efficacy

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

16.3.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

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

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

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

16.3.6 Recording/Reporting AEs and SAEs

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

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

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

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

Expected AEs includes the following:

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

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

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

The Trial Coordinator, Principle Investigator or Chief Investigator should be informed of any SAE within 24 hours.
All SAE report forms must be completed and the SAE logs updated. All SAEs must be followed up until a resolution is reached (i.e. recovered, recovering, recovered with sequelae, fatal, not recovered or unknown).

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

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

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

16.3.7 Evaluating AEs and SAEs

16.3.7.1 Assessment of Intensity

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

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

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

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

16.3.7.2 Assessment of Causality

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

16.3.8 Follow-up of AEs and SAEs

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

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

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

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

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

16.3.9 Prompt Reporting of SAEs

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

16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI

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

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

Dr. Laurence Klotz
c/o Marlene Kebabdjian
Sunnybrook Health Sciences Centre
2075 Bayview Avenue A304
Toronto, Ontario M4N 3M5 Canada
Phone: (416) 480-6100 ext 2890
E-mail:Laurence.Klotz@sunnybrook.ca
Marlene.kebabdjian@sunnybrook.ca

16.3.9.2 Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to the PI within 24 hours. The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the PI within the designated time frames. If the investigator does not have all information regarding as SAE, he/she will not wait to receive additional information before notifying the PI of the event and completing the form. The form will be updated when additional information is received.

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

16.3.10 Post-study AEs and SAEs

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

17. Study Administration

17.1 Regulatory and Ethical Considerations

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

17.1.1 Ethical Conduct of the Study and Ethics Approval

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

Participating sites from Ontario will use the Ontario Cancer Research Ethics Board (OCREB) as their Board of Record.
This study will be conducted in accordance with 'good clinical practice' (GCP) and all applicable regulatory requirements, including where applicable, the 2013 version of the Declaration of Helsinki.

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

If the protocol, the informed consent form or any other information that the REB has approved for presentation to potential subjects is amended during the study, the site investigator(s) is responsible for ensuring the REB reviews and approves, where applicable, these amended documents. The site investigator(s) must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining the REB approval of the amended form before new subjects consent to take part in the study suing this version of the form. Copies of the REB approval of the amended informed consent form/other information and the

approved amended informed consent form/other information must be forwarded to the PI promptly.

17.1.2 Informed Consent

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

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

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

17.1.3 Investigator Reporting Requirements

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

17.2 Study Monitoring

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

During these contacts, the monitor will:

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

This will be done in order to verify that the:

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

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

17.3 Quality Assurance

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

17.4 Study and Site Closure

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

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

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

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

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

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

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

17.5 Records Retention

Following closure of the study, the site investigator(s) must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed and whenever feasible, to allow any subsequent

review of data in conjunction with assessment of the facility, supporting systems and staff.

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

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

17.6 Data Management

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

17.7 Publication

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

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

9. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
10. Drafting the work or revising it critically for important intellectual content; AND
11. Final approval of the version to be published; AND
12. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people.The clinical trials.gov

registration number that will be allocated to this trial will be attached to any publications resulting from this trial.

Trial funding agencies (OICR, PCC and collaborators as appropriate) will be acknowledged in all publications.

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

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Appendices

Appendix 1: Time windows for data collection

For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3
For details on time windows permitted for each trial intervention to be completed please see Table 5 below.

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

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.

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 30-day 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. To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy. To be returned by post or at follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. 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.
Telephone reminder	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
Visit 4 Follow up for results And treatment Decision EQ-5D-5L Questionnaire	 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. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision. To be completed
Visit 5 **26 week follow up**	• Vitals, DRE • PSA • Optional blood, urine
Visit 6 1 year follow up 52 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. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
Visit 7 **78 week follow up**	• 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

Date of MRI scan: | | | | | | | | | |
day month year

Date of Report: | | | | | | | | | |
day month year

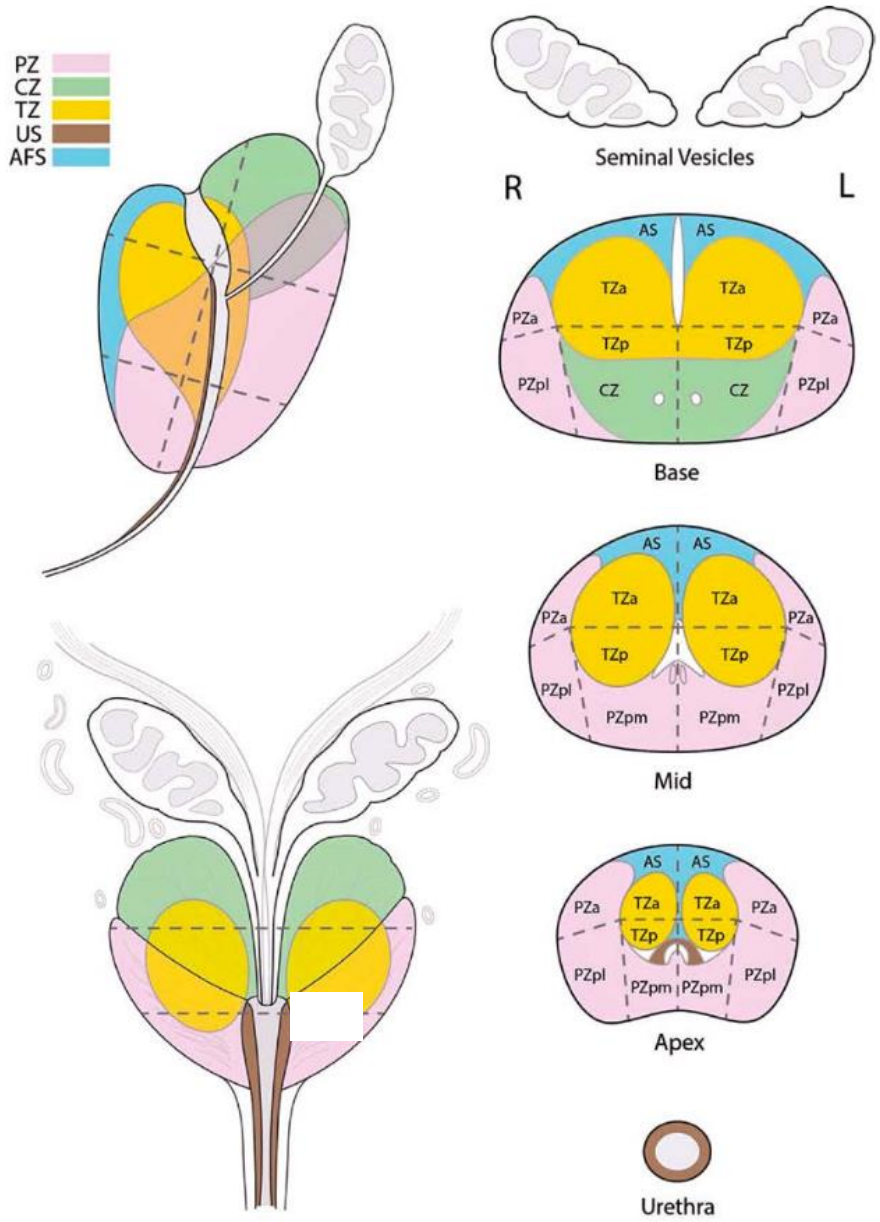
Reporting Radiologist:

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.

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…)



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**

If image quality is not good please comment:

_____

_____

_____

How to record locations

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

Number of candidate tumor sites:_____

Target 1 (Highest Pi-Rads score and then largest):

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:_____ mm^2/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): _____

Target 2:

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:_____ mm^2/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): _____

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:_____ mm^2/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:
_____
_____
_____
_____

_____ cm	(SI) x	_____ cm	(AP) x	_____ cm	(LR)	**Volume:**	_____	cc

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: _____

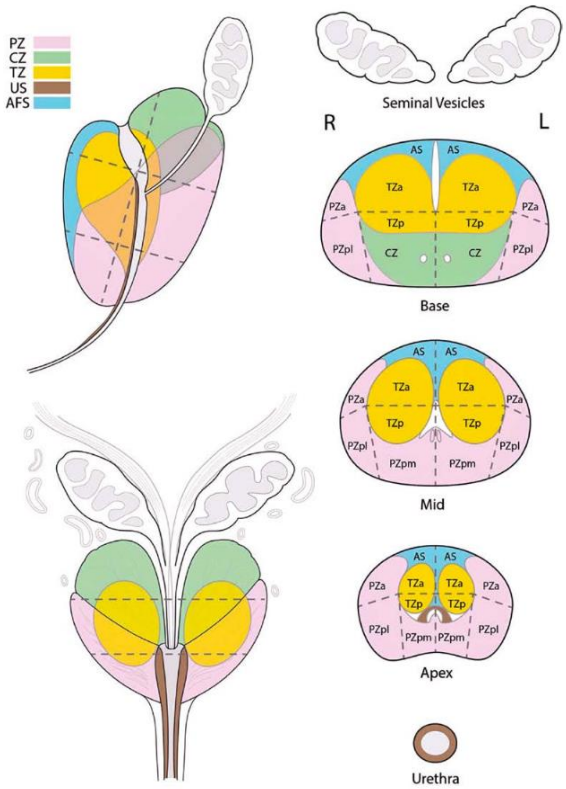
There was a change in lesions number or rank when adding DCE sequence **(Y/N):_____**

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___

If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2…)



Target 1:

Present (Y/N):_____

Change from Part 1 (Y/N):_____,

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:_____ mm^2/s $x10^{-6}$

Size: ___x___ x ___mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____,_____,_____,_____

_____,_____,_____,_____

Extraprostatic extension (Y/N/E-equivocal): _____

Target 2:

Present (Y/N):_____

Change from Part 1 (Y/N):_____

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:_____ mm^2/s $x10^{-6}$
Size: ___x___ x ___mm (Ax1 > Ax2 x SI)
Location(s) (largest to smallest area involved):
_____,_____,_____,_____
_____,_____,_____,_____
Extraprostatic extension (Y/N/E-equivocal): _____

Target 3:
Present (Y/N):_____
Change from Part 1 (Y/N):_____
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:_____ mm^2/s $x10^{-6}$
Size: ___x___ x ___mm (Ax1 > Ax2 x SI)
Location(s) (largest to smallest area involved):
_____,_____,_____,_____
_____,_____,_____,_____
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:
_____
_____
_____
_____

Safety:
Was there an immediate reaction to Gd contrast injection (Y/N):_____

If yes, please give details:

_____

_____

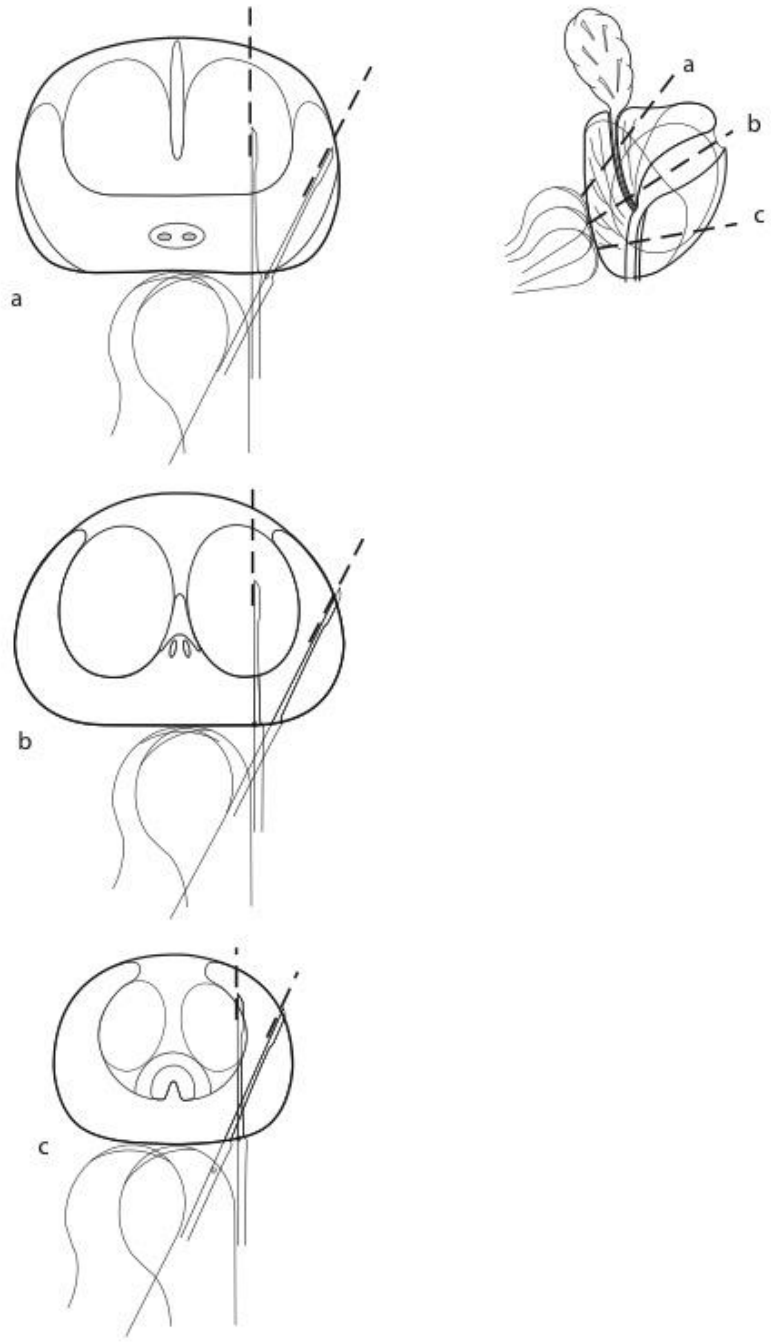
Will subject require an TRUS/MRI-fused biopsy (Pi-Rads >=3)? ❑No ❑Yes

Please send this form and a DVD with the images AND completed MRI Report to:

Marlene Kebabdjian
Sunnybrook Health Sciences Center
Urology Research, A304
2075 Bayview Avenue
Toronto, Ontario M4N 3M5

Appendix 3: Example of systematic TRUS guided biopsy schema

Figure depicting 12-core systematic TRUS guided biopsyschema that sites are recommended to follow. Axial/coronal sections of a prostate gland (left) showing biopsy courses of the 12 biopsies performed under ultrasound guidance with an end fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c, apex.F romHaffner*et al*[37].



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

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

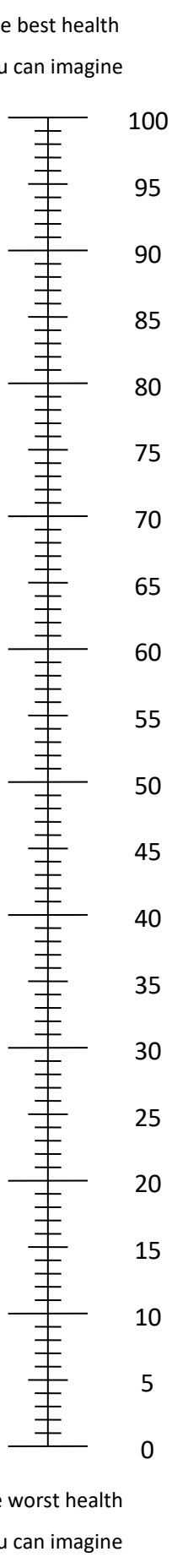
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐



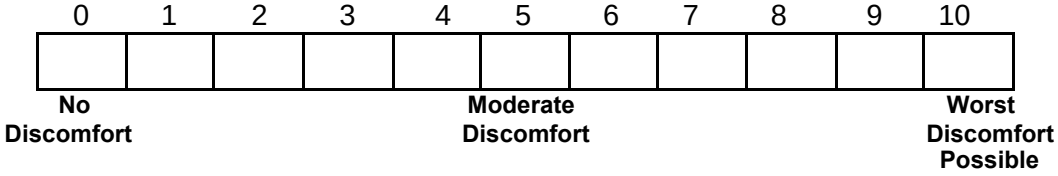
Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

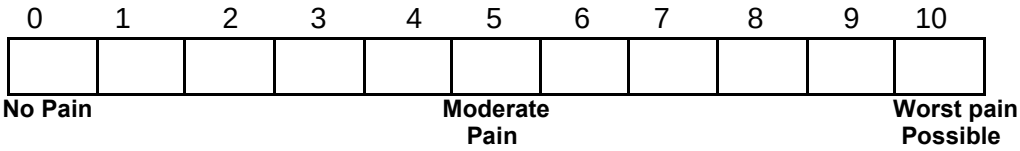
Please ask the patient to fill this out after the biopsy, before they leave the department.

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?



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



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.

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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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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
	☐ 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 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 ☐ 1 No ☐ 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
	☐ 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 biopsy procedure:

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

Yes ☐ 1 No ☐ 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
	☐ 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

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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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
☐	☐	☐	☐

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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
e.g. ciprofloxacin	*500mg*	*2*	*3*

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"):*

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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"):*

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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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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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June 30, 2017

PRECISE Trial: Amendment 3

Summary of Changes

The purpose of this Amendment is to provide comprehensive explanation regarding the correlative sample collection, it's custodianship and it's intended use.
The Amendment also identifies the collaborators involved in the PRECISE Trial.
In addition, minor administrative changes were made to the current protocol to avoid discrepancy. Minor errors were corrected.
The following changes were made:

- Version date to reflect Amendment 3: 30 June 2017
  - Study Objectives: Page 3, Secondary Objectives: #7 has been rephrased, to be more explanatory.
  - Section 5.2 Methods: additional paragraph identifying the plan for MRI follow up.
  - Section 9.2 Study Trial Schema: The trial schema has been revised to reflect the MRI follow-up schedule.
  - Section 9.3 Table 1: DRE has been given it's own line item, no longer being done at 6 and 18 months.
  - Section 9.3 Table 1: Urine will no longer be collected at 6 and 18 months.
  - Section 9.3 Table 2: DRE has been given it's own line item, no longer being done at 6 and 18 months.
  - Section 9.3 Table 2: Urine will no longer be collected at 6 and 18 months.
  - Section 9.3 Table 3: DRE has been given it's own line item, no longer being done at 6 and 18 months.
  - Section 9.3 Table 3: Urine will no longer be collected at 6 and 18 months.
  - Section 10.11: 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.
  - Section 10.12 Additional tests for biomarker discovery-Optional: the addition of general information regarding the assays being collected.
  - Addition of Section 10.12.2 Correlative Science Component: The addition of comprehensive information regarding Correlative Science Component –inclusion of biomarker, urine, semen, tissue testing; information has been added to this section to reflect the biomaterial testing that will take place during the study by each collaborator.
  - Addition of collaborators and banking address in newly added Section 10.12.2
  - Deletion of 'completed AEs' from page 54
  - Deletion of 'The first' in Section 16.3.6 Recording/Reporting AEs and SAEs
  - Appendix 2: MPMRI Reporting Proforma: revised, for clarity.

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.

3. **Short title**: **Pr**ostate **E**valuation for **C**linically **I**mportant disease: MRI vs **S**tandard **E**valuation procedures. (PRECISE)

Date: 30 June 2017

Version 4.0

Sponsor:
Canadian Urology Research Consortium (CURC)

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Confidential

The information provided in this document is strictly confidential and is intended solely for the guidance of the clinical investigation. Reproduction or disclosure of this document - whether in part or in full - to parties not associated with the clinical investigation, or its use for any other purpose, without the prior written consent of the PI is not permitted.

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: _____

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9030 ## 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	**Primary Objective** 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. **Secondary Objectives** 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 ≥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, all 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. ≥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 ≤ 20ng/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 ≤50mls/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. All subjects 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. All subjects in ARM A will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI. Subjects in ARM A who do not receive a subsequent biopsy will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (± I 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. Subjects in ARM A who do receive a MRI-targeted biopsy 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 (± I 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. All subjects in ARM B 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 (± I 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.
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 ≥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

Abbreviations:

ADC	Apparent diffusion coefficient
CI	Confidence interval
CRF	Case report form
DSMC	Data Safety and Monitoring Committee
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
EDC	Electronic Data Capture
ITT	Intention to treat
MCCL	Maximum cancer core length
MPMRI	Multi-parametric MRI, used interchangeably with MRI in this protocol.
MPMRI-TB	Multi-parametric magnetic resonance image-targeted biopsy of the prostate
MRI	Magnetic resonance imaging, used interchangeably with MPMRI in this protocol
MRI-TB	Magnetic resonance imaging targeted biopsy
MRS	Magnetic resonance spectroscopy
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PTC	Permission to Contact
PSA	Prostate specific antigen
REB	Research Ethics Board
STARD	Standards for the reporting of diagnostic studies
TRUS	Trans-rectal ultrasound
TSC	Trial Steering Committee
T2W	T2-weighted imaging

Definitions:

MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is used to determine the location of a suspicious target prior to biopsy.
Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure is not influenced by findings on MRI imaging. Currently this is the standard of care for prostate cancer in the province of Ontario.

5. Trial summary

5.1 Aim and Rationale

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

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

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

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

The potential implications of this trial include:

- 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

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 (+ I 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 for30-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 prostectomy) 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 be followed with serial PSA testing; PSA levels will increase if cancer is present. In both arms in addition to serial PSA testing all men who have no cancer found at systematic biopsy or targeted biopsy, have a negative MRI or enter active surveillance will have a followup MRI at 24. If a new Pi-Rads >=3 lesion is found on the followup MRI or there is progression of an existing lesion this lesion will undergo targeted biopsy as part of standard of care.

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

5.3 Participating Sites

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

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

5.4 Study outcomes

5.4.1 Primary outcome

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

5.4.2 Secondary outcomes

40. To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$ 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 $\geq$ 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 alone

6. Background

6.1 Prostate cancer diagnosis

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

6.2 Clinically significant versus clinically insignificant prostate cancer

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

This definition is likely overly stringent. An increasing consensus views all Gleason pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate cancers fall into this category, and are unlikely to progress and affect a man's life expectancy if left untreated. The widespread use of PSA testing has led to more men being diagnosed with insignificant cancer that does not warrant any treatment [13]; however they are typically monitored closely with active surveillance. This is associated with anxiety about harbouring untreated cancer, and the negative psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate cancer are also subjected to serial biopsies and other tests, requiring long term follow up. Further, many men with low risk disease receive radical treatment, either

because their physicians are not advocates of surveillance or because of anxiety [15].These treatments may expose them to morbidity including urinary incontinence and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate clinically significant cancer from clinically insignificant cancer will help reduce patient anxiety, alleviate further testing, and avoid radical treatment and associated morbidities.

6.3 Current standard of care: systematic TRUS guided biopsy

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

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

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

6.4.1 The role of imaging in prostate cancer diagnosis

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

6.4.2 Limitations of early MRI studies in prostate cancer

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

- **Poor reporting standards**. Many early studies failed to closely follow published guidelines for the standards of reporting of diagnostic studies (STARD) [23].

- **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.

6.4.3 Emerging role of MRI in the diagnosis of prostate cancer

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

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

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

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

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

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

6.4.3.1 MRI can influence the decision to perform a prostate biopsy

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

6.4.3.2 MRI can influence the biopsy technique

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

The biopsy operator can use the MRI images or report to direct biopsies into the area of the prostate where the tumour is located. The location of the tumour on the MRI (carried out in advance) is registered to the real-time ultrasound images with the use of software (software assisted registration or image-fusion) or without the use of software (visual registration or cognitive registration), while the prostate is visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted directly "in-bore", where the biopsy is conducted within an MRI scanner where the

target identified on MRI during a prior diagnostic scan is biopsied using guidance from serial MRI scans during the biopsy procedure, performed in an open magnet.

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

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

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

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

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

6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy

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

- **Broad definition of the study population.** The cancer detection rates depend on the prevalence of the condition in the population being investigated. This varies amongst men with no prior biopsy, prior negative biopsy and prior positive biopsy. In many studies the detection rates are not attributable to a clearly defined population.
- **MRI conduct and reporting.** The detail in which MRI is conducted and interpreted varies greatly amongst published studies.

- **Reporting of cancer detection.** The cancer detection by systematic and targeted cores is not always presented separately and cancer detection is not always specified by clinical significance. These are both essential in order to evaluate the technique.

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

6.5 Novelty of PRECISE

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

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

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

7. Trial objectives

7.1 Overall aim

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

7.2 Hypotheses

The proportion of men with clinically significant cancer detected by MRI-targeted biopsy will be no less than that detected by systematic TRUS guided biopsy.

7.3 Primary Objective

To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.

7.4 Secondary Objectives

53. To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy.
54. Proportion of men in each arm with clinically insignificant cancer detected.
55. Proportion of men in each arm with Gleason $\geq$4+3 detected.
56. Proportion of men in MRI arm who avoid biopsy.
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.
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).
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 $\geq$ 7 cancer detected on a repeat biopsy (systematic or targeted) by 2 years.
60. Proportion of men with post-biopsy adverse events
61. Health-related quality of life scores.
62. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
63. To determine the cost per diagnosis of cancer.
64. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield
65. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone

7.5 Explanation for non-inferiority hypothesis

Due to the putative advantages of MRI-TB in reducing the number of men who require a biopsy, reducing the number of cores required in each man who is biopsied, more accurate representation of disease burden, less insignificant disease detected and reducing the number of men at risk of complications of biopsy, the primary outcome of detection of clinically significant cancer in each arm will be compared using a non-inferiority hypothesis. Even if a similar amount of clinically significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these

advantages would support the use of MRI-TB instead of systematic TRUS guided biopsyin clinical practice.

7.6 Anticipated timeline of study progression

The study will commence once sponsorship, ethical approval and local approvals have been obtained at a participating site and once site initiation training has occurred and a letter of site activation has been issued from the coordinating centre. Additional sites may join after the study has commenced. At this time, five sites will participate. Assuming a minimum recruitment rate of 3-6 men per site per month, recruitment will be complete by 24 months, if not sooner. If accrual is slower than expected, an additional 1-2 sites will be recruited for year 2.

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

8.Study Population

8.1 Number of Subjects

Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy will be eligible for participation. Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

8.2 Subject inclusion criteria

In order to be eligible, all inclusion criteria must be met:

19. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;
20. ≥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.
21. Serum PSA ≤ 20ng/ml within 3 months of randomization
22. Fit to undergo all procedures listed in protocol;
23. Able to provide written informed consent.

8.3 Subject exclusion criteria

Men who meet the following criteria at the time of screening will be excluded:

19. Prior prostate biopsy

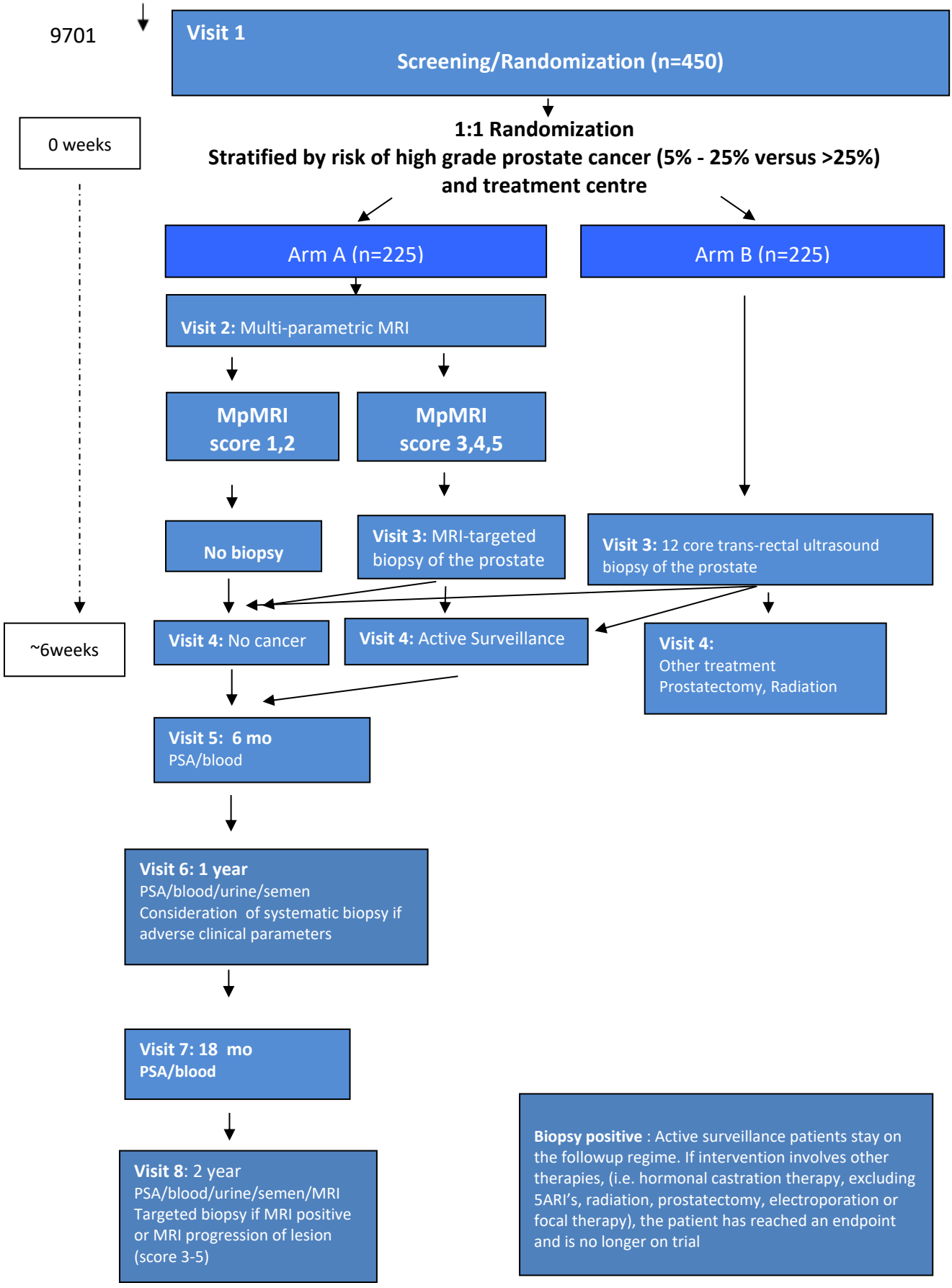
20. Prior treatment for prostate cancer
21. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min)
22. Contraindication to prostate biopsy
23. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work
24. Unfit to undergo any procedures listed in protocol.

9. Study design

9.1 Study design

The study is a multi-centre, open-label randomized controlled trial, with men randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or will be followed for two years if there is no suspicious areas identified by MRI. The unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-core systematic TRUS guided biopsy. All men in the study will be followed for two years or until they have had radical treatment (whichever comes first).

9.2 Study Trial Schema



9.3 Timeline of subject contact

Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial. The individual pathway that each subject experiences is dependent on both the arm he is randomized to and results of the tests.

Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require 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							

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4]PSA will have been done prior to visit 1 as part of screening.

[5] If MRI indicates a target, biopsy must be done

[6]After treatment decision men revert to standard of care.

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							

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4] tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[5]PSA will have been done prior to visit 1 as part of screening.

[6] See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue obtained for correlative science studies if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[7]After treatment decision men revert to standard of care.

9775
9776 **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 follow 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							

9777

[1]Urine sample will be required PRE and POST DRE, if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[2]Urine 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.
[3]Collected at baseline, and annually.
[4]PSA will have been done prior to visit 1 as part of screening.
[5] See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue obtained for correlative science studies if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[6]After treatment decision men revert to standard of care.

10. Trial Interventions and procedures

The following procedures will be applied as necessary to subjects enrolled in both arm of the trial.

10.1 EQ-5D-5L Questionnaires

For all subjects enrolled in trial

Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to evaluate health related quality of life. It takes approximately 2 minutes to complete.

- All subjects should complete the baseline questionnaire at the screening visit before leaving the department.
- Subjects who have a normal MRI and do not require a biopsy will complete an EQ-5D-5L questionnaire at Visit 4.
- Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date that the subject should fill out the questionnaires should be written on top of the questionnaire. (This can also be done at Visit 4).
- All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up visit.

10.2 Multiparametric MRI imaging procedure

For subjects in Arm A only

10.2.1 MRI Protocol

A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic phased array coil and an automated injector system with the subject in the supine position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS v2.

Within the specified PI-RADS 2 framework a common protocol will be formulated by a consensus of the radiologists involved in the trial at each site at a startup meeting. The highest agreed upon b-value image for DWI (at least 1400s/mm2) will be selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast media, injection rates and dynamic scanning temporal resolution will be matched for all sites. An optional multi b value DWI acquisition will be undertaken as well to allow for ancillary studies into non log linear apparent diffusion coefficient (ADC) models for tumor characterization. This is summarized in an MRI Operations Manual

Subjects will be asked to follow their local standard of care MRI examination preparation instructions for the MRI procedure.

10.2.2 MRI reporting

The MRI will be reported by an experienced radiologist using the MRI Reporting Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5 pointLikert score for purposes of comparison. Biopsy decisions will be based on the PI-RADS scores.

Lesions in the prostate will be scored on the following scale:

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)

The location of the suspicious areas in the prostate should be marked on a diagram of the prostate (see Appendix2) and the sector numbers containing each suspicious area should be recorded in the case report form.

Radiologists will be blinded to the PSA.

Imaging interpretation will be carried out at each site, however ensuring consistency and quality of imaging interpretation is crucial. A central imaging site will be designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site will perform the interpretation of all images for that site. The designated radiologist must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A startup meeting involving all radiologists will be held prior to start of accrual where each site will bring 5 MRI cases performed at their site for consensus review, scoring and discussion. This will provide a commonality of approach to interpretation among the radiologists before the study begins. After this startup meeting each site will

send one set of MRI images and its interpretation for central review for site qualification.

A copy of all images will be sent on CD/DVD to the central site for archiving.

10.3 No target identified on MPMRI (PI-RADS 1 or 2)

For subjects in Arm A only, who do not require a biopsy

Men who have MRIs that do not identify any suspicious lesion will not receive a biopsy. These subjects will benefit from being part of the trial as a result of not having to undergo an invasive biopsy procedure, avoiding the discomfort associated with the procedure, the risk of being diagnosed with clinically insignificant cancer and the risk of sepsis associated with the biopsy procedure. Studies suggest that if the MRI does not identify areas suspicious for cancer there is an85-95% chance that clinically significant cancer is not present[28, 34, 35].

As soon as the results of the MRI are discussed with the subject, their treatment decision will be recorded and they will return to standard of care management. As part of standard of care these subjects can undergo further PSA surveillance and / or prostate biopsies if indicated.

10.4 MRI-Targeted biopsy

For subjects in Arm A who do require a biopsy

10.4.1 MRI choice of targets for targeted biopsy

Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in MRI-targeted biopsy. Operator experience (number of targeted biopsies performed to date) will be recorded before each procedure. The number of biopsy operators should be kept to the minimum number possible.

Targets will be stratified by PI-RADS score and if the same score then by size and labeled T1, T2, T3…etc. If there are more than 3 lesions with a score of 3 or more only T1-T3 will be targeted. The radiologist should record the sectors involved with tumor in order of most to least involved using the PI-RADS v2 sector scheme.
The number of biopsy operators should be kept to the minimum number possible.

Subjects in the MRI cohort will not have systematic biopsies, with one exception. Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core biopsy will be conducted.

10.4.2 MRI Biopsy

The procedure will be performed in the outpatient departments of sites possessing the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI fusion system at their institution before they are qualified to participate as an operator in the study.

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will be performed via the trans-rectal route or via the trans-perineal route depending upon local practice.

Targeted biopsies should be performed by software-assisted fusion devices (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This software is safe and poses no risks to the subject since the same CE-marked ultrasound probes that are designed to perform the biopsy when performed as standard of care biopsy are used during targeted biopsy. Should the operator wish to not use the information provided by the software registration system and use cognitive (visual) registration alone they can do so, but should indicate this on the subject's case report form.

The samples per target will be 4cores spread across the target region for a maximum total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be conducted in order meaning T1 then T2 then T3.

Biopsy cores from different suspicious areas will be aliquoted separately. The vials will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there are) which should match the assignment of suspicious areas by the radiologist on the MRI report. The order of lettering a-d should match the order in which the biopsies were performed in each region. The first biopsy should be at the center of the target and the remaining fanning out from the center. Each core from the same suspicious area must be submitted separately. Alternative methods of storing cores that allow identification of the order of score samples from each target are acceptable.

10.5 Systematic TRUS guided biopsy

For all subjects in Arm B

Systematic TRUS guided biopsy is the current standard of care for the diagnosis of prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local site of recruitment.

A clinician competent in systematic TRUS guided biopsy will perform the procedure. The experience of the operator (number of systematic TRUS guided biopsies performed to date) will be recorded prior to each procedure. Software that guides clinicians in placing biopsy cores should not be used.

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

The subject will be positioned in left lateral position. 10-12 core biopsies will be taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed to the peripheral zone (See Appendix 3for standardized method for conducting 12-core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be given as per local guidelines.

10.6 Pathology

The 2005 International Society of Urological Pathology guidelines for Gleason Grading of Prostatic Carcinoma will be followed [43].

For men undergoing MRI-targeted biopsy it is required that pathology reported per suspicious area targeted and per targeted core. For systematic TRUS guided biopsy, each core will be reported and graded.

10.7 Post-procedural care

For all subjects in ARMS A and B receiving a biopsy

After a biopsy procedure the subject can be discharged within 2-3 weeks for results of the histopathology and treatment options to be discussed.

10.8 Immediate post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

A modified version of a self-reported questionnaire validated previously [39] in the assessment of post-biopsy complications will be completed immediately post-biopsy after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject should complete the immediate post-biopsy questionnaire before they leave the department. It aims to assess intensity of discomfort and pain associated with the procedure.

10.9 30-day post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

A modified version of a self-reported questionnaire validated previously [39] in the assessment of post-biopsy complications at 30 days post-biopsy should be given to all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home (Appendix 8). The subject should fill this out on day 30 following the procedure. It should take 5 minutes to fill out. The date that the participant should complete the questionnaire should be written on top of the questionnaire. Data on specific biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded. Contact with healthcare and resource used data following the biopsy will also be ascertained. The completed questionnaire can be returned to the investigator in a pre-addressed envelope.

Subjects should be reminded at 30 days to complete this questionnaire.

10.10 Results and treatment decision (Visit 4)

The results of the biopsies and/or MRI will be explained to the subject by the clinical care team during this visit, which is approximately 2-3 weeks after the biopsy. The research team should record the treatment decision in the subject file. Possibilities for treatment decision include but are not limited to:

- Further diagnostic test (e.g. PSA, biopsy, MRI)
- Active Surveillance
- Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- Hormone therapy

10.11 Follow up period

All study participants will be followed up for up to two years or until they have radical treatment. Each year, subjects will be surveyed to obtain the following information:

- time to cancer diagnosis
- Gleason score progression
- time to intervention on active surveillance
- time on active surveillance
- PSA
- All subjects in both Arm A and B who have remained either undiagnosed or untreated (on active surveillance) will have a follow up MRI 2 years after study entry.

10.11.1 Indications for biopsies off protocol

For subjects who are not biopsied due to a negative MRI, have negative or non-significant systematic biopsies, or who have a positive MRI but no or non-significant cancer on targeted biopsy, the following are guidelines for subjects management during the 2 year follow up period.

It is an accepted standard of care in Ontario for subjects on active surveillance or with a prior negative biopsy who have a worsening risk profile to undergo mpMRI followed by targeted biopsy. We propose the following guidelines for risk profile assessment and consideration of repeat biopsy

Subjects should continue to be followed with semi-annual PSA and DRE. A biopsy should be considered under one or more of the following circumstances:

1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.

2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase in PSA in 1 year.

3. Biopsy if a doubling of the risk of high grade cancer according to the NCI nomogram.

4. Biopsy if development of a suspicious nodule on DRE.

5. For men with a positive study MRI (especially PI-RADS 4 or 5) and a targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.

24. For men on the systematic biopsy arm which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these subjects.

These are guidelines and should be interpreted with clinical judgment.

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.)
PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI identifies a target.

10.12 Additional tests for biomarker discovery - Optional

Though not related to the primary outcome of this study, this cohort represents a unique opportunity to obtain human samples for future biomarker discovery studies. Participants will be consented to provide a blood, urine, semen, and tissue sample after the consent and screen visit, and subsequent visits for storage and use in future biomarker studies. In addition, men will be consented for use of the prostate biopsy tissue in the biomarker discovery studies.

We propose two initial biomarker analyses for men recruited to the PRECISE study. First we propose testing the utility of several genetic assays. These include the SELECT MDx test (a urine based genomic assay), the Telo PC test (an analysis of telomere structure in circulating tumour cells), the Exosome Dx assay (urine based exosome assay), the Mitomics assay (circulating mitochondrial DNA deletion assay), and the MDNA test (a urine based microRNA assay). We will test the hypothesis that alongside conventional PSA measurements, these tests may identify subjects whose MRI was initially negative for prostate cancer, but who are at high risk of harboring clinically significant disease as detected by the secondary MRI at 2 years. We will also test the association between serum biomarkers and clinically significant or clinically insignificant prostate cancer detected during the PRECISE study. We will also explore the potential for these assays to provide additional information over and above Gleason grade. These studies will be separately funded from PRECISE.

Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will be planned to assess markers which might identify men at higher risk of developing prostate cancer.

10.12.1 Samples to be collected for future biomarker discovery work (Optional)

Participants will be asked to consent to provide a blood, urine, semen, and tissue sample after the consent and screen visit and subsequent visits for storage and use in future biomarker studies. This will involve a separate consent form.

Samples include:

- Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- Urine – 75 mls urine
- Semen-1-5 cc (single ejaculate)
- Tissue-unstained biopsy sections -15 unstained slides from cancer, and
  -15 unstained slide from non-cancer cores (if possible)

10.12.2 Correlative Science Component

Within this protocol biomarker and genetic validation studies and biomarker discovery research will be incorporated to correlate molecular readouts with the presence of Gleason 4 or 5 pattern on biopsy. The goal of these studies is to develop a liquid based assay (serum, plasma, CTCs, urine, or semen) which accurately predicts the presence of clinically significant cancer. The correlative science component of Precise constitutes a major initiative, with multiple collaborators and planned studies. These are briefly summarized below.

Biomaterials (serum, plasma, buffy coat, PRE/POST DRE urine and tissue from biopsies) will be collected at times specified in the protocol. Sample collection will be restricted to subjects who have agreed to provide these samples in a separate optional informed consent. If a subject withdraws consent for the additional biomarker and genetic testing, subject's samples will be destroyed. The investigator must notify the sponsor site contact who will request the samples destruction.

Biomaterials for the correlative science studies will be identified with a unique identification code, date of collection and will not contain any personal identification information. The samples will be shipped to a secure long-term storage facility, identified as the Ontario Institute for Cancer Research, located at 661 University Ave, Suite 510, Toronto, ON M5G 0A3. Samples for the correlative science studies will be shipped stored and analyzed according to specified, specialized procedures in the Precise Correlative Science Manual.

A group of investigators led by Drs. Paul Boutros (OICR) and George Rodriguez (UWO) have obtained funding for a correlative science study nested in the Precise trial. This study is termed the 'Translational Research Initiative in Prostate Cancer', or TRIPC. Biomaterial will be collected for these studies as above. A summary of the planned studies is as follows:

Urine: The TRIPC project will measure the proteomes of urine specimens using either a whole proteome assay or Selective Reaction Monitoring - Mass Spectroscopy (SRM-MS) or Peptide Reaction Mass Spectroscopy (PRM-MS) for a panel of ~50 peptides. These peptides will be used to score two published biomarkers of disease aggressivity

(https://www.nature.com/articles/ncomms11906). The PRECISE data will then be used to retrain the parameters and weights of the biomarkers as an exploratory analysis.

Blood: Genotypes will be measured using either DNA-sequencing or genotyping arrays. The resulting data will be used to score five distinct biomarkers: a germline-incidence biomarker created by the PRACTICAL GWAS consortium, a biomarker of aggressive prostate cancer created by the PRACTICAL GWAS consortium, a panel of DNA repair genes identified by the SU2C group and two biomarkers of disease aggression identified by the CPC-GENE network. The PRECISE data will then be used to retrain the parameters and weights of the CPC-GENE biomarkers as an exploratory analysis. Second, methylation of cell-free DNA will be assessed using microarray platforms (either tiling or CpG island arrays) to score two existing signatures of aggressive prostate cancer.

Tissue
Tumour biopsies will be subject to OncoScan microarray profiling and/or DNA sequencing to measure methylome, somatic single nucleotide variants, copy number aberrations, genomic rearrangements and mitochondrial copy number. Seven signatures of aggressive prostate cancer will be scored: the proportion of the genome altered (PGA, Lalonde et al. Lancet Oncology), 100-locus and 31-locus signatures (Lalonde et al. European Urology), a multi-modal signature (Fraser et al. Nature), a mitochondrial signature (Hopkins et al. Nature Communications), and two unpublished signatures developed by the CPC-GENE network: of tumour evolution and of the tumour methylome. The PRECISE data will be used to retrain the parameters and weights of the biomarkers as an exploratory analysis.

A second group, led by Dr. Keith Jarvi, will analyze semen for biomarkers of significant prostate cancer. They will utilize **deep targeted Next-Generation sequencing of cell-free DNA and tumor cells Isolated from semen.**

- **Contact information**: Dr. Keith Jarvi/Dr. Andrei Drabovich
  Murray Koffler Urologic Wellness Centre, 60 Murray Street, 6/F
  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

sequenced by the Cancer Genome Atlas, Broad Institute and Memorial Sloan Kettering Cancer Center. 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 deplete 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 and/or 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

This group will be examining the telomere structure of circulating tumour cells (CTCs) using an established assay, the Telo PC test. The results of a 50 patient prostate cancer pilot study in men with intermediate risk prostate cancer who underwent radical prostatectomy showed that the TeloPC assay correctly predicted the status/aggressiveness of disease in each of the study's patients.[1] While all patients were diagnosed as intermediate risk using conventional biopsies prior to surgery, only 21 of the 50 patients who underwent RP showed disease upgrading upon post-surgical analysis and therefore were suitable for prostate removal. The TeloPC assay correctly predicted that 29 of the 50 patients had a stable form of prostate cancer.

The TeloPC assay includes filtration-based circulating tumour cell (CTC) enrichment combined with 3-dimensional (3D) analysis of telomeres to obtain 3D telomere

profiles of PCa patients with low-intermediate risk category.

- MiR Diagnostics
  1 Discovery Drive
  Rensselaer, NY 12144

This group will be examining urinary microRNAs. A panel of 56 miRNAs and snoRNAs, which have been demonstrated to be predictive of clinically significant prostate cancer, will be interrogated.

- Exosome Diagnostics, Inc.
  266 2 nd Ave.
  Waltham, MA 02451

This group will be interrogating non-coding RNAs extracted from urinary exosomes. They will assay exosomal RNA for three biomarkers known to be expressed in men with high-grade prostate cancer, using an algorithm that integrates this three-gene signature,

- MDNA Life Sciences, Inc.
  2054 Vista Parkway, Suite 400
  West Palm Beach, FL 33411

This group will evaluate the performance of the Prostate Mitomics test. This is a blood-based screening test which evaluates free plasma DNA for the presence of a mitochondrial DNA deletion. This deletion has been demonstrated to be associated with high grade prostate cancer. Nucleic acids will be extracted from each plasma sample using a commercially available reagent kit. The Prostate Mitomic Test is a quantitative real-time PCR test for a 3.4kb mitochondrial DNA deletion correlated with prostate cancer. Each sample will also be profiled for novel mitochondrial DNA mutations using standard laboratory techniques such as quantitative real-time PCR. Mutation frequency will be compared to clinical outcomes.

- Dr. Keith Jarvi/Dr. Andrei Drabovich
  Murray Koffler Urologic Wellness Centre
  60 Murray Street, 6/F
  Toronto, ON M5T 3L9

This group will interrogate prostatic epithelial cells in seminal fluid for the presence of genetic alterations known to be associated with high grade prostate cancer.

- MDx Health. Inc
  15279 Alton Parkway, Suite 100
  Irvine, CA 926188

This group will perform the Select MDx assay, a two gene mRNA assay performed on urine, to evaluate its performance in predicting the presence of clinically significant prostate cancer.

10.13 Long-term data linkage – Permission to Contact

The cohort of men who consent to participate in this study represent a uniquely characterized group. Their long-term outcomes will contribute to our understanding of the epidemiology of prostate cancer beyond the questions being addressed in this study.

Permission to Contact (PTC) is a feasible mechanism to engage subjects in research programs. This will allow researchers to contact study participants in the future to assess their willingness to respond to questionnaires. This potentially enables research that would complement the planned long-term follow up in terms of health status, for obtaining information about future biopsies not included in the study, and allow assessment of quality of life.

10.14 End of Study

The end of study assessment comprises an essential safety evaluation that should be completed prior to discharging any subject from the study.

- Adverse events;
- PSA measurement;
- EQ-5D-5L questionnaire;
- An MRI in those who did NOT have a biopsy;
- Complete CRF.

10.15 Risks and Benefits to Participants

An important consideration of this study is that men are being randomized to one of two biopsy techniques when it is not known which will be more effective. Both diagnostic tests are currently used in clinical practice at the institutions involved in the trial. Though systematic TRUS guided biopsy could be considered standard of care, there is enough evidence to support the concept that MRI-targeted biopsy may be at least as effective as systematic TRUS guided biopsy[27].

10.15.1 Risks to subjects

The intervention proposed in this trial (MRI-biopsy) do not offer participants any more risk than if they underwent standard of care (systematic TRUS guided biopsy) for the diagnosis of prostate cancer.

10.15.1.1 Risk of Systematic TRUS guided biopsy

Systematic TRUS guided biopsy can be associated with discomfort, haematuria, haematospermia and dysuria in a large proportion of subjects, which is self-resolving (See Table 4). There is a 4% risk of systemic urosepsis[46].

10.15.1.2 Risks of MPMRI

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.

10.15.1.3 Risks of MRI-targeted biopsy

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.

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
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%

10.15.2 Benefits to subjects

Subjects enrolled in this trial will benefit from the following:

- 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 will also ensure streamlined diagnostic investigations to promptly conduct the diagnostic test and communicate the test outcome for the subject.
- Subjects enrolled in the trial will benefit from the dedicated research team involved in their care in addition to the clinical team normally involved in their care.
- Subjects will benefit from additional discussions regarding the trial, which could increase their understanding of prostate cancer and help them to make a more informed decision about their health.
- Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will remove any risk of post-biopsy infection. MRI-randomized subjects may also benefit from a reduced probability of having a clinically insignificant prostate cancer diagnosed. Clinically insignificant prostate cancer is often treated definitively per subject preference despite the lack of evidence supporting the need. All definitive local therapies for prostate cancer carry the risk of peri-operative complications as well as long-term risk of incontinence and erectile dysfunction.

10.16 Concomitant medications

10.16.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF with indication, dose information and dates of administration. The definition of which medication would be considered outside the routine medical practice is up to the discretion of the investigator. All dietary and herbal supplement usage will be recorded in the CRF.

10.16.2 Non-Drug Therapies

Any occurrence of prostate-related surgical and/or non-surgical (or minimally invasive) intervention during the conduct of the study will be recorded in the CRF.

11. Schedule of Study Visits

11.1 Visit 1 (Screening/Randomization): Screening, Consent, Randomization

For all subjects enrolled in trial

Screening will occur any time following the referral of the subject. Ideally, this will be performed as soon as possible following receipt of referral.

Subjects will be consented only after they have had time to consider the study. This may happen on the same visit as the screening visit.

Randomization can happen immediately after the consent form is signed and eligibility is confirmed.

Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L questionnaire (Appendix 4), which is a validated 2-page questionnaire representing health related quality of life. It takes approximately 2 minutes to complete. This questionnaireshould be completed at the screening visit before the subject leaves the clinic.

If a subject agrees to the optional informed consent, from randomization until any point prior to a biopsy, optional blood, urine,semenand tissue samples will be collected for correlative studies.

Even if PSA testing was done prior to Visit 1, PSA should be obtained at Visit 1.

11.2 Visit 2 (MRI): ARM A, for men randomized to MRI

This will occur approximately within one week of randomization. Men will receive an MRI (see Section 10.2.)

11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate

For men randomized to ARM A, who have a lesion identified by MRI. This appointment will follow approximately one-two weeks 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 biopsy to occur in timely fashion. If the results of the MRI show 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.

Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after a biopsy, before the subject leaves the department.

Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and complete as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however, the questionnaire should be completed as close as possible to 30 days post-biopsy.

At the 30-days post biopsy interval, a member of the research team will call the subject to remind them to complete and return the 30-day questionnaires.

11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic TRUS-biopsy

For men randomized to ARM B only.

Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after the biopsy.
Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and it is to be completed as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-biopsy.

At 30-days post biopsy a member of the research team will call the subject to remind them to complete and return the 30-day questionnaires.

11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a biopsy

This appointment will include a follow up meeting with the investigator to discuss the results of the MRI as well as treatment decisions. This follow up should occur

after the availability of the MRI report. At this visit the subject will also complete a 30-day post intervention EQ-5D-5L Questionnaire.

Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8),which has been posted to them by the research team. 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-MRI, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-MRI.

At 30-days post MRI, a member of the research team will call the subject to remind them to complete the 30-day questionnaires.

11.6 Visit 4 (Post-test follow up): For all men who received a biopsy

This appointment will include a follow up meeting with the investigator to discuss the results of the biopsy as well as treatment decisions. This should be completed as soon as possible following the availability of any pathology results. The follow up appointment should be within 1 month of the biopsy. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.

The research team should record the treatment decision in the subject file.

Possibilities for treatment decision include but are not limited to:

- Further diagnostic test (e.g. PSA, biopsy, MRI)
- Active Surveillance
- Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- Hormone therapy

At this visit the subject will also receive a 30-day post intervention EQ-5D-5L Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy questionnaire (Appendix 8), which has been posted to them by the research team. The questionnaire needs to be completed on the 30th day post-intervention (i.e. post biopsy). However it will be accepted if completed up to 72 hours prior to or after the 30th day. A telephone reminder from the research team to the subject can take place.

11.7 Visit 5 (6 month follow up):26 week follow up

All subjects will have a 26 week visit

Subjects will have the following:

- Vitals, DRE
- PSA
- Optional sample collection (blood)

11.8 Visit 6 (1 year follow up): 52 week follow up

All subjects are planned to have a 52 week follow up visit.
Subjects will be followed to obtain the following information 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.
- 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, targeted only or both systematic + targets, not done because of negative MRI
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6 (year 2).

11.9 Visit 7 (18 month follow up): 78 week follow up

All subjects will have a 78 week visit
Subjects will have the following:

- Vitals, DRE
- PSA
- Optional sample collection (blood)

11.10 Visit 8 (2 year follow up): End of study

All study participants will be followed for up to two years or until they undergo radical treatment
Subjects will be followed to obtain the following information 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)

- 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

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 8.

12. Randomization

12.1 Randomization Procedure

Written informed consent will be obtained from all eligible subjects prior to commencing any study related procedures. The Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre, Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate subject randomization. Subjects will be allocated to the two treatment arms in an approximate 1:1 ratio by use of a dynamic allocation scheme[47].

After documentation of written informed consent and confirmation of subject eligibility, clinical centres will randomize the subject by accessing the CMC's web-based Interactive Registration/Randomization System (IRIS). Prior to randomization and treatment allocation, the subjects' individualized risk of high-grade prostate cancer, obtained using the PCPTRC 2.0 calculator found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp must be determined.

12.2 Stratification

Eligible, consenting subjectswill be stratified by: (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%); and (2) clinical centre

12.3 Blinding and measures taken to avoid bias

This study is unblinded, and all subjects will be aware of the treatment that they are receiving. As the MRI scan is unique to one of the arms it will not be possible to blind the participants or investigators as to what intervention is being received. Therefore, participants will be informed which arm they have been allocated to. Where possible, the data will be coded so as to blind individuals analyzing the data from which of the groups the data was from. Summary details of randomized allocation and outcomes will not be made available (unless specifically authorized by the Trial Steering Committee and/or Data Monitoring Committee) in order to maintain the overall blind of the trial.

Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be aware that the subject is part of the trial.
Pathologists will be blinded to the cohort allocation. Concealment may be challenging due to the different number of cores in the two groups, but this is unavoidable. This is unlikely to represent a significant source of bias.

13. Data

Type of data to be collected:

- EQ-5D–5L questionnaires. These will measure quality of life and which will be measured at specific times throughout the trial.
- Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and continuous data
- MRI – diagram representing MRI; categorical data for areas and scores of suspicion (e.g. Sector 1p, score of suspicion 4/5)
- MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and continuous data
- Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers yes/no)
- Treatment decisions – categorical data (e.g. radical treatment)
- PSA – continuous data (e.g. value of PSA in ng/ml)

Please see **Appendix1** for the time window for data collection.

14. Statistical Considerations

14.1 Sample Size Calculation

STATISTICAL methods

Primary Analysis

Absolute differences in the proportion of clinically significant cancer detected between arms will be calculated and compared using the Clopper-Pearson method. If the lower boundary of an one-sided, 97.5% confidence interval for the difference in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower bound is greater than zero, superiority can be claimed.

A supportive analysis will be performed by using a logistic regression model, evaluating the odds ratio for detecting high grade cancers, adjusted for stratification factors. MRI-guided biopsy would be considered non-inferior if the lower bound of the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower bound was calculated to approximate an absolute 5% difference of interest (NOTE: the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

Secondary Analyses

For each secondary outcome, where appropriate, a difference in proportions with 95% CI, or a difference in means with 95% CI, as appropriate, will be presented. Differences in the 1-year and 2-year rates along with 95% CI will be calculated for time-to-event outcomes.

χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for differences between allocation arms in secondary outcomes. Logistic regression and Cox proportional hazards regression will be used to examine the effect of allocation arm on outcomes, adjusted for stratification factors. All secondary outcomes will be two-sided and statistical significance will be set at the α=0.05 level. No statistical adjustments will be made due to multiple testing, however, results for secondary outcomes will be interpreted cautiously, acknowledging that tests were performed on secondary outcomes and numerous secondary tests were performed. Figures and tables will be used to illustrate results of interest.

Treatment Allocation and Stratification

Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by use of a dynamic allocation scheme. Specifically, the first 20 subjects will be randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a biased coin method will be used, whereby the number of subjects within each stratum will be calculated, and the next eligible subject will be allocated (with probability p=0.8) to the arm which reduces the imbalance. If no imbalance exists, allocation to each arm will occur with probability p=0.5.

Stratification

For treatment allocation, the subjects' individualized risk of high-grade prostate cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp. Eligible, consenting subjects will be stratified by:

(1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);

(2) clinical centre.

Sample Size

Rates of clinically significant cancer (Gleason ≥7) detection from targeted-alone biopsy in a population with no prior biopsy have been shown to be 42% [37] and 50% from another study [36].

Rates of clinically significant cancer detection from one the largest studies of systematic TRUS guided biopsy in men without prior biopsy are shown to be 27% [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than systematic TRUS guided biopsy.

For this study, it will be conservatively hypothesized that systematic TRUS guided biopsywill detect clinically significant cancer in 30% of men, and targeted biopsy will detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5% one sided-alpha, assuming a targeted biopsy detection rate of clinically significant cancer of 40%, and a detection rate for systematic TRUS guided biopsyof 30% and using a margin of clinical unimportance of 5%, 211 men per arm will be required. The choice of 5% as the margin of non-inferiority represents a difference that would be considered clinically important.

Thus total men required in study = **422**.

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.

Note that the rate of clinically significant cancers is very dependent on the population registered for this study. It is possible that fewer (or more) subjects will have clinically significant cancers than what is initially hypothesized. However, if the population rate of clinically significant cancers is less (i.e. the systematic TRUS guided biopsy detection rate is <30%) and other statistical assumptions remain as stated previously, the statistical power will increase. The minimum statistical power would be obtained if the clinically significant cancer detection rate was 45% for systematic TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84% power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the rate of clinically significant cancer in the population is miss-specified, assuming an absolute difference of 10% between targeted and systematic TRUS guided biopsydetection rates, and a 5% margin of non-inferiority.

Statistical Conventions

For categorical data, tables will be presented showing the n and percentage (n/N*100%) of subjects. Analyses will be presented by study allocation arm separately.

Duration of time will be described in either years, months or weeks, and calculated using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date – date of birth + 1)/365.25.

Transformations of the data in order to meet statistical assumptions may be considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to assess any of the model fittings. All the statistical analysis will be carried out using SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-project.org) or higher.

Missing Data

Missing values for the primary endpoint will be examined closely. Sources and reasons for the absence of data incurred as a result of subjects lost-to-follow up, dropouts, and intermittent missing values will be described and explored by various summary statistics as well as graphical displays between the two allocation arms. Subjects' lost-to-follow up or dropouts will be explored and the characteristics of those subjects will be described by allocation arm and tested using Fisher's exact tests or Wilcoxon rank sum tests.

Missing data for secondary endpoints will be described. The methods for evaluating missing data of the primary endpoint may be employed for endpoints of interest. For summarization of baseline data, the following conventions will be used for partial missing date information occurring prior to randomization (e.g. for medical history

or prior treatment). If year is missing, the date will be set at missing. If year is available, but month and date is missing, the month and date will be set to July 1st of the respective year. If date is missing, but year and month available, the day will be set to the 15th of the respective month.

14.2 Interim Analyses

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. Unless otherwise specified by one of these bodies, a futility analysis will be performed after approximately 200 subjects are enrolled and have their primary outcome ascertained. Simulation will be used to estimate the conditional probability of futility assuming the study was to continue to completion, and assuming the clinically significant cancer detection rate is 30% in both arms. If the conditional probability is 0.95 or higher that continuation of the study will result in a negative result, the DSMC will recommend a suspension of recruitment to the trial, and initiation of a quality assurance review. A decision to permanently close the study or continue with accrual will be determined by the Steering Committee, based on the results of the quality assurance review, and the recommendation of the DSMC.

Timing of Final Analysis

A single, final, analysis will occur after all subjects have undergone their initial biopsy and all data related to the initial biopsy is documented and validated. Follow-up analyses will be conducted after all subjects have completed two years of follow-up.

14.3 Populations:

The per protocol, study population will consist of all subjects who satisfy all eligibility criteria and are randomized to the study, who undergo MPMRI-TB or systematic TRUS guided biopsy and have their primary outcome measured. This population will be used for the primary analysis of non-inferiority.

The intent-to-treat (ITT) population will consist of all subjects randomized to the study, regardless of any protocol violations or if they do not complete the study as defined in the protocol. The ITT population will be used as a supportive analysis of the primary analysis, for all safety analyses, and for any analysis investigating superiority.

14.4 Primary Outcome

14.4.1 Detection rate of clinically significant cancer

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 intention to treat population.

Absolute differences in proportion of clinically significant cancer detected between arms will be calculated and compared. If the lower boundary of the 97.5% confidence interval for the difference in detection rates of MPMRI-TB compared to

systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower bound is greater than zero, superiority can be claimed.

The primary analysis will be conducted once all subjects have completed visit 4, when the results of the biopsy or MRI are given to the subject.

14.5 Secondary Outcomes

For each secondary outcome, where appropriate, a difference in proportions with 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

14.5.1 Proportion of men in each arm with clinically insignificant cancer detected

The proportion of men in each arm with clinically insignificant cancer (Gleason <7) will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.2 Proportion of men in each arm with Gleason ≥4+3 detected

The proportion of men in each arm with Gleason $\geq$ 4 +3 will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.3 Proportion of men in MPMRI arm who avoid biopsy.

14.5.4 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.

The proportion of men in each arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected, will be calculated based on histology results from biopsy procedures.

14.5.5 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)

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 andhaematospermia.

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

As the study design for clinical outcomes is one of non-inferiority, the primary economic analysis will be **cost minimization analysis**. The perspective of the economic analysis will be that of the public payer. The primary goal of the analysis will be to support arguments for public funding. Thus the costs of participant burden, logistical challenges, and expense of obtaining societal costs, will not be evaluated.

14.5.12.1 Data collection:

As part of the informed consent process, participants in Ontario will also consent to having their Ontario Health Insurance Number recorded, to be later transferred to the Institute for Clinical Evaluative Sciences (ICES) where it will be linked to a number of administrative claims databases recording health system resource utilization such as physician billing [Ontario Health Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity Level Reporting (ALR)];clinic and emergency department visits [National Ambulatory Care Reporting System (NACRS),Emergency Department visits); radiation (ALR); homecare (Home Care databases) and a few additional ones as determined necessary (e.g., Long-term care, Mental Health, Diabetes.The overall, number and proportion of health system resources will be determined.In this way we can capture comprehensive resource utilization related to on-trial management including any adverse events.

14.5.12.2 Health Insurance number handling and security

As the economic implications of this study are of prime importance to some of the funders, the request for data linkage will be part of the main consent form. If a participant indicates to the study team that they decline or withdraw consent, the OHIP number will be recorded as 9999-999-999-XX. The OHIP numbers will stay with the participating institution until after accrual is complete, and then they will all be transferred at one time under data sharing agreements between ICES and each institution. Data will be transferred using a secure electronic file transfer system established by ICES and managed by authorized ICES personnel responsible for receiving data. The file transfer system uses security safeguards including encryption and authentication.

ICES is a Prescribed Entity under the Personal Health Information Protection Act (PHIPA), and can receive and use personal health information for purposes of analysis and compiling statistical information and other research. Its policies and procedures for privacy protection and data security have been approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-monitored and requiring passkeys to access private offices and computers. ICES has extensive experience in the protection of confidentiality when using such data. It has a UNIX-based network that cannot be accessed externally. ICES data facilities are fully 'moated' (no connections to other computers). At ICES, routine procedures for data backup are instituted by a data management team. The data is burned onto a CD or placed on an external hard drive and placed in a locked vault. All ICES staff and scientific affiliates are required to sign agreements of confidentiality annually. Internal audits are conducted to monitor compliance with ICES policies, standards and procedures.

Study data with direct personal identifiers such as OHIP numbers will reside on a dedicated and secure server at ICES and will only be accessible by a named Data Covenantor. The Covenantor will encode

the OHIP number, replacing it with an ICES key number (IKN) (a code) and transferring it to a "moated" server for the study project. (The Data Covenantor is an ICES person named in our data sharing agreements and identified to the Office of the Information and Privacy Commissioner, who can access personal health information at ICES for the purposes of receiving, coding, transferring or destroying personal health information.) The coded study data will only be made available to the Principal Investigator and project staff directly responsible for data analysis (under the supervision of the investigator). No subject, physician or institution will be identified in the reporting of results

14.5.12.3 Cost calculation

Once the utilization of health services is determined from those cases linked to administrative databases, publicly available costs (2016$CAN) will be applied to health services. Costs for physician and laboratory services will be determined by applying that year's fee code. Costs for hospital care will be estimated using the Canadian Institute for Health Information (CIHI) Resource Intensity Weight method for the most recently available year. Outpatient prescription drug costs for participants not covered by ODB (those under age 65 and not on social assistance) will be considered to be the same as the trial arm-specific average for those with coverage. Costs will then be inflated using the healthcare-specific Consumer Price Index reported by Statistics Canada into constant Canadian dollars for the year the study ends. Due to the short time horizon, discounting will not be applied.

14.5.12.4 Primary Analysis

A within-trial analysis will be conducted to calculate the total cost for each arm and mean cost per subject for each arm. Frequency distributions and measures of central tendency (e.g. means and medians) will be determined for each resource category (e.g. hospitalizations)for each arm of the study. Confidence intervals for the difference in costs and resource utilization between the strategies overall and for each resource category will also be calculated. Univariate comparisons between the groups will be made primarily using nonparametric tests, such as Wilcoxan rank-sum test. In the primary analysis, assuming equivalence in the primary outcome, an arm with significantly lower mean costs will be considered the economically most attractive approach.

Should the clinical trial find a difference between the two arms on the primary endpoint, an incremental cost-benefit analysis will be calculated by deriving the additional cost per case of clinically significant cancer diagnosed, according to the following equation:

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{}$$

The cost of avoiding each additional case of clinically insignificant cancer diagnosed may also be similarly calculated. Consideration will be given to extending this analysis using economic modeling with incorporation of utility values from the EQ-5D to allow a lifetime perspective to be taken and the estimation of quality adjusted life years (QALYs).

14.5.12.5 Secondary Cost Analyses

One and multi-way sensitivity analyses will be carried out around major cost drivers by varying the costs over their observed ranges and conducting threshold analyses where appropriate. Sensitivity analyses will also be performed to evaluate potential limitations in the data, such as ODB costs as described above (though the proportion without ODB coverage should be similar in the two arms, and it is not expected to be a major cost-driver).

14.5.13 Missing Data

The impact of missing data will be explored in all analyses; sensitivity analyses/multiple imputation will be performed as appropriate.

15. Participant compliance and withdrawal

The study will be completed when at least 422 subjects have been randomized, have undergone a diagnostic test and completed follow up. Compliance to randomized treatment will be assessed by monitoring the completed forms, e.g. the systematic TRUS guided biopsy form or the MRI-targeted biopsy form.

In consenting to the study, subjects are consenting to study monitoring, imaging and biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to withdraw consent at any stage and their care will not be affected in any way. All communication surrounding the withdrawal and its reasons should be noted in the subject's record. Such cases should be reported to the PRECISE Study Operations Office. Data up to the time of withdrawal can be included in the study.

As the study diagnostic tests are for suspected cancer it is not anticipated that there will be significant loss to follow up.

15.1 Subject Withdrawal from Study

A subject may discontinue participation in this study at any time at the investigator's discretion or at the request of the subject.

If a subject discontinues at or before Visit 1 (randomization), he is not required to complete end of study assessments.

If a subject discontinues after Visit 1 (randomization) for any reason, the investigator should make every effort to complete the activities bulleted below.

- End of study assessments as outlined in **Section 10.17.**
- Any occurrence of death, prostatic surgical intervention, non-surgical treatment for prostate cancer after study withdrawal should be documented in the CRF and source documents.

Subjects who are discontinued from the study after randomization will not be replaced. Subjects withdrawn from the study retain their subject number if already given. New subjects will be allocated a new subject number.

In the event that a subject is prematurely discontinued from the study at any time due to an AE, the procedures describe in **Section 16.3** must be followed.

Subjects should be withdrawn from the study for any of the following criteria:

- Non-compliance with the requirements of the study.
- Request to discontinue treatment. This request can be made by either the subject or the investigator.
- Develops progressive disease.

15.2 Study completion

The primary end point will be reached when the last subject entered has their systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be followed for up to 2 years following study entry or until they have radical treatment. Subjects who are found to have significant prostate cancer and are treated will not be included in follow up for this period. This includes subjects diagnosed as part of study protocol, and subjects diagnosed during the follow up period by standard-of-care procedures. However, post MRI/biopsy questionnaires will not be required following non-protocol based procedures.

16. Data Monitoring, Quality Control and Safety

16.1 Stopping / discontinuation rules

The study will be completed when 450participants have been randomized, undergone a diagnostic test and completed follow up.

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. See Section 14.2.1.for further details on the interim analysis. Appropriate documentation as per the PI's requirement will be completed if stopping the trial is necessary and the ethics committee will be informed.

As the study is unblinded there will be no need for randomization code breaks.

16.2 Monitoring, quality control and assurance

Members of the trial team will be Good Clinical Practice (or equivalent) trained.

An independent DSMC will be appointed to monitor subject safety and the rate of recruitment of subjects in the study. They will meet at least once a year whilst the trial is ongoing for routine review of safety data and trial progression. They have the power to call additional meetings and review data at any point in the trial should they wish to do so.

The PI may also arrange an independent trial monitor to review the study data.

16.3 Assessment of safety

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

16.3.1 Definition of an Adverse Event (AE)

Adverse events (AE) will be defined as “any untoward medical occurrence in a clinical trial subject undergoing any intervention in the trial, which does not necessarily have a causal relationship with this treatment”.

Only adverse events specific to biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded. Please refer to section 16.3.6 of the protocol.

16.3.2 Definition of a Serious Adverse Event (SAE)

Serious adverse events (SAE) will be defined as “any untoward medical occurrence as a result of any intervention in the trial that:

(a) results in death

(b) is life-threatening

The term ‘life-threatening’ in the definition of ‘serious’ refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) requires hospitalisation or prolongation of existing hospitalisation

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at a hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physicians’ office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether ‘hospitalization’; occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen form baseline is not considered an AE.

(d) results in disability / incapacity

The term disability means substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital abnormality/birth defect.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.

16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as a serious adverse event. Progression of the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death due to progressive disease is to be recorded on 'Record of Death' CRF page and not as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

16.3.4 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

16.3.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings or other abnormal assessments that are judged by the investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The trial interventions are routinely carried out in clinical practice for investigation of suspected cancer and the risks of the interventions are therefore not any greater than if a man was not part of the trial. The risks of the procedures are relatively low, as detailed in Section 11.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

16.3.6 Recording/Reporting AEs and SAEs

The AE reporting period for this study begins at randomization and will be recorded until 30-days post-biopsy. In the event that the subject does not undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

Only adverse events specific to biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded.

AEs will be recorded by a member of the research team or clinical team on an AE report form. All SAEs must be recorded on a SAE report form. SAE report forms should be sent to the CTG who will keep a log of AEs and SAEs. AE and SAE logs will be reviewed by the DSMC.

For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria as a SAE, will be collected and reported.

Expected AEs includes the following:

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

In addition, small risks of allergic reactions are associated with the intravenous administration of gadolinium, the contrast agent used in MRI scans, as described in section 10.18.1.2.This contrast agent is used consistently in MRI scanning and is not limited to this trial.

If any of these symptoms are accompanied by events consistent with the definition of an SAE as specified above, then the event will be considered an SAE.

The Trial Coordinator, Principle Investigator or Chief Investigator should be informed of any SAE within 24 hours.

All SAE report forms must be completed and the SAE logs updated. All SAEs must be followed up until a resolution is reached (i.e. recovered, recovering, recovered with sequelae, fatal, not recovered or unknown).

Local sites may have specific institutional protocols for reporting SAEs, which should be followed in addition.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

16.3.7 Evaluating AEs and SAEs

16.3.7.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. Degree of severity and change in severity will be recorded by means of National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

An event that is classified as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

16.3.7.2 Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the CIB and or Product Information, for marketed products, in the determination of his/her assessment.

16.3.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the PI of the study, on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

The PI may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the PI will be provided with any post-mortem findings.

New or updated information will be recorded on the originally completed SAE CRF, with all changes signed and dated by the investigator or designate. The updated SAE CRF should be resent to the PI.

16.3.9 Prompt Reporting of SAEs

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to the PI (CURC) within 24 hours.

16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI

The Site Investigator must immediately inform the PI (CURC) of all SAEs (within 24 hours) at the following fax number: 1-416-480-6121.

The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing addresses is as follows:

Dr. Laurence Klotz
c/o Marlene Kebabdjian
Sunnybrook Health Sciences Centre
2075 Bayview Avenue A304
Toronto, Ontario M4N 3M5 Canada
Phone: (416) 480-6100 ext 2890
E-mail:Laurence.Klotz@sunnybrook.ca
Marlene.kebabdjian@sunnybrook.ca

16.3.9.2 Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to the PI within 24 hours. The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed

by the investigator (or designee), and forwarded to the PI within the designated time frames. If the investigator does not have all information regarding as SAE, he/she will not wait to receive additional information before notifying the PI of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 16.3.6.2.

16.3.10 Post-study AEs and SAEs

If the investigator learns of any SAE at any time after a subject has been discharged from the study, and such event(s) is (are) reasonably related to the study intervention, the investigator should promptly notify the PI (CURC).

17. Study Administration

17.1 Regulatory and Ethical Considerations

An important consideration is that men are being randomized to one of two biopsy techniques when it is not known which will be more effective in diagnosing clinically significant prostate cancer. Both diagnostic tests are currently used in everyday clinical practice at the institutions involved in the trial. Though systematic TRUS guided biopsy could be considered standard of care, there is enough evidence to support the concept that MPMRI-targeted biopsy may be as effective, if not more so, than systematic TRUS guided biopsy[27]. This study aims to confirm this.

17.1.1 Ethical Conduct of the Study and Ethics Approval

The PI and each participating site will obtain approval to conduct the study from the Research Ethics Board (REB) prior to initiating the study.

Participating sites from Ontario will use the Ontario Cancer Research Ethics Board (OCREB) as their Board of Record.
This study will be conducted in accordance with 'good clinical practice' (GCP) and all applicable regulatory requirements, including where applicable, the 2013 version of the Declaration of Helsinki.

The investigator is responsible for ensuring that this protocol, the site's informed consent form and any other information that will be present to potential subjects are reviewed and approved by the appropriate REB. The investigator agrees to allow the REB direct access to all relevant regulatory documents. The PI will provide the site investigator(s) with relevant document(s)/data that are needed for REB review and approval of the study. Before CRFs can be shipped to the site, the PI must receive copies of the REB approval, the approved informed consent form and any other information that the REB has approved for presentation to potential subjects.

If the protocol, the informed consent form or any other information that the REB has approved for presentation to potential subjects is amended during the study, the site investigator(s) is responsible for ensuring the REB reviews and approves, where

applicable, these amended documents. The site investigator(s) must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining the REB approval of the amended form before new subjects consent to take part in the study suing this version of the form. Copies of the REB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the PI promptly.

17.1.2 Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

The subject's consent to participate in the study should be obtained after a full explanation has been provided of the procedures to be given. Subjects should be given sufficient time (at least 24 hours) after being given the study subject information sheet to consider and discuss participation in the study with family and friends.

A contact number will be given to the subject should he wish to discuss any aspect of the study. Following this, the clinician will determine that the subject is fully informed of the study and their participation, in accordance with Good Clinical Practice Guidelines. Subjects will always be asked to sign a consent form. One copy will be given to the subject, one copy will be kept with subject's hospital notes and one copy should be kept in the local investigator's file.

17.1.3 Investigator Reporting Requirements

The investigator is responsible for reporting SAEs to the REB in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the REB.

17.2 Study Monitoring

This study will be monitored by a CRA. The CRA will contact the sites by telephone on a predetermined basis and would conduct a monitoring visits based on the data entered in the EDC and queries.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and

any amendments), GCP and all applicable regulatory requirements

The investigator agrees to allow CRA personnel direct access to all relevant documents and to allocate his/her time and the time of his/her staff to CRA personnel to discuss findings and any relevant issues.

17.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, regulatory agencies may conduct a regulatory inspection of the study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditory/inspector to discuss findings and any relevant issues.

17.4 Study and Site Closure

Upon completion of the study, the site investigator(s) will conduct the following activities:

- Return of all study data to the Sponsor (CURC)
- Submission of all study data and data queries to OCOG
- Review of site study records for completeness

In addition, the Principal Investigator has the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including but not limited to, safety or ethical issues or severe non-compliance. If the PI determines such action is needed, the PI will discuss this with the site investigator (including the reasons for taking such action) at that time. When feasible, the PI will provide advance notification to the site investigator of the impending action prior to it taking effect.

Individual site Investigators may also terminate their participation in the study at any time. If the investigator determines such action is needed, the investigator will discuss this with the PI(including the reasons for taking such action) at that time. When feasible, the investigator will provide advance notification to the PIof the impending action prior to it taking effect.

The PI will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the REB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the PI. In addition, the investigator has the responsibility to return any used/unused clinical supplies.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the PI.

17.5 Records Retention

Following closure of the study, the site investigator(s) must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff.

The site investigator(s) will retain study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study as dictated by any institutional requirements or local laws or regulations of Health Canada standards/procedures; otherwise, the retention period will default to 25 years.

The site investigator(s) must inform the PI of any changes in the archival arrangements, including but not limited to the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. The PI should be informed of this change if it affects their access to the information in case of an audit.

17.6 Data Management

Subject data are collected by the investigator or designee using the CRF within an Electronic Data Capture (EDC) system. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures. Database lock will occur when data management quality control procedures are completed.

17.7 Publication

The results from the study will be analyzed and published as soon as possible and is appropriate. All study-related communications can only be presented or published after approval from all relevant members involved in the trial.

All publications shall include appropriate indication named authors as agreed on by the members involved in the trial. For the main study reports, senior and first authorship will be determined by agreement of the Chief Investigator, the Principle Investigator at time of manuscript drafting. Authorship will be based on recommendations of the International Committee of Medical Journal Editors (www.ICMJE.org) where all authors meet the following for criteria:

13. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
14. Drafting the work or revising it critically for important intellectual content; AND
15. Final approval of the version to be published; AND

16. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people.The clinical trials.gov registration number that will be allocated to this trial will be attached to any publications resulting from this trial.

Trial funding agencies (OICR, PCC and collaborators as appropriate) will be acknowledged in all publications.

The members of the trial steering committee will be listed with their affiliations in the acknowledgements/appendix of the main publication.

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Appendices

Appendix 1: Time windows for data collection

For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3
For details on time windows permitted for each trial intervention to be completed please see Table 5 below.

Table 5: Details of time windows permitted for all trial interventions.

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.

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 30-day 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. To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy. To be returned by post or at follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. 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.
Telephone reminder	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
Visit 4 Follow up for results And treatment Decision EQ-5D-5L Questionnaire	 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. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision. To be completed
Visit 5 **26 week follow up**	• Vitals, DRE • PSA • Optional blood
Visit 6 1 year follow up 52 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. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
Visit 7 **78 week follow up**	• 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.).

11651
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Appendix 2: MPMRI Reporting Proforma

Date of MRI scan: ☐☐☐☐☐☐☐☐☐
day month year

Date of Report: ☐☐☐☐☐☐☐☐☐
day month year

Reporting Radiologist:

Form Completion Instructions:

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.

IMPORTANT SUBMISSION INSTRUCTIONS:

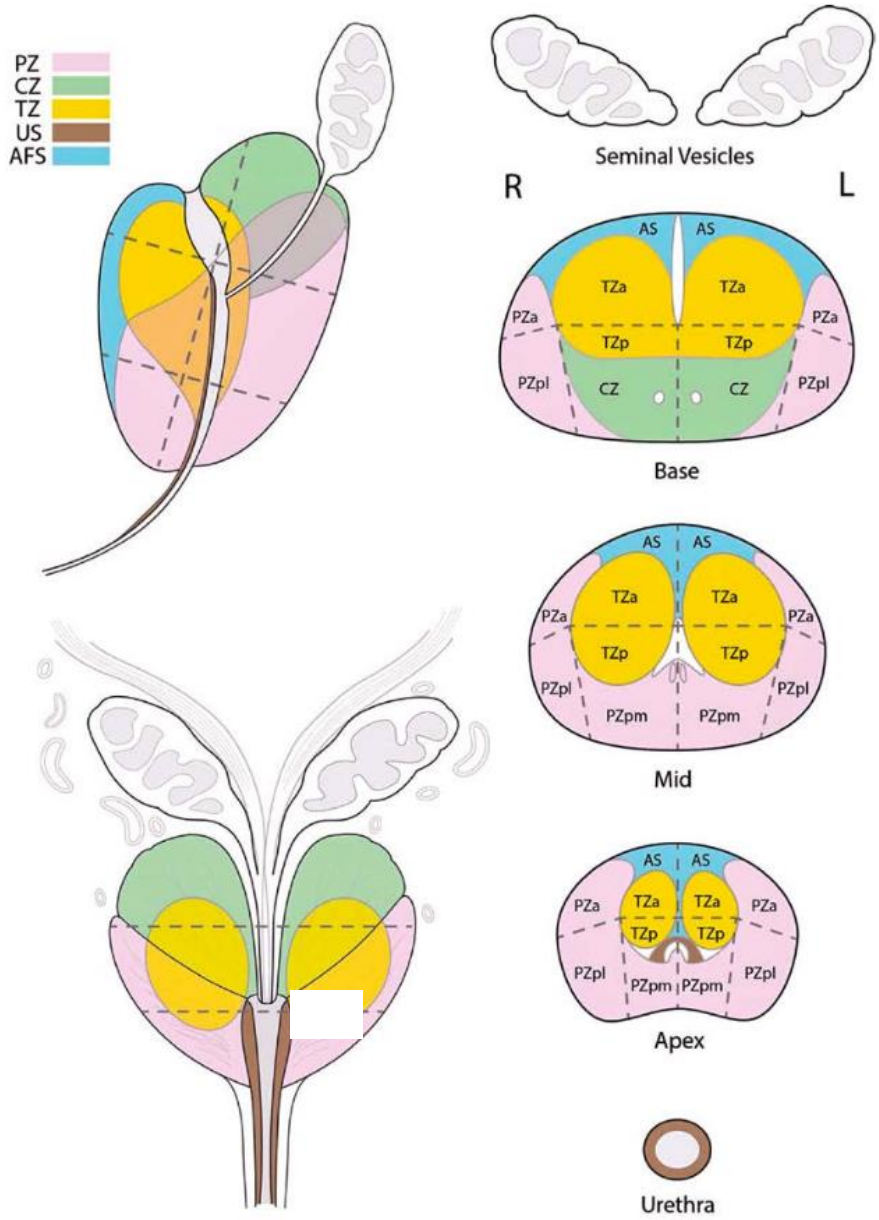
Please send this completed case report form and a DVD with the images AND completed MRI Report to:

Marlene Kebabdjian
Sunnybrook Health Sciences Centre
Urology Research, A304
2075 Bayview Avenue, A304
Toronto, Ontario, M4N 3M5

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…)



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**

If image quality is not good please comment:

_____

_____

_____

How to record locations

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

Number of candidate tumor sites:_____ I

If none, please proceed to Section B

Section A:

Target 1 *(Highest Pi-Rads score and then largest):*

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal _____

Target 2:

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal

There are more than 3 targets seen (Y/N): _____
If yes give describe:
_____
_____
_____

Section B:

LSV invasion: ❑ No ❑ Yes ❑ Equivocal	**RSV invasion:** ❑ No ❑ Yes ❑ Equivocal
Adenopathy: ❑ No ❑ Yes ❑ Equivocal	**Worst PI-RADS Score: _____**

Other Findings:
_____
_____

_____ cm	(SI) x	_____ cm	(AP) x	_____ cm	(LR)	**Volume:**	**_____**	cc

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**

If image quality is not good please comment:

_____
_____
_____
_____

Number of candidate tumor sites: _____

If none, please proceed to Section C

There was a change in lesions number or rank when adding DCE sequence: ❑ No ❑ Yes

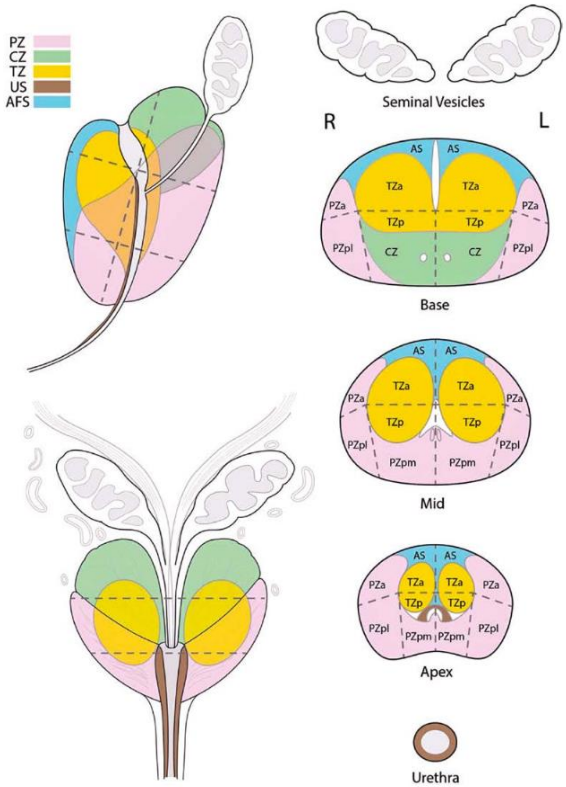
If Yes, please give the correspondence between Target numbers with and without DCE (i.e. Target 1 without DCE = Target x with DCE) and **fill in all fields below to avoid confusion. Also draw lesions on diagram below again**

Also draw lesions on diagram on next page again.

Correspondence:

Old T1 = New T___ Old T2 = New T___ Old T3 = New T___

If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2…)



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):___

Mean ADC: _____ Min ADC – single voxel:_____ mm^2/s $x10^{-6}$

Size: ___x___ x ___mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____,_____,_____,_____

_____,_____,_____,_____

Extraprostatic extension: ❑ No ❑ Yes ❑ Equivocal

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:_____ mm^2/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:_____ mm^2/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

Adenopathy: ❑ No ❑ Yes ❑ Equivocal	**Worst PI-RADS Score: _____**

Other Findings:

_____

_____

Safety:

Was there an immediate reaction to Gd contrast injection: ❑ No ❑ Yes

If yes, please give details:

_____

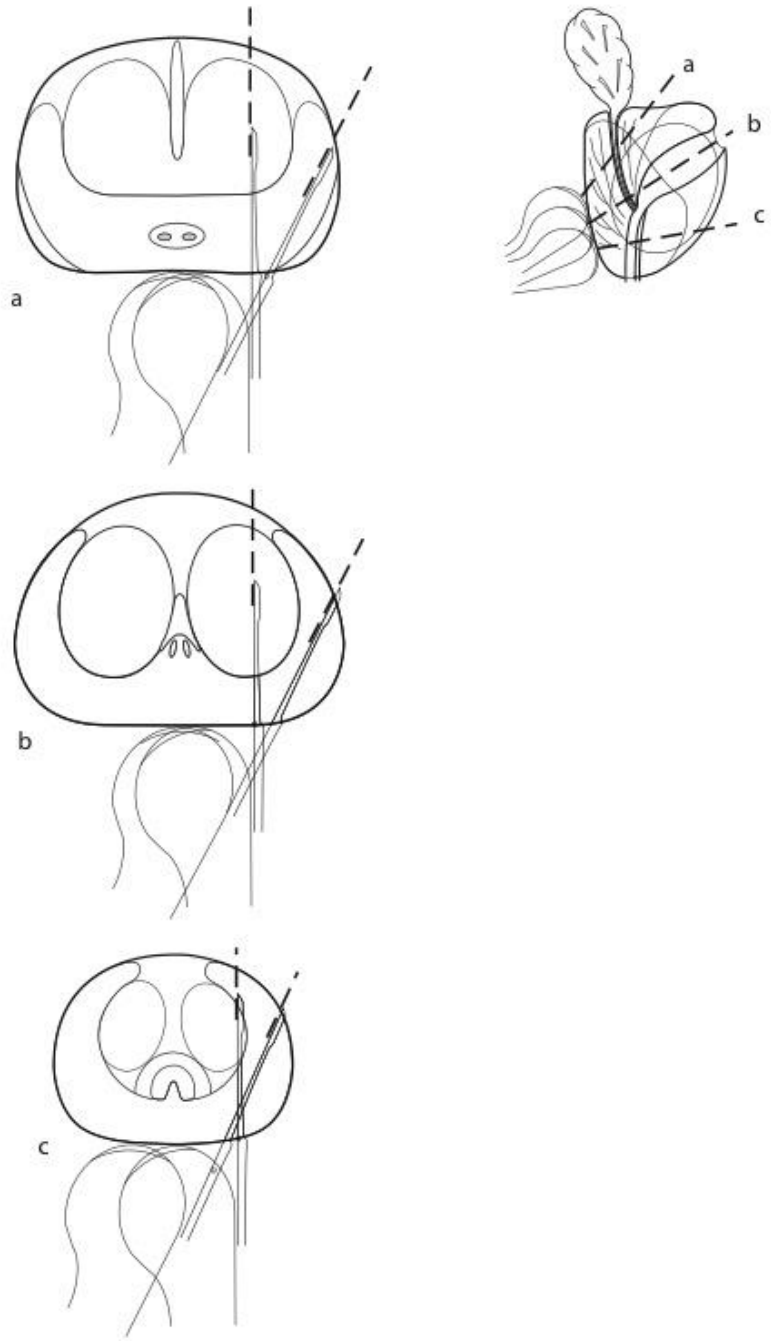
_____

Will subject require an TRUS/MRI-fused biopsy (Pi-Rads >=3)?	**❑No (PI-RADS 1, 2)**	**❑Yes (PI-RADS 3, 4 or 5)**

Appendix 3: Example of systematic TRUS guided biopsy schema

Figure depicting 12-core systematic TRUS guided biopsyschema that sites are recommended to follow. Axial/coronal sections of a prostate gland (left) showing biopsy courses of the 12 biopsies performed under ultrasound guidance with an end fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,

12017 apex.F romHaffner*et al*[37].



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 ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

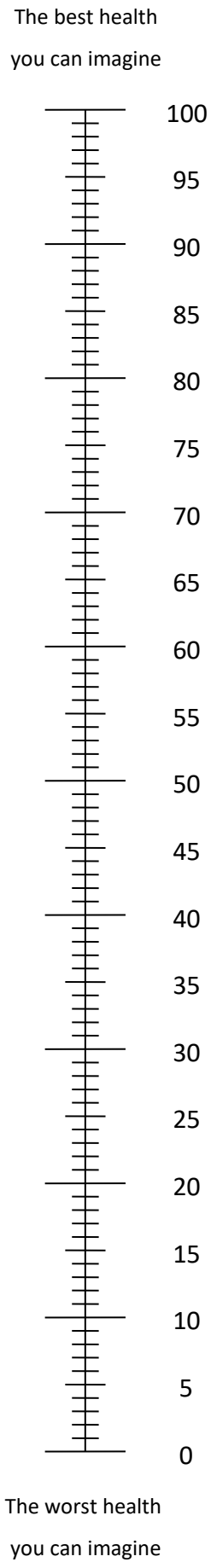
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐



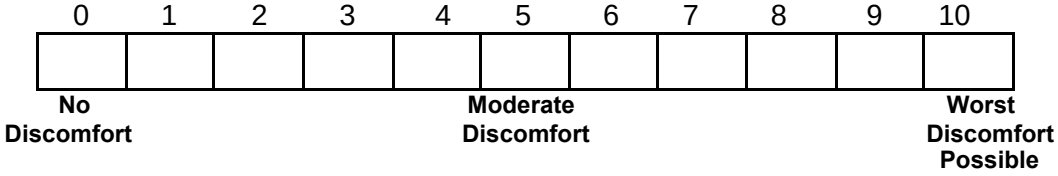
12075 # Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

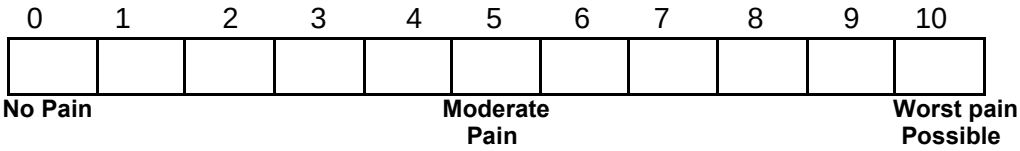
Please ask the patient to fill this out after the biopsy, before they leave the department.

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?



2. Overall, how much pain did the biopsy procedure cause you?



Please complete the next page of questions

12076
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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

12079 # 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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

12080

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 ☐ 1 No ☐ 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
	☐ 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 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 ☐ 1 No ☐ 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
	☐ 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 biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes ☐ 1 No ☐ 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
	☐ 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

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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
☐	☐	☐	☐

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
e.g. ciprofloxacin	*500mg*	*2*	*3*

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"):*

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"):*

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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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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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April 10, 2018

PRECISE Trial: Amendment 4
Protocol version 5.0: 10 April 2018
Summary of Changes

Minor administrative changes were made throughout the current protocol to avoid discrepancy. Minor errors were corrected.
The following changes were made:

- **Version date to reflect:** Amendment 4: 10 April 2018
- **The following has been amended throughout the protocol:** *Inclusion criteria:* Addition of stipulation: Serum PSA ≤ 20ng/ml; within 3 months of randomization
  Rationale: *to clarify the need for PSA at screening, without duplicating PSA bloodwork*

- **ADDITION of EOS/Withdrawal visit on Table 1, 2, 3:** *now includes:* EOS/Withdrawal visit, documenting all requirements for this visit.
  Rationale: to clarify/separate what is needed at a withdrawal visit, and EOS study visit independent of the study completion.
- **ADDITION of stipulation to section 10.11.1 Indications for biopsies off protocol:**
  now includes: Subjects should continue to be followed with semi-annual PSA and DRE (not required, at the discretion of the PI).
  Rationale: to clarify that the DRE is not mandatory and left up to the discretion of the PI.
- **ADDITION of tumour bank information to section 10.12.2 Correlative Science Component:**
  the following has been added: Biomaterial will be stored, anonymized, at the Ontario Institute of Cancer Research (OICR) Biobank, under the direction of Dr. John Bartlett. Dr. Bartlett is the Program Director, Diagnostic Development, at OICR. The material will not be used for commercial purposes. No personal information will be kept at OICR. Personal identifying information on the patients in the PRECISE trial is held by the Ontario Clinical Oncology Group (OCOG), who are performing the data management function for the study. Access to the biomaterial will be under the control of the PRECISE steering committee. Access has already been approved for the Translational Research in Prostate Cancer (TRIPC) research group led by Dr. Paul Boutros. Future researchers interested in using the biomaterial will apply to the Precise steering committee for approval, based on the scientific merit of the study.
  Rationale: to provide more information regarding the storage of samples at OICR.
- **ADDITION of vendor information to section 10.12.2 Correlative Science Component:**
  The following has been added (3D Signatures): The urine samples will be used to establish the sensitivity of the procedures and the precision of the analytic algorithyms to identify those with significant prostate cancer.

The long term goal of the project is to develop a non-invasive methodology that can be used to identify genetic alterations that identify a group of patients at high risk for clinically significant prostate cancer.
Rationale: to provide more information regarding the 3D Signatures collection purposes.

July 24, 2018

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**: **Pr**ostate **E**valuation for **C**linically **I**mportant disease: MRI vs **S**tandard **E**valuation procedures. (PRECISE)

Date: 10 April 2018

Version 5.0

Sponsor:
Canadian Urology Research Consortium (CURC)

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Confidential

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: 10 April 2018
Version 5.0

The signatory agrees to the content of the final clinical study protocol as presented.

Signature: _____

Name: _____

Title: _____

Date: _____

Site name: _____

12228

12229 ## 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	**Primary Objective** 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. **Secondary Objectives** 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. 54. Proportion of men in each arm with clinically insignificant cancer detected. 55. Proportion of men in each arm with Gleason ≥4+3 detected. 56. Proportion of men in MRI arm who avoid biopsy. 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. 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). 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 60. Proportion of men with post-biopsy adverse events 61. Health-related quality of life scores. 62. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy. 63. To determine the cost per diagnosis of cancer. 64. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield 65. 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) 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, all inclusion criteria must be met. 21. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy; 22. ≥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. 23. Serum PSA ≤ 20ng/ml; within 3 months of randomization 24. Fit to undergo all procedures listed in protocol; 25. Able to provide written informed consent.
Exclusion Criteria	Men who meet the following criteria at the time of screening will be excluded: 25. Prior prostate biopsy; 26. Prior treatment for prostate cancer; 27. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min); 28. Contraindication to prostate biopsy; 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; 30. 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. All subjects 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. All subjects in ARM A will complete an EQ-5D-5L questionnaire and an immediate post-MRI/TRUS Fusion Biopsy questionnaire following the MRI. Subjects in ARM A who do not receive a subsequent biopsy will complete an EQ-5D-5L questionnaire when they find out the results of the MRI 3 weeks (± I 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. Subjects in ARM A who do receive a MRI-targeted biopsy 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 (± I 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. All subjects in ARM B 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 (± I 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.
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 ≥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

Abbreviations:

ADC	Apparent diffusion coefficient
CI	Confidence interval
CRF	Case report form
DSMC	Data Safety and Monitoring Committee
DRE	Digital rectal examination
DWI	Diffusion weighted imaging
DCE	Dynamic contrast enhancement
EDC	Electronic Data Capture
ITT	Intention to treat
MCCL	Maximum cancer core length
MPMRI	Multi-parametric MRI, used interchangeably with MRI in this protocol.
MPMRI-TB	Multi-parametric magnetic resonance image-targeted biopsy of the prostate
MRI	Magnetic resonance imaging, used interchangeably with MPMRI in this protocol
MRI-TB	Magnetic resonance imaging targeted biopsy
MRS	Magnetic resonance spectroscopy
PI	Principal Investigator
PI-RADS	Prostate Imaging Reporting and Data System
PTC	Permission to Contact
PSA	Prostate specific antigen
REB	Research Ethics Board
STARD	Standards for the reporting of diagnostic studies
TRUS	Trans-rectal ultrasound
TSC	Trial Steering Committee
T2W	T2-weighted imaging

Definitions:

MPMRI-targeted biopsy	A biopsy technique where an MPMRI scan is used to determine the location of a suspicious target prior to biopsy.
Systematic TRUS guided biopsy	A biopsy approach where conduct of procedure is not influenced by findings on MRI imaging. Currently this is the standard of care for prostate cancer in the province of Ontario.

5. Trial summary

5.1 Aim and Rationale

The standard pathway for prostate cancer diagnosis is trans-rectal ultrasound guided (TRUS) biopsy of the prostate following an elevated PSA. TRUS guidance is performed primarily for anatomic guidance as the ultrasound poorly discriminates between cancerous and non-cancerous tissue. TRUS guided prostate biopsies are concentrated in areas of the peripheral zone, thought to harbor the majority of cancer.

An alternative pathway for prostate cancer diagnosis in men with elevated PSA is to perform multi-parametric magnetic resonance imaging (MPMRI) to localize cancer. This information is used to direct a subsequent biopsy, known as an MRI-targeted biopsy. MRI-targeted biopsy has been shown in preliminary studies to detect a similar or greater amount of clinically significant cancer than systematic TRUS guided biopsy and has several other potential advantages including: the ability to differentiate between clinically significant and insignificant cancer, reducing unnecessary biopsy and fewer numbers of biopsy cores, reducing biopsy-related side-effects.

A 'clinically insignificant cancer' is cancer that is unlikely to progress or to affect an individual's life expectancy and therefore does not warrant treatment. However when diagnosed with low grade cancer that is likely to be insignificant, a large proportion of subjects request treatment in case a more significant cancer is present[1].A challenge in this area is that subjects are typically not aware that their cancer is clinically insignificant, and often view the early diagnosis and aggressive treatment they have been subjected to as life-saving.

A prostate cancer detection procedure that differentiates clinically significant cancer from clinically insignificant cancer is therefore a major unmet need.

The potential implications of this trial include:

- 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

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 (± I 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 for30-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 prostectomy) 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 be followed with serial PSA testing; PSA levels will increase if cancer is present. In both arms in addition to serial PSA testing all men who have no cancer found at systematic biopsy or targeted biopsy, have a negative MRI or enter active surveillance will have a followup MRI at 24 months. If a new Pi-Rads >=3 lesion is found on the followup MRI or there is progression of an existing lesion this lesion will undergo targeted biopsy as part of standard of care.

As recruitment is expected to take up to 24 months (see section 7.6) and each subject will be followed up for two years, the estimated maximal duration of this study is four years in total. The primary endpoint will be reached at approximately 2 years after study initiation.

5.3 Participating Sites

This is a multi-centre study. Institutions participating in the study must be able to perform both the systematic TRUS guided biopsy and the MRI-TB. They must be able to randomize men to one of these two diagnostic tests.

We expect to recruit 3-6 subjects per month per site, based on recruitment rates from previous diagnostic trials performed by the centers involved. A typical centre sees 15-30 eligible men per month. We expect 5recruitment sites, with 100 men to be recruited at each site over an 18-24 month period (see section 7.6).

5.4 Study outcomes

5.4.1 Primary outcome

To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.

5.4.2 Secondary outcomes

53. To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$ 7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy.
54. Proportion of men in each arm with clinically insignificant cancer detected.
55. Proportion of men in each arm with Gleason $\geq$4+3 detected.
56. Proportion of men in MRI arm who avoid biopsy.
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.
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).
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 $\geq$ 7 cancer detected on a repeat biopsy (systematic or

targeted) by 2 years.
60. Proportion of men with post-biopsy adverse events
61. Health-related quality of life scores.
62. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
63. To determine the cost per diagnosis of cancer.
64. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield
65. To determine if a radiologist Likert score not based on PI-RADS has a better target yield than PI-RADS alone

6. Background

6.1 Prostate cancer diagnosis

Prostate cancer is the most common male cancer in the Western world with an incidence of 24,000 new cases in Canada and 233,000 in the USA[5, 6]. It is the second most common cause of cancer death in European and North American men, with 2,900 deaths per year in Canada and 90,000 deaths per year in Europe[5, 6]. The incidence of the disease has increased by 22% over the last decade due to the widespread use of the prostate specific antigen (PSA) blood test; by 2030 the Canadian Cancer Society estimates the incidence of prostate cancer will be 42,225.As prostate cancer is a histopathological diagnosis, men with raised PSA or abnormal digital rectal examination (DRE) are usually referred for a prostate biopsy. Over one million prostate biopsies are performed in North America and Europe every year[7].

6.2 Clinically significant versus clinically insignificant prostate cancer

Clinically significant prostate cancer is cancer that is likely to progress and affect a man's life expectancy if left untreated. Though there is no universally agreed upon definition on what histological parameters define clinically significant cancer, most agree that larger volume cancers with a higher Gleason grade are more likely to be clinically significant; an historically accepted threshold is a tumour volume above 0.5milliliters or any Gleason pattern 4 or 5 cancer[8-11].

This definition is likely overly stringent. An increasing consensus views all Gleason pattern 3 (Gleason score 6) cancers and many Gleason3 plus small amounts of pattern 4 cancers as likely insignificant[12]. About half of newly diagnosed prostate cancers fall into this category, and are unlikely to progress and affect a man's life expectancy if left untreated. The widespread use of PSA testing has led to more men being diagnosed with insignificant cancer that does not warrant any treatment [13]; however they are typically monitored closely with active surveillance. This is associated with anxiety about harbouring untreated cancer, and the negative psychological effects of being a 'survivor' [14]. Men diagnosed with low risk prostate cancer are also subjected to serial biopsies and other tests, requiring long term follow up. Further, many men with low risk disease receive radical treatment, either

because their physicians are not advocates of surveillance or because of anxiety [15].These treatments may expose them to morbidity including urinary incontinence and erectile dysfunction [16]. Thus, diagnostic tests that clearly differentiate clinically significant cancer from clinically insignificant cancer will help reduce patient anxiety, alleviate further testing, and avoid radical treatment and associated morbidities.

6.3 Current standard of care: systematic TRUS guided biopsy

The European association of Urology and NICE guidelines recommend systematic TRUS guided biopsy as the current standard of care for the diagnosis of prostate cancer [4, 17].This procedure has several advantages: it can be delivered quickly in an outpatient clinic under local anesthetic, it can be offered at most Urology centres, and the expertise is widely distributed.

Limitations of systematic TRUS guided biopsy are as follows: the procedure requires the operator to take 10-12 samples in the peripheral zone, where it is thought that the majority of prostate cancer can be found (See Appendix 2)[18]. The ultrasound guidance used during the procedure is useful for visualizing the prostate and assessing the location of the needle within the prostate but has a poor ability to discriminate tumour from normal tissue [19], which means that the systematic TRUS guided biopsy can potentially miss some cancer. Systematic TRUS guided biopsy has been shown to have a high false negative rate of 30-45% [20, 21].As a systematic TRUS guided biopsy is not specifically targeted to the location of a suspected significant cancer, there is also a greater chance that a significant cancer may be missed.

6.4 The emerging role of MRI in prostate cancer diagnosis and treatment

6.4.1 The role of imaging in prostate cancer diagnosis

Although used to diagnose many other solid organ cancers such as breast, renal and colorectal cancer, imaging is not part of the traditional prostate cancer diagnostic pathway. Imaging in prostate cancer, is typically limited to stage the disease following histological diagnosis. Magnetic resonance imaging (MRI) is used in many centres to assess for extra-capsular extension during prostate cancer staging. In the past five years however, the possibility of using multi-parametric MRI (MPMRI)for diagnosing prostate cancer prior to biopsy, has generated tremendous interest[22].

6.4.2 Limitations of early MRI studies in prostate cancer

Early literature reported conflicting results on the ability of MRI to detect prostate cancer. A recent systematic review of the literature showed that the quality of studies evaluating MRI was disappointing [22]. Limitations of reported studies include:

- **Poor reporting standards**. Many early studies failed to closely follow published guidelines for the standards of reporting of diagnostic studies (STARD) [23].

- **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.

6.4.3 Emerging role of MRI in the diagnosis of prostate cancer

Since the publication of these early reports, improvements in diagnostic technology have changed the field and more evidence supporting the role of pre-biopsy MRI has been published. Magnetic field strength has increased from 0.5 Tesla to 1.5 Tesla and 3.0 Tesla. The introduction of shorter pulse sequences allows faster image acquisition and the addition of functional sequences including magnetic resonance spectroscopy (MRS), diffusion weighted imaging (DWI) and dynamic contrast enhanced imaging (DCE). Clinicians are increasingly aware of and are accounting for biopsy artifacts.

The combination of anatomical sequences (T2-weighted imaging) and functional sequences (MRS and/or DWI and/or DCE) is termed multi-parametric MRI. Combining the sequences improves the validity of the test [25, 26].

A systematic review determined that 60% of men with a clinical suspicion of prostate cancer will have a suspicious area identified on MRI [27]. In studies correlating MRI with radical prostatectomy specimens, MRI demonstrates sensitivity, specificity, positive predictive value and negative predictive value of 90%, 88%, 77% and 95% respectively for the identification of prostate tumours greater than 0.5ml [28]. Systematic reviews and meta-analysis of recent studies have demonstrated sensitivity and specificity consistently between 70-90% for the detection of clinically significant prostate cancer[26, 29-31].

As a result of this accumulating evidence, MRI is increasingly used in clinical practice in the diagnostic pathway for prostate cancer. The results of MRI can influence the decision to perform a prostate biopsy, as well as the technique and targeting used during the biopsy.

MRI has tremendous potential to enhance the outcome of men on active surveillance. 30% of men diagnosed with low risk prostate cancer (Gleason 6, PSA < 10) harbor higher-grade disease. This occult high-grade disease "*the wolf in sheep's clothing",* is responsible for the 3-5% of prostate cancer deaths that have been reported in long term surveillance series that did not incorporate MRI[32, 33]. The early use of MRI in men on surveillance has the potential both to reduce the need for confirmatory biopsies, and to identify the *wolf in sheep's clothing* earlier, prior to the development of metastasis.

This was the rationale for the very successful ASIST study, which recently successfully completed its accrual. The ASIST study was led by Dr. Klotz (PI), and sponsored *in toto* by the Ontario Institute of Cancer Research. The project was managed by the Canadian Urology Research Consortium (CURC). It randomized 273 men recently diagnosed with low risk prostate cancer, on surveillance, between systematic confirmatory biopsy and MRI with targeted and systematic biopsy. The primary end point, similar to PRECISE, was the proportion of men in each group with Gleason 7 or higher prostate cancer. The study had numerous secondary end points and correlative science components. We expect to report the initial results by 3Q 2016.We believe that the success and potential impact of the ASIST trial has created strong momentum to proceed with the PRECISE trial, which has even greater potential to substantially influence prostate cancer screening and diagnosis.

6.4.3.1 MRI can influence the decision to perform a prostate biopsy

With reported negative predictive values of 95% [28, 34,35], MRI can help determine whether a prostate biopsy is necessary; if the MRI does not identify a suspicious area the biopsy can be avoided. Using MRI, 40-50% of men referred with clinical suspicion of prostate cancer might avoid a biopsy [27]. The recent National Institute for Health Research (NIHR) Health Technology Assessment (HTA) report [11] acknowledged the value of MRI in this context. The NIHR HTA report suggests that using MRI to reduce the number of men who undergo biopsy, can be cost effective despite the costs associated with MRI[11]. Cost savings for the publically funded health care system accrue as a result of reduced number of biopsies and costs of attendant complications, and reduced treatment of clinically insignificant cancer.

6.4.3.2 MRI can influence the biopsy technique

For men who receive a MRI scan and then go on to biopsy of the prostate, the MRI information is used to influence the prostate biopsy technique. This is known as MRI-targeted biopsy (MRI-TB) of the prostate, and can be carried out in a number of ways.

The biopsy operator can use the MRI images or report to direct biopsies into the area of the prostate where the tumour is located. The location of the tumour on the MRI (carried out in advance) is registered to the real-time ultrasound images with the use of software (software assisted registration or image-fusion) or without the use of software (visual registration or cognitive registration), while the prostate is visualized in real-time using trans rectal ultrasound. MRI-TB can also be conducted directly "in-bore", where the biopsy is conducted within an MRI scanner where the

target identified on MRI during a prior diagnostic scan is biopsied using guidance from serial MRI scans during the biopsy procedure, performed in an open magnet.

For the PRECISE study, the biopsy will be performed using an image fusion-targeting device. Two devices have been FDA approved: the Artemis, made by Eigen, and the Urostation, made by Koelis. These devices import the MR target into the TRUS image, and direct the biopsy needle into the target.

6.4.4 Prostate cancer detection rates of MRI-targeted biopsy are similar to other methods

A systematic review determined that 60% of men with a clinical suspicion of prostate cancer will have a suspicious area identified on MRI [27]. One study found that a prostate biopsy strategy using only MPMRI-targeted cores resulted in the same detection rate of clinically significant cancer as 20-sector transperineal biopsies[36]. Other studies also show that a targeted-alone approach would detect a similar amount of clinically significant cancer when compared to a 10-12 core systematic TRUS guided biopsy[37]. A targeted-alone approach detects 17% less clinically insignificant cancer compared to systematic TRUS guided biopsy[38].

The detection rates achieved with a targeted-alone biopsy strategy require fewer biopsy cores than systematic TRUS guided biopsy. Thus on a per-core analysis, targeted biopsy is more efficient than systematic TRUS guided biopsy, with cancer detected in 30% of all targeted cores in a pooled analysis of 1252 targeted cores compared to 7% of all systematic TRUS guided biopsy cores in a pooled analysis of 5441 systematic cores [27]. As well, the MRI targeted biopsy provides more material for histopathological analysis as the maximum cancer core length obtained from targeted biopsies can be greater than that obtained from systematic biopsies[37].

Robust comparative evidence from randomized controlled trials is needed to determine if MRI scans can improve our ability over systematic TRUS guided biopsy to diagnose clinically significant cancer and our ability to avoid detecting clinically insignificant cancer.

6.4.5 Limitations of studies reporting MPMRI-targeted prostate biopsy

Despite encouraging results of MRI-targeted biopsy, it is not yet part of routine clinical practice for prostate cancer diagnosis. Most existing studies have cohort study designs which make interpretation difficult as they do not conform well to STARD [23] recommendations [27]. Limitations of these studies include:

- **Broad definition of the study population.** The cancer detection rates depend on the prevalence of the condition in the population being investigated. This varies amongst men with no prior biopsy, prior negative biopsy and prior positive biopsy. In many studies the detection rates are not attributable to a clearly defined population.
- **MRI conduct and reporting.** The detail in which MRI is conducted and interpreted varies greatly amongst published studies.

- **Reporting of cancer detection.** The cancer detection by systematic and targeted cores is not always presented separately and cancer detection is not always specified by clinical significance. These are both essential in order to evaluate the technique.

There is a strong need for a randomized controlled trial comparing MRI-targeted biopsy to systematic TRUS guided biopsy so that the role of this technique in clinical practice can be established.

6.5 Novelty of PRECISE

PRECISE is the first randomized study in biopsy-naïve men in which men are randomized to an MRI targeted-alone biopsy arm (i.e. no biopsies of MR-normal areas of prostate and no biopsy at all if the MR is non-suspicious) or a systematic TRUS guided biopsy arm. This will allow evaluation of the efficacy of the MRI-targeted biopsy approach in the detection of clinically significant cancer. In order to evaluate a biopsy technique that could replace standard of care, the standard of care test, i.e. systematic TRUS guided biopsy, must be included in one of the arms to allow a direct comparison.

Other constituencies with an interest in MRI in prostate cancer (University College, London; Lille, France; Oslo, Norway; Heidelberg, Germany; New York University, New York) have considered similar studies, however in these centres MRI has largely replaced systematic TRUS guided biopsy, notwithstanding the lack of evidence to date. As a result, these centres have acknowledged that randomization to a standard biopsy arm (ie systematic TRUS guided biopsy) would no longer be feasible as equipoise has been lost.

In Ontario, and in almost all other Canadian provinces, prostate MPMRI is not recommended for the indication of an elevated PSA in men who have not had a biopsy. In this country, men at risk for prostate cancer, in almost all cases, proceed to a TRUS guided systematic biopsy. We believe that the opportunity to avoid a biopsy will make entry into this trial very appealing to potential candidates. Further, the barriers, both financial and physical, to obtaining a quality MRI outside of the health care system are substantial. Thus we believe men who are randomized to the systemic biopsy arm will in almost all cases proceed with biopsy avoiding significant contamination (i.e. men randomized to the systematic biopsy arm seeking out an MRI instead).

7. Trial objectives

7.1 Overall aim

The aim of this study is to assess the efficacy of MRI-targeted biopsy compared to standard of care systematic TRUS guided biopsy in the detection of clinically significant and clinically insignificant prostate cancer in men without prior biopsy. The implication of this trial is that MRI-targeted biopsy could replace systematic TRUS guided biopsy as the standard of care in the diagnosis of prostate cancer.

7.2 Hypotheses

The proportion of men with clinically significant cancer detected by MRI-targeted biopsy will be no less than that detected by systematic TRUS guided biopsy.

7.3 Primary Objective

To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$ 7) detected by MRI-targeted biopsy is no less than systematic TRUS guided biopsy.

7.4 Secondary Objectives

66. To determine whether the proportion of men with clinically significant cancer (Gleason $\geq$7) detected by MRI-targeted biopsy is greater than systematic TRUS guided biopsy.
67. Proportion of men in each arm with clinically insignificant cancer detected.
68. Proportion of men in each arm with Gleason $\geq$4+3 detected.
69. Proportion of men in MRI arm who avoid biopsy.
70. 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.
71. 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).
72. 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 $\geq$ 7 cancer detected on a repeat biopsy (systematic or targeted) by 2 years.
73. Proportion of men with post-biopsy adverse events
74. Health-related quality of life scores.
75. Proportion with Gleason grade upgrading in men undergoing radical prostatectomy.
76. To determine the cost per diagnosis of cancer.
77. To determine the impact of the addition of Gd based contrast compared to a non contrast abbreviated MRI protocol on target yield
78. To determine if a radiologist Likert score not based on Pi-Rads has a better target yield than Pi_Rads alone

7.5 Explanation for non-inferiority hypothesis

Due to the putative advantages of MRI-TB in reducing the number of men who require a biopsy, reducing the number of cores required in each man who is biopsied, more accurate representation of disease burden, less insignificant disease detected and reducing the number of men at risk of complications of biopsy, the primary outcome of detection of clinically significant cancer in each arm will be compared using a non-inferiority hypothesis. Even if a similar amount of clinically significant cancer is identified by MRI-TB to systematic TRUS guided biopsy, these

advantages would support the use of MRI-TB instead of systematic TRUS guided biopsyin clinical practice.

7.6 Anticipated timeline of study progression

The study will commence once sponsorship, ethical approval and local approvals have been obtained at a participating site and once site initiation training has occurred and a letter of site activation has been issued from the coordinating centre. Additional sites may join after the study has commenced. At this time, five sites will participate. Assuming a minimum recruitment rate of 3-6 men per site per month, recruitment will be complete by 24 months, if not sooner. If accrual is slower than expected, an additional 1-2 sites will be recruited for year 2.

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

8.Study Population

8.1 Number of Subjects

Approximately 450 men with a clinical suspicion of prostate cancer, based on PSA or results of digital rectal exam, with no prior biopsy will be eligible for participation. Subjects must satisfy all inclusion and exclusion criteria. A sufficient number will be enrolled (estimate: 450) to achieve at least 211 completed subjects per arm.

8.2 Subject inclusion criteria

In order to be eligible, all inclusion criteria must be met:

25. Men at least 18 years of age referred with clinical suspicion of prostate cancer who have been advised to have a prostate biopsy;
26. ≥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.
27. Serum PSA ≤ 20ng/ml within 3 months of randomization
28. Fit to undergo all procedures listed in protocol;
29. Able to provide written informed consent.

8.3 Subject exclusion criteria

Men who meet the following criteria at the time of screening will be excluded:

25. Prior prostate biopsy

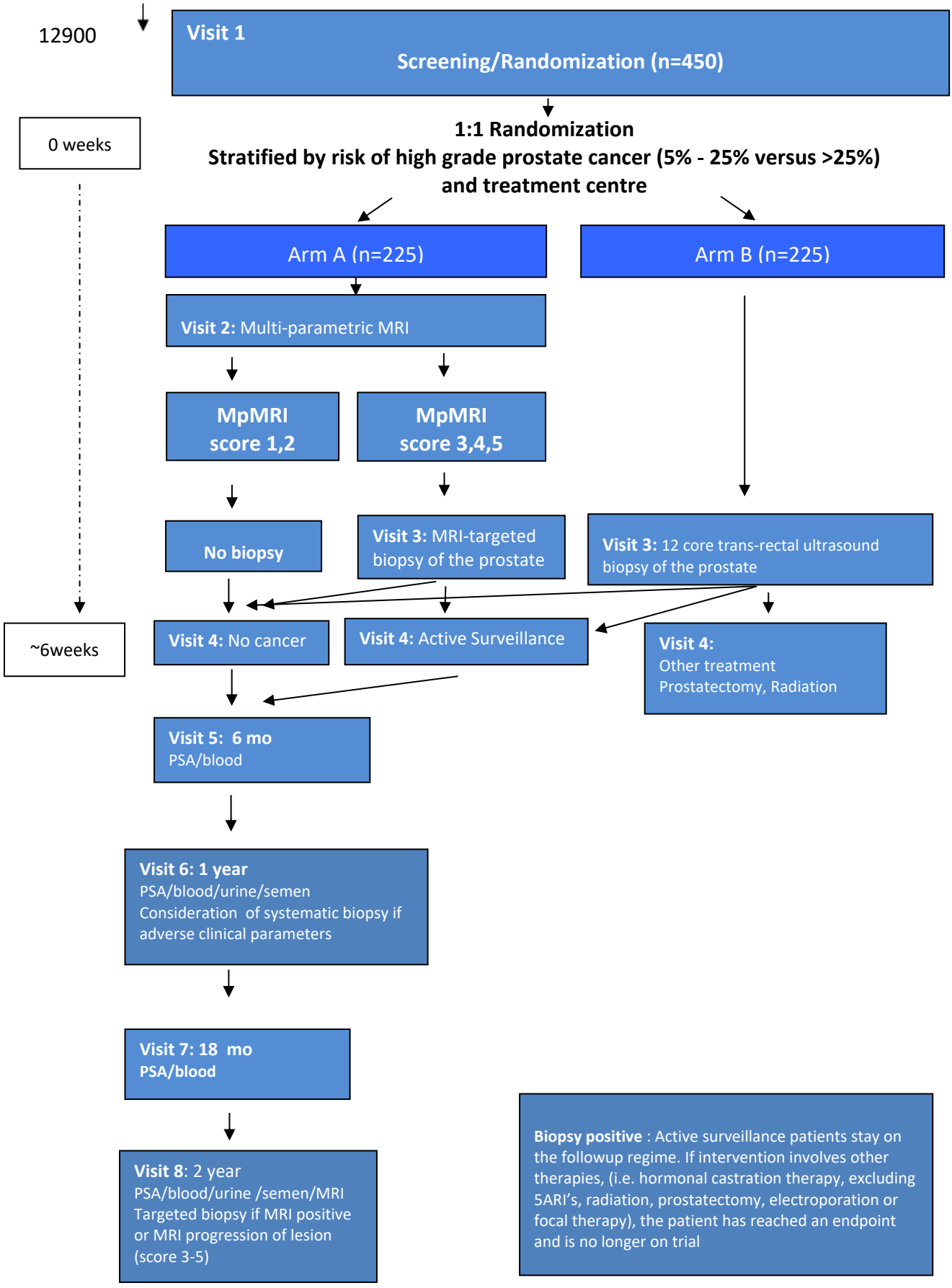
26. Prior treatment for prostate cancer
27. Contraindication to MRI (e.g. claustrophobia, pacemaker, estimated GFR ≤50mls/min)
28. Contraindication to prostate biopsy
29. Men in whom artifact would reduce the quality of the MRI, i.e. previous hip replacement surgery, metallic hip replacement or extensive pelvic orthopaedic metal work
30. Unfit to undergo any procedures listed in protocol.

9. Study design

9.1 Study design

The study is a multi-centre, open-label randomized controlled trial, with men randomized in a 1:1 ratio to one of two arms (see Trial Schema, section 9.2). Men in Arm A will undergo a MRI followed by either a targeted biopsy of suspicious areas or will be followed for two years if there is no suspicious areas identified by MRI. The unbiopsied men will have a repeat MRI at 2 years. Men in Arm B will undergo a 12-core systematic TRUS guided biopsy. All men in the study will be followed for two years or until they have had radical treatment (whichever comes first).

9.2 Study Trial Schema



9.3 Timeline of subject contact

Tables 1, 2 and 3 illustrate the three individual subject pathways possible in the trial. The individual pathway that each subject experiences is dependent on both the arm he is randomized to and results of the tests.

Table 1: ARM A: Men randomized to MRI arm who have a normal MRI and do not require 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								

[1]Urine sample will be required ONLY if the subject has agreed to the Correlative Science collection, for PRE and POST DRE urine samples. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4]Creatinine requirements as per institutional Radiology (MRI) SOPs

[5]PSA greater than 3 months of randomization, must be repeated at screening .

[6] If MRI indicates a target, biopsy must be done

[7]After treatment decision men revert to standard of care.

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								

[1]Urine sample will be required ONLY if the subject has agreed to the Correlative Science collection, for PRE and POST DRE urine samples. See correlative manual for instruction.

[2]Urine 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.

[3]Collected at baseline, and annually.

[4] tissue should be obtained if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[5] Creatinine requirements as per institutional Radiology (MRI) SOPs

[6]PSA greater than 3 months of randomization, must be repeated at screening

[7] See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue obtained for correlative science studies if subject has agreed to the Correlative Science component. See correlative manual for instruction.

[8]After treatment decision men revert to standard of care.

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12978 **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 follow up	Visit 7 18 mos	Visit 8 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								

[1]Urine sample will be required ONLY if the subject has agreed to the Correlative Science collection, for PRE and POST DRE urine samples. See correlative manual for instruction.
[2]Urine 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.
[3]Collected at baseline, and annually.
[4] Creatinine requirements as per institutional Radiology (MRI) SOPs
[5]PSA greater than 3 months of randomization, must be repeated at screening
[6] See protocol Section 10.11.1: If MRI indicates a target, biopsy must be done, and tissue obtained for correlative science studies if subject has agreed to the Correlative Science component. See correlative manual for instruction.
[7]After treatment decision men revert to standard of care.

10. Trial Interventions and procedures

The following procedures will be applied as necessary to subjects enrolled in both arm of the trial.

10.1 EQ-5D-5L Questionnaires

For all subjects enrolled in trial

Once enrolled into the study, all men will be asked to fill out an EQ-5D-5L questionnaire (Appendix 4), which is a validated 2-page questionnaire which aims to evaluate health related quality of life. It takes approximately 2 minutes to complete.

- All subjects should complete the baseline questionnaire at the screening visit before leaving the department.
- Subjects who have a normal MRI and do not require a biopsy will complete an EQ-5D-5L questionnaire at Visit 4.
- Subjects undergoing MRI-targeted biopsy or a systematic TRUS guided biopsy will be given an EQ-5D-5L questionnaire to fill out at 30 days post biopsy. The date that the subject should fill out the questionnaires should be written on top of the questionnaire. (This can also be done at Visit 4).
- All subjects should complete the EQ-5D-5L questionnaire at the 2 year follow up visit.

10.2 Multiparametric MRI imaging procedure

For subjects in Arm A only

10.2.1 MRI Protocol

A non-endorectal coil MRI will be carried out in 3.0 Tesla scanner with a pelvic phased array coil and an automated injector system with the subject in the supine position. T2-weighted (T2W), diffusion weighted (DWI) and dynamic contrast

enhanced (DCE) scans will be acquired as per the requirements set out by PI-RADS v2.

Within the specified PI-RADS 2 framework a common protocol will be formulated by a consensus of the radiologists involved in the trial at each site at a startup meeting. The highest agreed upon b-value image for DWI (at least 1400s/mm2) will be selected for all sites to ensure consistency. Similarly, the spatial resolution, contrast media, injection rates and dynamic scanning temporal resolution will be matched for all sites. An optional multi b value DWI acquisition will be undertaken as well to allow for ancillary studies into non log linear apparent diffusion coefficient (ADC) models for tumor characterization. This is summarized in an MRI Operations Manual

Subjects will be asked to follow their local standard of care MRI examination preparation instructions for the MRI procedure.

10.2.2 MRI reporting

The MRI will be reported by an experienced radiologist using the MRI Reporting Proforma(See Appendix 2) to be filed in the study folder. The MPMRI will be scored based on the PI-RADS v2 scoring system [2]. Radiologists will also provide a 5 pointLikert score for purposes of comparison. Biopsy decisions will be based on the PI-RADS scores.

Lesions in the prostate will be scored on the following scale:

- 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)

The location of the suspicious areas in the prostate should be marked on a diagram of the prostate (see Appendix2) and the sector numbers containing each suspicious area should be recorded in the case report form.

Radiologists will be blinded to the PSA.

Imaging interpretation will be carried out at each site, however ensuring consistency and quality of imaging interpretation is crucial. A central imaging site will be designated with a lead radiologist (Sunnybrook, MH). A single radiologist at each site will perform the interpretation of all images for that site. The designated radiologist must have experience of interpreting at least 200 MRI's using PI-RADS 1 or 2.A startup meeting involving all radiologists will be held prior to start of accrual where each site will bring 5 MRI cases performed at their site for consensus review, scoring

and discussion. This will provide a commonality of approach to interpretation among the radiologists before the study begins. After this startup meeting each site will send one set of MRI images and its interpretation for central review for site qualification.

A copy of all images will be sent on CD/DVD to the central site for archiving.

10.3 No target identified on MPMRI (PI-RADS 1 or 2)

For subjects in Arm A only, who do not require a biopsy

Men who have MRIs that do not identify any suspicious lesion will not receive a biopsy. These subjects will benefit from being part of the trial as a result of not having to undergo an invasive biopsy procedure, avoiding the discomfort associated with the procedure, the risk of being diagnosed with clinically insignificant cancer and the risk of sepsis associated with the biopsy procedure. Studies suggest that if the MRI does not identify areas suspicious for cancer there is an85-95% chance that clinically significant cancer is not present[28, 34, 35].

As soon as the results of the MRI are discussed with the subject, their treatment decision will be recorded and they will return to standard of care management. As part of standard of care these subjects can undergo further PSA surveillance and / or prostate biopsies if indicated.

10.4 MRI-Targeted biopsy

For subjects in Arm A who do require a biopsy

10.4.1 MRI choice of targets for targeted biopsy

Men whose prostates contain a suspicious area with a PI-RADS score of 3,4 or 5 will subsequently undergo targeted biopsy by a Urologist or Radiologist experienced in MRI-targeted biopsy. Operator experience (number of targeted biopsies performed to date) will be recorded before each procedure. The number of biopsy operators should be kept to the minimum number possible.

Targets will be stratified by PI-RADS score and if the same score then by size and labeled T1, T2, T3…etc. If there are more than 3 lesions with a score of 3 or more only T1-T3 will be targeted. The radiologist should record the sectors involved with tumor in order of most to least involved using the PI-RADS v2 sector scheme.
The number of biopsy operators should be kept to the minimum number possible.

Subjects in the MRI cohort will not have systematic biopsies, with one exception. Those whose MRI is grade 3M (a multifocal pattern suggesting multifocal small volume cancer, with PSA Density >0.15 and no focal lesion), a systematic 12 core biopsy will be conducted.

10.4.2 MRI Biopsy

The procedure will be performed in the outpatient departments of sites possessing the required equipment by a clinician competent in TRUS/MRI-targeted biopsy. An operator must have performed at least 50 targeted biopsy cases on the TRUS/MRI

fusion system at their institution before they are qualified to participate as an operator in the study.

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulants/antiplatelets will be discontinued up to 10 days before biopsy and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

Prophylactic quinolone antibiotics shall be given as per local guidelines. Biopsies will be performed via the trans-rectal route or via the trans-perineal route depending upon local practice.

Targeted biopsies should be performed by software-assisted fusion devices (i.e.(Artemis, made by Eigen, or Urostation, by Koelis)[34, 36, 37, 40,41].This software is safe and poses no risks to the subject since the same CE-marked ultrasound probes that are designed to perform the biopsy when performed as standard of care biopsy are used during targeted biopsy. Should the operator wish to not use the information provided by the software registration system and use cognitive (visual) registration alone they can do so, but should indicate this on the subject's case report form.

The samples per target will be 4cores spread across the target region for a maximum total of 12 cores as a maximum of 3 targets can be identified. Biopsies should be conducted in order meaning T1 then T2 then T3.

Biopsy cores from different suspicious areas will be aliquoted separately. The vials will be labeled "T1a-d", "T2a-d" and "T3a-d" (according to how many targets there are) which should match the assignment of suspicious areas by the radiologist on the MRI report. The order of lettering a-d should match the order in which the biopsies were performed in each region. The first biopsy should be at the center of the target and the remaining fanning out from the center. Each core from the same suspicious area must be submitted separately. Alternative methods of storing cores that allow identification of the order of score samples from each target are acceptable.

10.5 Systematic TRUS guided biopsy

For all subjects in Arm B

Systematic TRUS guided biopsy is the current standard of care for the diagnosis of prostate cancer [4, 17]. Systematic TRUS guided biopsy can be performed at the local site of recruitment.

A clinician competent in systematic TRUS guided biopsy will perform the procedure. The experience of the operator (number of systematic TRUS guided biopsies performed to date) will be recorded prior to each procedure. Software that guides clinicians in placing biopsy cores should not be used.

Coumarin anticoagulant, clopidogrel treatment and other relevant anticoagulant/antiplatelet medication will be discontinued5 to 10 days before biopsy

and advice sought as to appropriate substitutes if indicated. Aspirin will be continued at the discretion of the physician doing the biopsy.

The subject will be positioned in left lateral position. 10-12 core biopsies will be taken as per guidelines [42] under appropriate anaesthesia. Biopsies will be directed to the peripheral zone (See Appendix 3for standardized method for conducting 12-core systematic TRUS guided biopsy). Prophylactic quinolone antibiotics shall be given as per local guidelines.

10.6 Pathology

The 2005 International Society of Urological Pathology guidelines for Gleason Grading of Prostatic Carcinoma will be followed [43].

For men undergoing MRI-targeted biopsy it is required that pathology reported per suspicious area targeted and per targeted core. For systematic TRUS guided biopsy, each core will be reported and graded.

10.7 Post-procedural care

For all subjects in ARMS A and B receiving a biopsy

After a biopsy procedure the subject can be discharged within 2-3 weeks for results of the histopathology and treatment options to be discussed.

10.8 Immediate post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

A modified version of a self-reported questionnaire validated previously [39] in the assessment of post-biopsy complications will be completed immediately post-biopsy after MRI-TB and after systematic TRUS guided biopsy (Appendix 7). The subject should complete the immediate post-biopsy questionnaire before they leave the department. It aims to assess intensity of discomfort and pain associated with the procedure.

10.9 30-day post-biopsy questionnaire

For all subjects in ARMS A and B receiving a biopsy

A modified version of a self-reported questionnaire validated previously [39] in the assessment of post-biopsy complications at 30 days post-biopsy should be given to all subjects undergoing MRI-TB or systematic TRUS guided biopsy to take home (Appendix 8). The subject should fill this out on day 30 following the procedure. It should take 5 minutes to fill out. The date that the participant should complete the questionnaire should be written on top of the questionnaire. Data on specific biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded. Contact with healthcare and resource used data following the biopsy will also be ascertained. The completed questionnaire can be returned to the investigator in a pre-addressed envelope.

Subjects should be reminded at 30 days to complete this questionnaire.

10.10 Results and treatment decision (Visit 4)

The results of the biopsies and/or MRI will be explained to the subject by the clinical care team during this visit, which is approximately 2-3 weeks after the biopsy. The research team should record the treatment decision in the subject file. Possibilities for treatment decision include but are not limited to:

- Further diagnostic test (e.g. PSA, biopsy, MRI)
- Active Surveillance
- Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- Hormone therapy

10.11 Follow up period

All study participants will be followed up for up to two years or until they have radical treatment. Each year, subjects will be surveyed to obtain the following information:

- time to cancer diagnosis
- Gleason score progression
- time to intervention on active surveillance
- time on active surveillance
- PSA
- All subjects in both Arm A and B who have remained either undiagnosed or untreated (on active surveillance) will have a follow up MRI 2 years after study entry.

10.11.1 Indications for biopsies off protocol

For subjects who are not biopsied due to a negative MRI, have negative or non-significant systematic biopsies, or who have a positive MRI but no or non-significant cancer on targeted biopsy, the following are guidelines for subjects management during the 2 year follow up period.

It is an accepted standard of care in Ontario for subjects on active surveillance or with a prior negative biopsy who have a worsening risk profile to undergo mpMRI followed by targeted biopsy. We propose the following guidelines for risk profile assessment and consideration of repeat biopsy

Subjects should continue to be followed with semi-annual PSA and DRE (not required, at the discretion of the PI). A biopsy should be considered under one or more of the following circumstances:

1. For men with PSA density < 0.15, biopsy if an increase in PSA density > 0.15.

2. For men with PSA density > 0.15, or a baseline PSA > 10, biopsy if a 50% increase in PSA in 1 year.

3. Biopsy if a doubling of the risk of high grade cancer according to the NCI nomogram.

4. Biopsy if development of a suspicious nodule on DRE.

5. For men with a positive study MRI (especially PI-RADS 4 or 5) and a targeted biopsy which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15.

30. For men on the systematic biopsy arm which was negative or showed only Gleason 6 cancer, biopsy if there is a 50% or more increase in PSA over 1 year or a PSA density > 0.15. An MRI and targeted biopsy may be warranted in these subjects.

These are guidelines and should be interpreted with clinical judgment.

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.)
PSA and biopsy results will be evaluated in subjects in whom the 2 year MRI identifies a target.

10.12 Additional tests for biomarker discovery - Optional

Though not related to the primary outcome of this study, this cohort represents a unique opportunity to obtain human samples for future biomarker discovery studies. Participants will be consented to provide a blood, urinesemen, and tissue sample after the consent and screen visit, and subsequent visits for storage and use in future biomarker studies. In addition, men will be consented for use of the prostate biopsy tissue in the biomarker discovery studies.

We propose two initial biomarker analyses for men recruited to the PRECISE study. First we propose testing the utility of several genetic assays. These include the SELECT MDx test (a urine based genomic assay), the Telo PC test (an analysis of telomere structure in circulating tumour cells), the Exosome Dx assay (urine based exosome assay), the Mitomics assay (circulating mitochondrial DNA deletion assay), and the MDNA test (a urine based microRNA assay). We will test the hypothesis that alongside conventional PSA measurements, these tests may identify subjects whose MRI was initially negative for prostate cancer, but who are at high risk of harboring clinically significant disease as detected by the secondary MRI at 2 years. We will also test the association between serum biomarkers and clinically significant or clinically insignificant prostate cancer detected during the PRECISE study. We will also explore the potential for these assays to provide additional information over and above Gleason grade. These studies will be separately funded from PRECISE.

Sequential blood sampling during the 2 years of follow up (prior to a 2 year MRI) will be planned to assess markers which might identify men at higher risk of developing prostate cancer.

10.12.1 Samples to be collected for future biomarker discovery work (Optional)

Participants will be asked to consent to provide a blood, urinesemen and tissue sample after the consent and screen visit and subsequent visits for storage and use in future biomarker studies. This will involve a separate consent form.

Samples include:

- Blood –10mls serum, 15mls plasma, 10mls whole blood, 5mls buffy coat
- Urine – 75 mls urine
- Semen 1-5cc (single ejaculate)
- Tissue-unstained biopsy sections -15 unstained slides from cancer, and
  -15 unstained slide from non-cancer cores (if possible)

10.12.2 Correlative Science Component

Within this protocol biomarker and genetic validation studies and biomarker discovery research will be incorporated to correlate molecular readouts with the presence of Gleason 4 or 5 pattern on biopsy. The goal of these studies is to develop a liquid based assay (serum, plasma, CTCs, urine semen) which accurately predicts the presence of clinically significant cancer. The correlative science component of Precise constitutes a major initiative, with multiple collaborators and planned studies. These are briefly summarized below.

Biomaterials (serum, plasma, buffy coat, PRE/POST DRE urine and tissue from biopsies) will be collected at times specified in the protocol. Sample collection will be restricted to subjects who have agreed to provide these samples in a separate optional informed consent. If a subject withdraws consent for the additional biomarker and genetic testing, subject's samples will be destroyed. The investigator must notify the sponsor site contact who will request the samples destruction.
Biomaterials for the correlative science studies will be identified with a unique identification code, date of collection and will not contain any personal identification information. The samples will be shipped to a secure long-term storage facility, identified as the Ontario Institute for Cancer Research, located at 661 University Ave, Suite 510, Toronto, ON M5G 0A3. Samples for the correlative science studies will be shipped stored and analyzed according to specified, specialized procedures in the Precise Correlative Science Manual.

Biomaterial will be stored, anonymized, at the Ontario Institute of Cancer Research (OICR) Biobank, under the direction of Dr. John Bartlett. Dr. Bartlett is the Program Director, Diagnostic Development, at OICR. The material will not be used for commercial purposes. No personal information will be kept at OICR. Personal identifying information on the patients in the PRECISE trial is held by the Ontario Clinical Oncology Group (OCOG), who are performing the data management function for the study. Access to the biomaterial will be under the control of the PRECISE steering committee. Access has already been approved for the Translational Research in Prostate Cancer (TRIPC) research group led by Dr. Paul Boutros. Future

researchers interested in using the biomaterial will apply to the Precise steering committee for approval, based on the scientific merit of the study.

A group of investigators led by Drs. Paul Boutros (OICR) and George Rodriguez (UWO) have obtained funding for a correlative science study nested in the Precise trial. This study is termed the 'Translational Research Initiative in Prostate Cancer', or TRIPC. Biomaterial will be collected for these studies as above. A summary of the planned studies is as follows:

Urine: The TRIPC project will measure the proteomes of urine specimens using either a whole proteome assay or Selective Reaction Monitoring - Mass Spectroscopy (SRM-MS) or Peptide Reaction Mass Spectroscopy (PRM-MS) for a panel of ~50 peptides. These peptides will be used to score two published biomarkers of disease aggressivity (https://www.nature.com/articles/ncomms11906). The PRECISE data will then be used to retrain the parameters and weights of the biomarkers as an exploratory analysis.

Blood: Genotypes will be measured using either DNA-sequencing or genotyping arrays. The resulting data will be used to score five distinct biomarkers: a germline-incidence biomarker created by the PRACTICAL GWAS consortium, a biomarker of aggressive prostate cancer created by the PRACTICAL GWAS consortium, a panel of DNA repair genes identified by the SU2C group and two biomarkers of disease aggression identified by the CPC-GENE network. The PRECISE data will then be used to retrain the parameters and weights of the CPC-GENE biomarkers as an exploratory analysis. Second, methylation of cell-free DNA will be assessed using microarray platforms (either tiling or CpG island arrays) to score two existing signatures of aggressive prostate cancer.

Tissue
Tumour biopsies will be subject to OncoScan microarray profiling and/or DNA sequencing to measure methylome, somatic single nucleotide variants, copy number aberrations, genomic rearrangements and mitochondrial copy number. Seven signatures of aggressive prostate cancer will be scored: the proportion of the genome altered (PGA, Lalonde et al. Lancet Oncology), 100-locus and 31-locus signatures (Lalonde et al. European Urology), a multi-modal signature (Fraser et al. Nature), a mitochondrial signature (Hopkins et al. Nature Communications), and two unpublished signatures developed by the CPC-GENE network: of tumour evolution and of the tumour methylome. The PRECISE data will be used to retrain the parameters and weights of the biomarkers as an exploratory analysis.

A second group led by Dr. Keith Jarvi, will analyze semen for biomarkers of significant prostate cancer. They will utilize **deep targeted Next Generation sequencing of cell free DNA and tumor cells isolated from semen.**

- **Contact Information:** Dr. Keith Jarvi
  Murray Koffler Urologic Wellness Centre, 60 Murray Street, 6/F

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) wich 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 log 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

This group will be examining the telomere structure of circulating tumour cells (CTCs) using an established assay, the Telo PC test. The results of a 50 patient prostate cancer pilot study in men with intermediate risk prostate cancer who underwent radical prostatectomy showed that the TeloPC assay correctly predicted the status/aggressiveness of disease in each of the study's patients.[1] While all patients were diagnosed as intermediate risk using conventional biopsies prior to surgery, only 21 of the 50 patients who underwent RP showed disease upgrading upon post-surgical analysis and therefore were suitable for prostate removal. The TeloPC assay correctly predicted that 29 of the 50 patients had a stable form of prostate cancer.

The TeloPC assay includes filtration-based circulating tumour cell (CTC) enrichment combined with 3-dimensional (3D) analysis of telomeres to obtain 3D telomere profiles of PCa patients with low-intermediate risk category.

- MiR Diagnostics
  1 Discovery Drive
  Rensselaer, NY 12144

This group will be examining urinary microRNAs and other non-coding RNAs from urinary exosomes. A panel of 56 miRNAs and snoRNAs, which have been demonstrated to be predictive of clinically significant prostate cancer, will be interrogated. The urine samples will be used to establish the sensitivity of the procedures and the precision of the analytic algorithyms to identify those with significant prostate cancer. The long term goal of the project is to develop a non-invasive methodology that can be used to identify genetic alterations that identify a group of patients at high risk for clinically significant prostate cancer.

- Exosome Diagnostics, Inc.
  266 2 nd Ave.
  Waltham, MA 02451

This group will be interrogating non-coding RNAs extracted from urinary exosomes. They will assay exosomal RNA for three biomarkers known to be expressed in men with high-grade prostate cancer, using an algorithm that integrates this three-gene signature,

- MDNA Life Sciences, Inc.
  2054 Vista Parkway, Suite 400
  West Palm Beach, FL 33411

This group will evaluate the performance of the Prostate Mitomics test. This is a blood-based screening test which evaluates free plasma DNA for the presence of a mitochondrial DNA deletion. This deletion has been demonstrated to be associated with high grade prostate cancer. Nucleic acids will be extracted from each plasma

sample using a commercially available reagent kit. The Prostate Mitomic Test is a quantitative real-time PCR test for a 3.4kb mitochondrial DNA deletion correlated with prostate cancer. Each sample will also be profiled for novel mitochondrial DNA mutations using standard laboratory techniques such as quantitative real-time PCR. Mutation frequency will be compared to clinical outcomes.

- MDx Health. Inc
  15279 Alton Parkway, Suite 100
  Irvine, CA 926188

This group will perform the Select MDx assay, a two gene mRNA assay performed on urine, to evaluate its performance in predicting the presence of clinically significant prostate cancer.

10.13 Long-term data linkage – Permission to Contact

The cohort of men who consent to participate in this study represent a uniquely characterized group. Their long-term outcomes will contribute to our understanding of the epidemiology of prostate cancer beyond the questions being addressed in this study.

Permission to Contact (PTC) is a feasible mechanism to engage subjects in research programs. This will allow researchers to contact study participants in the future to assess their willingness to respond to questionnaires. This potentially enables research that would complement the planned long-term follow up in terms of health status, for obtaining information about future biopsies not included in the study, and allow assessment of quality of life.

10.14 End of Study

The end of study assessment comprises an essential safety evaluation that should be completed prior to discharging any subject from the study.

- Adverse events;
- PSA measurement;
- EQ-5D-5L questionnaire;
- An MRI in those who did NOT have a biopsy;
- Complete CRF.

10.15 Risks and Benefits to Participants

An important consideration of this study is that men are being randomized to one of two biopsy techniques when it is not known which will be more effective. Both diagnostic tests are currently used in clinical practice at the institutions involved in the trial. Though systematic TRUS guided biopsy could be considered standard of care, there is enough evidence to support the concept that MRI-targeted biopsy may be at least as effective as systematic TRUS guided biopsy[27].

10.15.1 Risks to subjects

The intervention proposed in this trial (MRI-biopsy) do not offer participants any more risk than if they underwent standard of care (systematic TRUS guided biopsy) for the diagnosis of prostate cancer.

10.15.1.1 Risk of Systematic TRUS guided biopsy

Systematic TRUS guided biopsy can be associated with discomfort, haematuria, haematospermia and dysuria in a large proportion of subjects, which is self-resolving (See Table 4). There is a 4% risk of systemic urosepsis[46].

10.15.1.2 Risks of MPMRI

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.

10.15.1.3 Risks of MRI-targeted biopsy

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.

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
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%

10.15.2 Benefits to subjects

Subjects enrolled in this trial will benefit from the following:

- 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 will also ensure streamlined diagnostic investigations to promptly conduct the diagnostic test and communicate the test outcome for the subject.
- Subjects enrolled in the trial will benefit from the dedicated research team involved in their care in addition to the clinical team normally involved in their care.
- Subjects will benefit from additional discussions regarding the trial, which could increase their understanding of prostate cancer and help them to make a more informed decision about their health.

- Subjects randomized to the MRI arm may benefit by avoiding a biopsy. This will remove any risk of post-biopsy infection. MRI-randomized subjects may also benefit from a reduced probability of having a clinically insignificant prostate cancer diagnosed. Clinically insignificant prostate cancer is often treated definitively per subject preference despite the lack of evidence supporting the need. All definitive local therapies for prostate cancer carry the risk of peri-operative complications as well as long-term risk of incontinence and erectile dysfunction.

10.16 Concomitant medications

10.16.1 Permitted Medications

All concomitant medications taken during the study will be recorded in the CRF with indication, dose information and dates of administration. The definition of which medication would be considered outside the routine medical practice is up to the discretion of the investigator. All dietary and herbal supplement usage will be recorded in the CRF.

10.16.2 Non-Drug Therapies

Any occurrence of prostate-related surgical and/or non-surgical (or minimally invasive) intervention during the conduct of the study will be recorded in the CRF.

11. Schedule of Study Visits

11.1 Visit 1 (Screening/Randomization): Screening, Consent, Randomization

For all subjects enrolled in trial

Screening will occur any time following the referral of the subject. Ideally, this will be performed as soon as possible following receipt of referral.
Subjects will be consented only after they have had time to consider the study. This may happen on the same visit as the screening visit.
Randomization can happen immediately after the consent form is signed and eligibility is confirmed.

Once enrolled into the study, subjects will be asked to fill out an EQ-5D-5L questionnaire (Appendix 4), which is a validated 2-page questionnaire representing health related quality of life. It takes approximately 2 minutes to complete. This questionnaireshould be completed at the screening visit before the subject leaves the clinic.

If a subject agrees to the optional informed consent, from randomization until any point prior to a biopsy, optional blood, urine semen and tissue samples will be collected for correlative studies.

If PSA testing was done greater than 3 months of randomization, this must be repeated at screening/Visit 1.

11.2 Visit 2 (MRI): ARM A, for men randomized to MRI

This will occur approximately within one week of randomization. Men will receive an MRI (see Section 10.2.)

11.3 Visit 3 (Biopsy): ARM A, MRI-Targeted Biopsy of Prostate

For men randomized to ARM A, who have a lesion identified by MRI. This appointment will follow approximately one-two weeks 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 biopsy to occur in timely fashion. If the results of the MRI show 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.

Men with a positive MRI (i.e. PI-RADS score of 3-5) will receive a MRI targeted biopsy of the prostate (see Section 10.6). Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after a biopsy, before the subject leaves the department.

Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and complete as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as questionnaire is completed at 30-60 days post-biopsy, it will be acceptable, however, the questionnaire should be completed as close as possible to 30 days post-biopsy.

At the 30-days post biopsy interval, a member of the research team will call the subject to remind them to complete and return the 30-day questionnaires.

11.4 Visit 3 (Biopsy): ARM B, for men randomized to a systematic TRUS-biopsy

For men randomized to ARM B only.

Men will receive a standardized TRUS-guided biopsy(see Section 10.7.) Men will complete an Immediate Post Biopsy Questionnaire (Appendix 7) ideally completed and returned immediately after the biopsy.
Subjects will be given a 30-day post-biopsy questionnaire to take home after biopsy and it is to be completed as instructed on day 30 post-biopsy. This is to be returned by post or at the 30 day follow up appointment (Visit 4). If Visit 4 is earlier than 30 days post biopsy then this questionnaire can be given to the research team when 30 days is reached. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-

biopsy, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-biopsy.

At 30-days post biopsy a member of the research team will call the subject to remind them to complete and return the 30-day questionnaires.

11.5 Visit 4 (Post-test follow up): ARM A, for men who did not receive a biopsy

This appointment will include a follow up meeting with the investigator to discuss the results of the MRI as well as treatment decisions. This follow up should occur after the availability of the MRI report. At this visit the subject will also complete a 30-day post intervention EQ-5D-5L Questionnaire.

Subjects will complete a Post-MRI 30-day questionnaire (Appendix 8),which has been posted to them by the research team. 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. As long as the questionnaire is completed at 30-60 days post-MRI, it will be acceptable, however the questionnaire should be completed as close as possible to 30 days post-MRI.

At 30-days post MRI, a member of the research team will call the subject to remind them to complete the 30-day questionnaires.

11.6 Visit 4 (Post-test follow up): For all men who received a biopsy

This appointment will include a follow up meeting with the investigator to discuss the results of the biopsy as well as treatment decisions. This should be completed as soon as possible following the availability of any pathology results. The follow up appointment should be within 1 month of the biopsy. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision.

The research team should record the treatment decision in the subject file.

Possibilities for treatment decision include but are not limited to:

- Further diagnostic test (e.g. PSA, biopsy, MRI)
- Active Surveillance
- Radical treatment (e.g. radical prostatectomy, radical radiotherapy)
- Focal therapy (e.g. high intensity focused ultrasound, cryotherapy)
- Hormone therapy

At this visit the subject will also receive a 30-day post intervention EQ-5D-5L Questionnaire to complete. Subjects will also complete a 30-day Post Biopsy questionnaire (Appendix 8), which has been posted to them by the research team. The questionnaire needs to be completed on the 30th day post-intervention (i.e. post biopsy). However it will be accepted if completed up to 72 hours prior to or after the

30th day. A telephone reminder from the research team to the subject can take place.

11.7 Visit 5 (6 month follow up):26 week follow up

All subjects will have a 26 week visit
Subjects will have the following:

- Vitals, DRE (not required, at discretion of PI)
- PSA
- Optional sample collection (blood)

11.8 Visit 6 (1 year follow up): 52 week follow up

All subjects are planned to have a 52 week follow up visit.
Subjects will be followed to obtain the following information 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.
- 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, targeted only or both systematic + targets, not done because of negative MRI
- Optional sample collection (blood, urine)

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 6 (year 2).

11.9 Visit 7 (18 month follow up): 78 week follow up

All subjects will have a 78 week visit
Subjects will have the following:

- Vitals, DRE (not required, at discretion of PI)
- PSA
- Optional sample collection (blood)

11.10 Visit 8 (2 year follow up): End of study

All study participants will be followed for up to two years or until they undergo radical treatment
Subjects will be followed to obtain the following information 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)

- 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

Follow-up will cease once treatment beyond active surveillance is undertaken (prostatectomy, radiation therapy, focal therapy, etc.).

Those subjects randomized to ARM A but who did not have an MRI-targeted biopsy will have an additional MRI at Visit 8.

12. Randomization

12.1 Randomization Procedure

Written informed consent will be obtained from all eligible subjects prior to commencing any study related procedures. The Ontario Clinical Oncology Group (OCOG) Coordinating and Methods Centre (CMC) located at the Research Centre, Juravinski Hospital and Cancer Centre, Hamilton, Ontario will centrally coordinate subject randomization. Subjects will be allocated to the two treatment arms in an approximate 1:1 ratio by use of a dynamic allocation scheme[47].

After documentation of written informed consent and confirmation of subject eligibility, clinical centres will randomize the subject by accessing the CMC's web-based Interactive Registration/Randomization System (IRIS). Prior to randomization and treatment allocation, the subjects' individualized risk of high-grade prostate cancer, obtained using the PCPTRC 2.0 calculator found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp must be determined.

12.2 Stratification

Eligible, consenting subjectswill be stratified by: (1) individualized risk of high-grade prostate cancer (5% to 25%, >25%); and (2) clinical centre

12.3 Blinding and measures taken to avoid bias

This study is unblinded, and all subjects will be aware of the treatment that they are receiving. As the MRI scan is unique to one of the arms it will not be possible to blind the participants or investigators as to what intervention is being received. Therefore, participants will be informed which arm they have been allocated to. Where possible, the data will be coded so as to blind individuals analyzing the data from which of the groups the data was from. Summary details of randomized allocation

and outcomes will not be made available (unless specifically authorized by the Trial Steering Committee and/or Data Monitoring Committee) in order to maintain the overall blind of the trial.

Radiologists will be blinded to subject information. (e.g. PSA level Radiologists will be aware that the subject is part of the trial.
Pathologists will be blinded to the cohort allocation. Concealment may be challenging due to the different number of cores in the two groups, but this is unavoidable. This is unlikely to represent a significant source of bias.

13. Data

Type of data to be collected:

- EQ-5D–5L questionnaires. These will measure quality of life and which will be measured at specific times throughout the trial.
- Systematic TRUS guided biopsy– pathology – categorical (e.g. Gleason grade) and continuous data
- MRI – diagram representing MRI; categorical data for areas and scores of suspicion (e.g. Sector 1p, score of suspicion 4/5)
- MRI-targeted biopsy – pathology – categorical (e.g. Gleason grade) and continuous data
- Post-biopsy immediate and 30-day questionnaires – categorical data (e.g. fevers yes/no)
- Treatment decisions – categorical data (e.g. radical treatment)
- PSA – continuous data (e.g. value of PSA in ng/ml)

Please see **Appendix1** for the time window for data collection.

14. Statistical Considerations

14.1 Sample Size Calculation

STATISTICAL methods

Primary Analysis

Absolute differences in the proportion of clinically significant cancer detected between arms will be calculated and compared using the Clopper-Pearson method. If the lower boundary of an one-sided, 97.5% confidence interval for the difference in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower bound is greater than zero, superiority can be claimed.

A supportive analysis will be performed by using a logistic regression model, evaluating the odds ratio for detecting high grade cancers, adjusted for stratification factors. MRI-guided biopsy would be considered non-inferior if the lower bound of the two-sided, 95% confidence interval for the odds ratio exceeds 0.78. This lower

bound was calculated to approximate an absolute 5% difference of interest (NOTE: the unadjusted odds ratio is 0.78 when treatment A is 30% and treatment B is 25%).

Secondary Analyses

For each secondary outcome, where appropriate, a difference in proportions with 95% CI, or a difference in means with 95% CI, as appropriate, will be presented. Differences in the 1-year and 2-year rates along with 95% CI will be calculated for time-to-event outcomes.

χ^2 tests, t-tests or Wilcoxon rank sum tests, and log-rank tests will be used to test for differences between allocation arms in secondary outcomes. Logistic regression and Cox proportional hazards regression will be used to examine the effect of allocation arm on outcomes, adjusted for stratification factors. All secondary outcomes will be two-sided and statistical significance will be set at the α=0.05 level. No statistical adjustments will be made due to multiple testing, however, results for secondary outcomes will be interpreted cautiously, acknowledging that tests were performed on secondary outcomes and numerous secondary tests were performed. Figures and tables will be used to illustrate results of interest.

Treatment Allocation and Stratification

Subjects will be allocated to the two allocation arms in an approximate 1:1 ratio by use of a dynamic allocation scheme. Specifically, the first 20 subjects will be randomly allocated to arm in an approximate 1:1 ratio. After the first 20 subjects, a biased coin method will be used, whereby the number of subjects within each stratum will be calculated, and the next eligible subject will be allocated (with probability p=0.8) to the arm which reduces the imbalance. If no imbalance exists, allocation to each arm will occur with probability p=0.5.

<u>Stratification</u>

For treatment allocation, the subjects' individualized risk of high-grade prostate cancer will be determined. Risk will be assessed using the PCPTRC 2.0 calculator, found at http://deb.uthscsa.edu/URORiskCalc/Pages/calcs.jsp. Eligible, consenting subjects will be stratified by:

(1) individualized risk of high-grade prostate cancer (5% to 25%, >25%);

(2) clinical centre.

Sample Size

Rates of clinically significant cancer (Gleason ≥7) detection from targeted-alone biopsy in a population with no prior biopsy have been shown to be 42% [37] and 50% from another study [36].

Rates of clinically significant cancer detection from one the largest studies of systematic TRUS guided biopsy in men without prior biopsy are shown to be 27% [49]. Therefore, based on these results, it may be assumed that targeted-biopsy will detect clinically significant cancer in >15% more men (i.e. 42% versus 27%) than systematic TRUS guided biopsy.

For this study, it will be conservatively hypothesized that systematic TRUS guided biopsywill detect clinically significant cancer in 30% of men, and targeted biopsy will detect clinically significant cancer in 10% more men (i.e. 40% total) than systematic TRUS guided biopsy. For the non-inferiority hypothesis, using 90% power and 2.5% one sided-alpha, assuming a targeted biopsy detection rate of clinically significant cancer of 40%, and a detection rate for systematic TRUS guided biopsyof 30% and using a margin of clinical unimportance of 5%, 211 men per arm will be required. The choice of 5% as the margin of non-inferiority represents a difference that would be considered clinically important.

Thus total men required in study = **422**.

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.

Note that the rate of clinically significant cancers is very dependent on the population registered for this study. It is possible that fewer (or more) subjects will have clinically significant cancers than what is initially hypothesized. However, if the population rate of clinically significant cancers is less (i.e. the systematic TRUS guided biopsy detection rate is <30%) and other statistical assumptions remain as stated previously, the statistical power will increase. The minimum statistical power would be obtained if the clinically significant cancer detection rate was 45% for systematic TRUS guided biopsy and 55% for targeted biopsy, which would still achieve >84% power. Therefore, the sample size is sufficient to ensure non-inferiority, even if the rate of clinically significant cancer in the population is miss-specified, assuming an absolute difference of 10% between targeted and systematic TRUS guided biopsydetection rates, and a 5% margin of non-inferiority.

Statistical Conventions

For categorical data, tables will be presented showing the n and percentage (n/N*100%) of subjects. Analyses will be presented by study allocation arm separately.

Duration of time will be described in either years, months or weeks, and calculated using: (last date – first date + 1) / X, where X=365.25 for years, X=30.4 for months, or X=7 for weeks. Example: Age (in years) will be calculated as: (randomization date – date of birth + 1)/365.25.

Transformations of the data in order to meet statistical assumptions may be considered. Type-1 error will be set to 5%. Standard diagnostic tools will be used to assess any of the model fittings. All the statistical analysis will be carried out using SAS version-9 and over for Windows (Cary, NC) or R version 3.2.2. (www.r-project.org) or higher.

Missing Data

Missing values for the primary endpoint will be examined closely. Sources and reasons for the absence of data incurred as a result of subjects lost-to-follow up,

dropouts, and intermittent missing values will be described and explored by various summary statistics as well as graphical displays between the two allocation arms. Subjects' lost-to-follow up or dropouts will be explored and the characteristics of those subjects will be described by allocation arm and tested using Fisher's exact tests or Wilcoxon rank sum tests.

Missing data for secondary endpoints will be described. The methods for evaluating missing data of the primary endpoint may be employed for endpoints of interest. For summarization of baseline data, the following conventions will be used for partial missing date information occurring prior to randomization (e.g. for medical history or prior treatment). If year is missing, the date will be set at missing. If year is available, but month and date is missing, the month and date will be set to July 1st of the respective year. If date is missing, but year and month available, the day will be set to the 15th of the respective month.

14.2 Interim Analyses

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. Unless otherwise specified by one of these bodies, a futility analysis will be performed after approximately 200 subjects are enrolled and have their primary outcome ascertained. Simulation will be used to estimate the conditional probability of futility assuming the study was to continue to completion, and assuming the clinically significant cancer detection rate is 30% in both arms. If the conditional probability is 0.95 or higher that continuation of the study will result in a negative result, the DSMC will recommend a suspension of recruitment to the trial, and initiation of a quality assurance review. A decision to permanently close the study or continue with accrual will be determined by the Steering Committee, based on the results of the quality assurance review, and the recommendation of the DSMC.

Timing of Final Analysis

A single, final, analysis will occur after all subjects have undergone their initial biopsy and all data related to the initial biopsy is documented and validated. Follow-up analyses will be conducted after all subjects have completed two years of follow-up.

14.3 Populations:

The per protocol, study population will consist of all subjects who satisfy all eligibility criteria and are randomized to the study, who undergo MPMRI-TB or systematic TRUS guided biopsy and have their primary outcome measured. This population will be used for the primary analysis of non-inferiority.

The intent-to-treat (ITT) population will consist of all subjects randomized to the study, regardless of any protocol violations or if they do not complete the study as defined in the protocol. The ITT population will be used as a supportive analysis of the primary analysis, for all safety analyses, and for any analysis investigating superiority.

14.4 Primary Outcome

14.4.1 Detection rate of clinically significant cancer

The proportion of men in each arm with clinically significant cancer (Gleason ≥7) will be calculated based on histology results from biopsy procedures. Analysis will be on the intention to treat population.

Absolute differences in proportion of clinically significant cancer detected between arms will be calculated and compared. If the lower boundary of the 97.5% confidence interval for the difference in detection rates of MPMRI-TB compared to systematic TRUS guided biopsy is less than -5% then MPMRI-TB will be deemed non-inferior. In the event that the lower bound is greater than zero, superiority can be claimed.

The primary analysis will be conducted once all subjects have completed visit 4, when the results of the biopsy or MRI are given to the subject.

14.5 Secondary Outcomes

For each secondary outcome, where appropriate, a difference in proportions with 95% CI, or a difference in means with 95% CI, as appropriate, will be presented.

14.5.1 Proportion of men in each arm with clinically insignificant cancer detected

The proportion of men in each arm with clinically insignificant cancer (Gleason <7) will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.2 Proportion of men in each arm with Gleason ≥4+3 detected

The proportion of men in each arm with Gleason ≥ 4 +3 will be calculated based on histology results from biopsy procedures. In addition, the numbers with clinically insignificant cancer identified by MRI alone will also be included.

14.5.3 Proportion of men in MPMRI arm who avoid biopsy.

14.5.4 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.

The proportion of men in each arm whom the PI-RADS score for suspicion of clinically significant cancer was 3, 4 or 5 but no clinically significant cancer was detected, will be calculated based on histology results from biopsy procedures.

14.5.5 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)

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 andhaematospermia.

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

As the study design for clinical outcomes is one of non-inferiority, the primary economic analysis will be **cost minimization analysis**. The perspective of the economic analysis will be that of the public payer. The primary goal of the analysis will be to support arguments for public funding. Thus the costs of participant burden, logistical challenges, and expense of obtaining societal costs, will not be evaluated.

14.5.12.1 Data collection:

As part of the informed consent process, participants in Ontario will also consent to having their Ontario Health Insurance Number recorded, to be later transferred to the Institute for Clinical Evaluative Sciences (ICES) where it will be linked to a number of administrative claims databases recording health system resource utilization such as physician billing [Ontario Health Insurance Plan (OHIP); laboratory and diagnostic tests (OHIP); hospitalization and surgery [Discharge AbstractDatabase (DAD)]; medications [Ontario Drug Benefit (ODB) Formulary, New Drug Funding Program (NDFP), and Activity Level Reporting (ALR)];clinic and emergency department visits [National Ambulatory Care Reporting System (NACRS),Emergency Department visits); radiation (ALR); homecare (Home Care databases) and a few additional ones as determined necessary (e.g., Long-term care, Mental Health, Diabetes.The overall, number and proportion of health system resources will be determined.In this way we can capture comprehensive resource utilization related to on-trial management including any adverse events.

14.5.12.2 Health Insurance number handling and security

As the economic implications of this study are of prime importance to some of the funders, the request for data linkage will be part of the main consent form. If a participant indicates to the study team that they decline or withdraw consent, the OHIP number will be recorded as 9999-999-999-XX. The OHIP numbers will stay with the participating institution until after accrual is complete, and then they will all be transferred at one time under data sharing agreements between ICES and each institution. Data will be transferred using a secure electronic file transfer system established by ICES and managed by authorized ICES personnel responsible for receiving data. The file transfer system uses security safeguards including encryption and authentication.

ICES is a Prescribed Entity under the Personal Health Information Protection Act (PHIPA), and can receive and use personal health information for purposes of analysis and compiling statistical information and other research. Its policies and procedures for privacy protection and data security have been approved by Ontario's Privacy Commissioner. ICES is a secure facility, video-monitored and requiring passkeys to access private offices and computers. ICES has extensive experience in the protection of confidentiality when using such data. It has a UNIX-based network that cannot be accessed externally. ICES data facilities are fully 'moated' (no connections to other computers). At ICES, routine procedures for data backup are instituted by a data management team. The data is burned onto a CD or placed on an

external hard drive and placed in a locked vault. All ICES staff and scientific affiliates are required to sign agreements of confidentiality annually. Internal audits are conducted to monitor compliance with ICES policies, standards and procedures.

> Study data with direct personal identifiers such as OHIP numbers will reside on a dedicated and secure server at ICES and will only be accessible by a named Data Covenantor. The Covenantor will encode the OHIP number, replacing it with an ICES key number (IKN) (a code) and transferring it to a "moated" server for the study project. (The Data Covenantor is an ICES person named in our data sharing agreements and identified to the Office of the Information and Privacy Commissioner, who can access personal health information at ICES for the purposes of receiving, coding, transferring or destroying personal health information.) The coded study data will only be made available to the Principal Investigator and project staff directly responsible for data analysis (under the supervision of the investigator). No subject, physician or institution will be identified in the reporting of results

14.5.12.3 Cost calculation

Once the utilization of health services is determined from those cases linked to administrative databases, publicly available costs (2016$CAN) will be applied to health services. Costs for physician and laboratory services will be determined by applying that year's fee code. Costs for hospital care will be estimated using the Canadian Institute for Health Information (CIHI) Resource Intensity Weight method for the most recently available year. Outpatient prescription drug costs for participants not covered by ODB (those under age 65 and not on social assistance) will be considered to be the same as the trial arm-specific average for those with coverage. Costs will then be inflated using the healthcare-specific Consumer Price Index reported by Statistics Canada into constant Canadian dollars for the year the study ends. Due to the short time horizon, discounting will not be applied.

14.5.12.4 Primary Analysis

A within-trial analysis will be conducted to calculate the total cost for each arm and mean cost per subject for each arm. Frequency distributions and measures of central tendency (e.g. means and medians) will be determined for each resource category (e.g. hospitalizations)for each arm of the study. Confidence intervals for the difference in costs and resource utilization between the strategies overall and for each resource category will also be calculated. Univariate comparisons between the groups will be made primarily using nonparametric tests, such as Wilcoxan rank-sum test. In the primary analysis, assuming equivalence in the primary outcome, an arm with significantly lower mean costs will be considered the economically most attractive approach.

Should the clinical trial find a difference between the two arms on the primary endpoint, an incremental cost-benefit analysis will be calculated by deriving the additional cost per case of clinically significant cancer diagnosed, according to the following equation:

$$\text{Cost-benefit} = \frac{\text{Cost}_{(\text{Arm A})} - \text{Cost}_{(\text{Arm B})}}{\text{Diagnoses}_{(\text{Arm A})} - \text{Diagnoses}_{(\text{Arm B})}}$$

The cost of avoiding each additional case of clinically insignificant cancer diagnosed may also be similarly calculated. Consideration will be given to extending this analysis using economic modeling with incorporation of utility values from the EQ-5D to allow a lifetime perspective to be taken and the estimation of quality adjusted life years (QALYs).

14.5.12.5 Secondary Cost Analyses

One and multi-way sensitivity analyses will be carried out around major cost drivers by varying the costs over their observed ranges and conducting threshold analyses where appropriate. Sensitivity analyses will also be performed to evaluate potential limitations in the data, such as ODB costs as described above (though the proportion without ODB coverage should be similar in the two arms, and it is not expected to be a major cost-driver).

14.5.13 Missing Data

The impact of missing data will be explored in all analyses; sensitivity analyses/multiple imputation will be performed as appropriate.

15. Participant compliance and withdrawal

The study will be completed when at least 422 subjects have been randomized, have undergone a diagnostic test and completed follow up. Compliance to randomized treatment will be assessed by monitoring the completed forms, e.g. the systematic TRUS guided biopsy form or the MRI-targeted biopsy form.

In consenting to the study, subjects are consenting to study monitoring, imaging and biopsy procedures, follow-up, data collection and analysis. Subjects are allowed to withdraw consent at any stage and their care will not be affected in any way. All communication surrounding the withdrawal and its reasons should be noted in the subject's record. Such cases should be reported to the PRECISE Study Operations Office. Data up to the time of withdrawal can be included in the study.

As the study diagnostic tests are for suspected cancer it is not anticipated that there will be significant loss to follow up.

15.1 Subject Withdrawal from Study

A subject may discontinue participation in this study at any time at the investigator's discretion or at the request of the subject.

If a subject discontinues at or before Visit 1 (randomization), he is not required to complete end of study assessments.

If a subject discontinues after Visit 1 (randomization) for any reason, the investigator should make every effort to complete the activities bulleted below.

- End of study assessments as outlined in **Section 10.14.**
- Any occurrence of death, prostatic surgical intervention, non-surgical treatment for prostate cancer after study withdrawal should be documented in the CRF and source documents.

Subjects who are discontinued from the study after randomization will not be replaced. Subjects withdrawn from the study retain their subject number if already given. New subjects will be allocated a new subject number.

In the event that a subject is prematurely discontinued from the study at any time due to an AE, the procedures describe in **Section 16.3** must be followed.

Subjects should be withdrawn from the study for any of the following criteria:

- Non-compliance with the requirements of the study.
- Request to discontinue treatment. This request can be made by either the subject or the investigator.
- Develops progressive disease.

15.2 Study completion

The primary end point will be reached when the last subject entered has their systematic biopsy or MRI and targeted biopsy if indicated. All subjects will be followed for up to 2 years following study entry or until they have radical treatment. Subjects who are found to have significant prostate cancer and are treated will not be included in follow up for this period. This includes subjects diagnosed as part of study protocol, and subjects diagnosed during the follow up period by standard-of-care procedures. However, post MRI/biopsy questionnaires will not be required following non-protocol based procedures.

16. Data Monitoring, Quality Control and Safety

16.1 Stopping / discontinuation rules

The study will be completed when 450participants have been randomized, undergone a diagnostic test and completed follow up.

The Trial Steering Committee (TSC), Data Safety and Monitoring Committee (DSMC) or Trial PI may recommend cessation of the trial or suggestion modifications to trial conduct if there are concerns about subject safety or futility. See Section 14.2.1.for further details on the interim analysis. Appropriate documentation as per the PI's requirement will be completed if stopping the trial is necessary and the ethics committee will be informed.

As the study is unblinded there will be no need for randomization code breaks.

16.2 Monitoring, quality control and assurance

Members of the trial team will be Good Clinical Practice (or equivalent) trained.

An independent DSMC will be appointed to monitor subject safety and the rate of recruitment of subjects in the study. They will meet at least once a year whilst the trial is ongoing for routine review of safety data and trial progression. They have the power to call additional meetings and review data at any point in the trial should they wish to do so.

The PI may also arrange an independent trial monitor to review the study data.

16.3 Assessment of safety

The investigator is responsible for the detection and documentation of events meeting the criteria and definition of an AE or SAE as provided in this protocol. During this study, when there is a safety evaluation, the investigator or site staff will be responsible for detecting AEs and SAEs, as detailed in this section of the protocol.

16.3.1 Definition of an Adverse Event (AE)

Adverse events (AE) will be defined as "any untoward medical occurrence in a clinical trial subject undergoing any intervention in the trial, which does not necessarily have a causal relationship with this treatment".

Only adverse events specific to biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded. Please refer to section 16.3.6 of the protocol.

16.3.2 Definition of a Serious Adverse Event (SAE)

Serious adverse events (SAE) will be defined as "any untoward medical occurrence as a result of any intervention in the trial that:

(a) results in death

(b) is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

(c) requires hospitalisation or prolongation of existing hospitalisation

In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at a hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physicians' office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfils any other serious criteria, the event is serious. When in doubt as to whether 'hospitalization'; occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen form baseline is not considered an AE.

(d) results in disability / incapacity

The term disability means substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption.

(e) is a congenital abnormality/birth defect.

Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardise the subject or may require medical or surgical intervention to prevent one of the outcomes listed in the above definition. These should also be considered serious. Examples of such events are invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependence or drug abuse.

16.3.3 Disease-Related Events or Outcomes Not Qualifying as SAEs

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as a serious adverse event. Progression of the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death due to progressive disease is to be recorded on 'Record of Death' CRF page and not as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with study medication or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

16.3.4 Lack of Efficacy

"Lack of efficacy" will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

16.3.5 Clinical Laboratory Abnormalities and Other Abnormal Assessments as AEs and SAEs

Abnormal laboratory findings or other abnormal assessments that are judged by the investigator as **clinically significant** (CS) will be recorded as AEs or SAEs if they meet the definition of an AE or SAE. Clinically significant abnormal laboratory findings or

other abnormal assessments that are detected during the study or are present at baseline and significantly worsen following the start of the study will be reported as AEs or SAEs. However, clinically significant abnormal findings or other abnormal assessments that are associated with the disease being studied, unless judged by the investigator as more severe than expected for the subject's condition or that are present or detected at the start of the study and do not worsen, will not be reported as AEs or SAEs.

The trial interventions are routinely carried out in clinical practice for investigation of suspected cancer and the risks of the interventions are therefore not any greater than if a man was not part of the trial. The risks of the procedures are relatively low, as detailed in Section 11.

The investigator will exercise his or her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant.

16.3.6 Recording/Reporting AEs and SAEs

The AE reporting period for this study begins at randomization and will be recorded until 30-days post-biopsy. In the event that the subject does not undergo biopsy, AEs and SAEs should be recorded until 30-days post MRI.

Only adverse events specific to biopsy-related complications including pain, fever, hematuria, hematochezia, hematospermia, urinary retention and urinary incontinence will be recorded. Any other adverse events will not be recorded.

AEs will be recorded by a member of the research team or clinical team on an AE report form. All SAEs must be recorded on a SAE report form. SAE report forms should be sent to the CTG who will keep a log of AEs and SAEs. AE and SAE logs will be reviewed by the DSMC.

For the purposes of this study, only those AEs deemed POSSIBLY, PROBABLY, or DEFINITELY related to the study procedures (ie, MRI or biopsy), or meets the criteria as a SAE, will be collected and reported.

Expected AEs includes the following:

- Pain
- Blood in the urine
- Blood in the semen
- Blood in the stool or back passage
- Erectile dysfunction
- Urinary incontinence
- Urinary tract infection
- Fevers

In addition, small risks of allergic reactions are associated with the intravenous administration of gadolinium, the contrast agent used in MRI scans, as described in

section 10.18.1.2.This contrast agent is used consistently in MRI scanning and is not limited to this trial.

If any of these symptoms are accompanied by events consistent with the definition of an SAE as specified above, then the event will be considered an SAE.

The Trial Coordinator, Principal Investigator or Chief Investigator should be informed of any SAE within 24 hours.
All SAE report forms must be completed and the SAE logs updated. All SAEs must be followed up until a resolution is reached (i.e. recovered, recovering, recovered with sequelae, fatal, not recovered or unknown).

Local sites may have specific institutional protocols for reporting SAEs, which should be followed in addition.

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation relative to the event. The investigator will then record all relevant information regarding an AE/SAE on the CRF.

The investigator will attempt to establish a diagnosis of the event based on signs, symptoms and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

16.3.7 Evaluating AEs and SAEs

16.3.7.1 Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study. Degree of severity and change in severity will be recorded by means of National Cancer Institute, Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.03.

If the event is not listed in the NCI CTCAE (v.4.03), the assessment will be based on the investigator's clinical judgment. The intensity of each AE and SAE recorded in the CRF should be assigned to one of the following categories:

Mild: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
Moderate: An event that is sufficiently discomforting to interfere with normal everyday activities.
Severe: An event that prevents normal everyday activities.

An event that is classified as severe should not be confused with a SAE. Severity is a category utilized for rating the intensity of an event; both AEs and SAEs can be assessed as severe.

16.3.7.2 Assessment of Causality

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. The investigator will use clinical judgment to determine the relationship. Alternative causes and the temporal relationship of the event to the investigational product will be considered and investigated. The investigator will also consult the CIB and or Product Information, for marketed products, in the determination of his/her assessment.

16.3.8 Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each subject and provide further information to the PI of the study, on the subject's condition.

All AEs and SAEs documented at a previous visit/contact and are ongoing, will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, until the condition stabilizes, until the event is otherwise explained or until the subject is lost to follow-up. Once resolved, the appropriate AE/SAE CRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE.

The PI may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a subject dies during participation in the study or during a recognized follow-up period, the PI will be provided with any post-mortem findings.

New or updated information will be recorded on the originally completed SAE CRF, with all changes signed and dated by the investigator or designate. The updated SAE CRF should be resent to the PI.

16.3.9 Prompt Reporting of SAEs

Once the investigator determines that an event meets the protocol definition of an SAE, the SAE will be reported to the PI (CURC) within 24 hours.

16.3.9.1 Responsibility for Reporting Serious Adverse Events to PI

The Site Investigator must immediately inform the PI (CURC) of all SAEs (within 24 hours) at the following fax number: 1-416-480-6121.

The PI contact list for SAE receipt, fax numbers, telephone numbers and mailing addresses is as follows:

Dr. Laurence Klotz
c/o Marlene Kebabdjian
Sunnybrook Health Sciences Centre
2075 Bayview Avenue A304

Toronto, Ontario M4N 3M5 Canada
Phone: (416) 480-6100 ext 2890
E-mail:Laurence.Klotz@sunnybrook.ca
Marlene.kebabdjian@sunnybrook.ca

16.3.9.2 Completion and Transmission of the SAE Reports

Once an investigator becomes aware that an SAE has occurred in a study subject, she/he will report the information to the PI within 24 hours. The SAE CRF will always be completed as thoroughly as possible with all available details of the event, signed by the investigator (or designee), and forwarded to the PI within the designated time frames. If the investigator does not have all information regarding as SAE, he/she will not wait to receive additional information before notifying the PI of the event and completing the form. The form will be updated when additional information is received.

The investigator will always provide an assessment of causality at the time of the initial report as described in Section 16.3.6.2.

16.3.10 Post-study AEs and SAEs

If the investigator learns of any SAE at any time after a subject has been discharged from the study, and such event(s) is (are) reasonably related to the study intervention, the investigator should promptly notify the PI (CURC).

17. Study Administration

17.1 Regulatory and Ethical Considerations

An important consideration is that men are being randomized to one of two biopsy techniques when it is not known which will be more effective in diagnosing clinically significant prostate cancer. Both diagnostic tests are currently used in everyday clinical practice at the institutions involved in the trial. Though systematic TRUS guided biopsy could be considered standard of care, there is enough evidence to support the concept that MPMRI-targeted biopsy may be as effective, if not more so, than systematic TRUS guided biopsy[27]. This study aims to confirm this.

17.1.1 Ethical Conduct of the Study and Ethics Approval

The PI and each participating site will obtain approval to conduct the study from the Research Ethics Board (REB) prior to initiating the study.

Participating sites from Ontario will use the Ontario Cancer Research Ethics Board (OCREB) as their Board of Record.
This study will be conducted in accordance with 'good clinical practice' (GCP) and all applicable regulatory requirements, including where applicable, the 2013 version of the Declaration of Helsinki.

The investigator is responsible for ensuring that this protocol, the site's informed consent form and any other information that will be present to potential subjects are reviewed and approved by the appropriate REB. The investigator agrees to allow

the REB direct access to all relevant regulatory documents. The PI will provide the site investigator(s) with relevant document(s)/data that are needed for REB review and approval of the study. Before CRFs can be shipped to the site, the PI must receive copies of the REB approval, the approved informed consent form and any other information that the REB has approved for presentation to potential subjects.

If the protocol, the informed consent form or any other information that the REB has approved for presentation to potential subjects is amended during the study, the site investigator(s) is responsible for ensuring the REB reviews and approves, where applicable, these amended documents. The site investigator(s) must follow all applicable regulatory requirements pertaining to the use of an amended informed consent form including obtaining the REB approval of the amended form before new subjects consent to take part in the study suing this version of the form. Copies of the REB approval of the amended informed consent form/other information and the approved amended informed consent form/other information must be forwarded to the PI promptly.

17.1.2 Informed Consent

Informed consent will be obtained before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

The subject's consent to participate in the study should be obtained after a full explanation has been provided of the procedures to be given. Subjects should be given sufficient time (at least 24 hours) after being given the study subject information sheet to consider and discuss participation in the study with family and friends.

A contact number will be given to the subject should he wish to discuss any aspect of the study. Following this, the clinician will determine that the subject is fully informed of the study and their participation, in accordance with Good Clinical Practice Guidelines. Subjects will always be asked to sign a consent form. One copy will be given to the subject, one copy will be kept with subject's hospital notes and one copy should be kept in the local investigator's file.

17.1.3 Investigator Reporting Requirements

The investigator is responsible for reporting SAEs to the REB in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his or her site and notification of study closure to the REB.

17.2 Study Monitoring

This study will be monitored by a CRA. The CRA will contact the sites by telephone on a predetermined basis and would conduct a monitoring visits based on the data entered in the EDC and queries.

During these contacts, the monitor will:

- Check the progress of the study
- Review study data collected
- Conduct source document verification
- Identify any issues and address their resolution

This will be done in order to verify that the:

- Data are authentic, accurate and complete
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (and any amendments), GCP and all applicable regulatory requirements

The investigator agrees to allow CRA personnel direct access to all relevant documents and to allocate his/her time and the time of his/her staff to CRA personnel to discuss findings and any relevant issues.

17.3 Quality Assurance

To ensure compliance with GCP and all applicable regulatory requirements, regulatory agencies may conduct a regulatory inspection of the study. Such audits/inspections can occur at any time during or after completion of the study. If an audit or inspection occurs, the investigator and institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditory/inspector to discuss findings and any relevant issues.

17.4 Study and Site Closure

Upon completion of the study, the site investigator(s) will conduct the following activities:

- Return of all study data to the Sponsor (CURC)
- Submission of all study data and data queries to OCOG
- Review of site study records for completeness

In addition, the Principal Investigator has the right to temporarily suspend or prematurely discontinue this study either at a single site or at all sites at any time for reasons including but not limited to, safety or ethical issues or severe non-compliance. If the PI determines such action is needed, the PI will discuss this with the site investigator (including the reasons for taking such action) at that time. When feasible, the PI will provide advance notification to the site investigator of the impending action prior to it taking effect.

Individual site Investigators may also terminate their participation in the study at any time. If the investigator determines such action is needed, the investigator will discuss this with the PI(including the reasons for taking such action) at that time. When feasible, the investigator will provide advance notification to the PIof the impending action prior to it taking effect.

The PI will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform

the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the REB promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must be returned to the PI. In addition, the investigator has the responsibility to return any used/unused clinical supplies.

Financial compensation to investigators and/or institutions will be in accordance with the agreement established between the investigator and the PI.

17.5 Records Retention

Following closure of the study, the site investigator(s) must maintain all site study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed and whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems and staff.

The site investigator(s) will retain study records to comply with all applicable regulatory requirements. The minimum retention time will meet the strictest standard applicable to that site for the study as dictated by any institutional requirements or local laws or regulations of Health Canada standards/procedures; otherwise, the retention period will default to 25 years.

The site investigator(s) must inform the PI of any changes in the archival arrangements, including but not limited to the following: archival at an off-site facility, transfer of ownership of the records in the event the investigator leaves the site. The PI should be informed of this change if it affects their access to the information in case of an audit.

17.6 Data Management

Subject data are collected by the investigator or designee using the CRF within an Electronic Data Capture (EDC) system. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database. Clinical data management will be performed in accordance with applicable standards and data cleaning procedures. Database lock will occur when data management quality control procedures are completed.

17.7 Publication

The results from the study will be analyzed and published as soon as possible and is appropriate. All study-related communications can only be presented or published after approval from all relevant members involved in the trial.

All publications shall include appropriate indication named authors as agreed on by the members involved in the trial. For the main study reports, senior and first authorship will be determined by agreement of the Chief Investigator, the Principal Investigator at time of manuscript drafting. Authorship will be based on

recommendations of the International Committee of Medical Journal Editors (www.ICMJE.org) where all authors meet the following for criteria:

17. Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
18. Drafting the work or revising it critically for important intellectual content; AND
19. Final approval of the version to be published; AND
20. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people.The clinical trials.gov registration number that will be allocated to this trial will be attached to any publications resulting from this trial.

Trial funding agencies (OICR, PCC and collaborators as appropriate) will be acknowledged in all publications.

The members of the trial steering committee will be listed with their affiliations in the acknowledgements/appendix of the main publication.

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Appendices

Appendix 1: Time windows for data collection

For the overall schedule of visits for each arm please see Section 9.3, Tables 1-3
For details on time windows permitted for each trial intervention to be completed please see Table 5 below.

Table 5: Details of time windows permitted for all trial interventions.

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.

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 30-day 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. To be given to subject to take home after biopsy and completed as instructed on day 30 post-biopsy. To be returned by post or at follow up appointment (Visit 4). 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. If Visit 4 is on or later than 30 days then this can be returned at the Visit 4 appointment. 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.
Telephone reminder	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
Visit 4 Follow up for results And treatment Decision EQ-5D-5L Questionnaire	 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. Depending on local Urology service structure, these results may need to be discussed at an MDT meeting to inform treatment decision. To be completed
Visit 5 **26 week follow up**	• Vitals, DRE • PSA • Optional blood
Visit 6 1 year follow up 52 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. • results of any off protocol biopsies or MRI • optional sample collection (blood, urine)
Visit 7 **78 week follow up**	• 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: | | | | | | | | | |
day month year

Date of Report: | | | | | | | | | |
day month year

Reporting Radiologist:

Form Completion Instructions:

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.

IMPORTANT SUBMISSION INSTRUCTIONS:

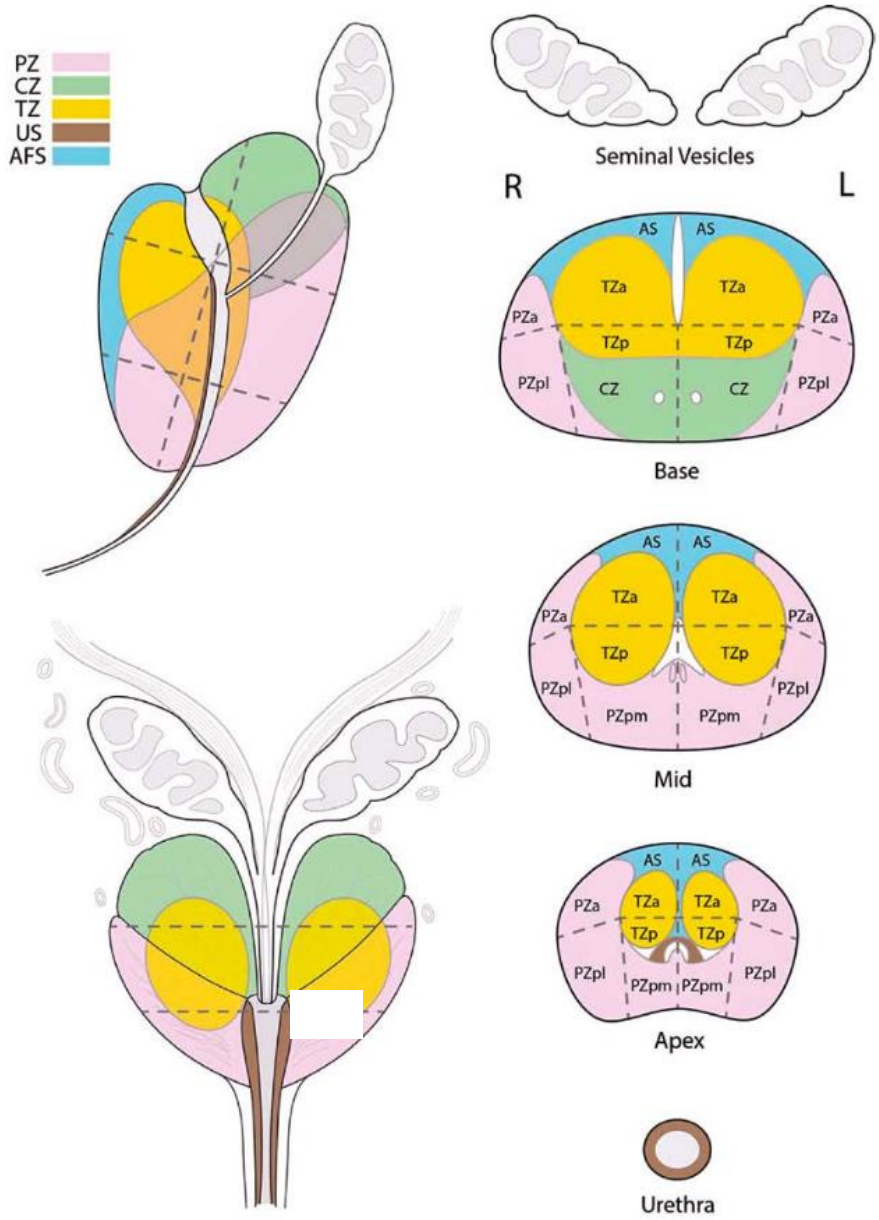
Please send this completed case report form and a DVD with the images AND completed MRI Report to:

Marlene Kebabdjian
Sunnybrook Health Sciences Centre
Urology Research, A304
2075 Bayview Avenue, A304
Toronto, Ontario, M4N 3M5

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…)



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**

If image quality is not good please comment:

_____

_____

_____

How to record locations

Location Code Format: (L/R), (B/M/A), Pi-RadsZone (AS, TZa, TZp, CZ, PZa, PZpl, PZpm)

Number of candidate tumor sites:_____

If none, please proceed to Section B

Section A:

Target 1 *(Highest Pi-Rads score and then largest):*

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal _____

Target 2:

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal

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:_____ mm^2/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: ❑ No ❑ Yes ❑ Equivocal

There are more than 3 targets seen (Y/N): _____
If yes give describe:
_____
_____
_____

Section B:

LSV invasion: ❑ No ❑ Yes ❑ Equivocal	**RSV invasion:** ❑ No ❑ Yes ❑ Equivocal
Adenopathy: ❑ No ❑ Yes ❑ Equivocal	**Worst PI-RADS Score: _____**

Other Findings:
_____
_____

_____ cm	(SI) x	_____ cm	(AP) x	_____ cm	(LR)	**Volume:**	**_____**	cc

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**

If image quality is not good please comment:

_____
_____
_____
_____

Number of candidate tumor sites: _____

If none, please proceed to Section C

There was a change in lesions number or rank when adding DCE sequence: ❑ No ❑ Yes

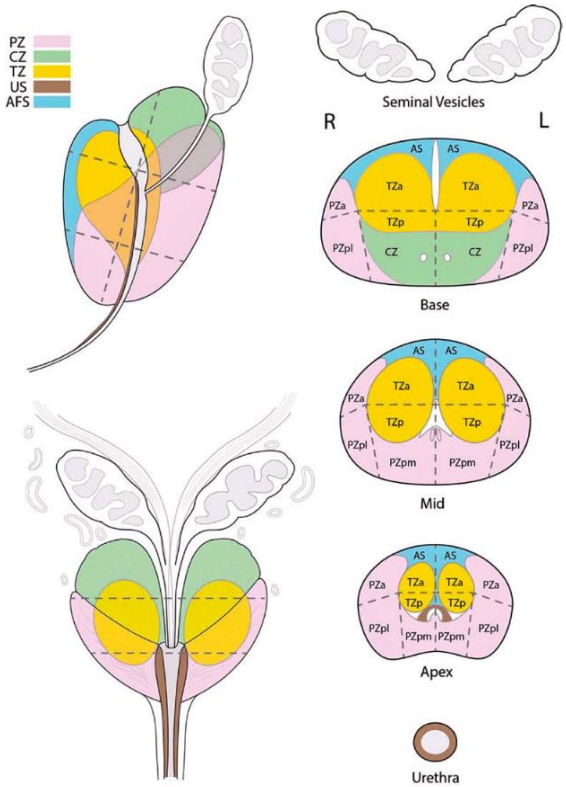
If Yes, please give the correspondence between Target numbers with and without DCE (i.e. Target 1 without DCE = Target x with DCE) and **fill in all fields below to avoid confusion. Also draw lesions on diagram below again**

Also draw lesions on diagram on next page again.

Correspondence:

Old T1 = New T___ Old T2 = New T___ Old T3 = New T___

If there is change from Part 1 please redraw all lesions on diagram below annotating each with the T index (i.e T1; T2…)



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):___

Mean ADC: _____ Min ADC – single voxel:_____ mm^2/s $x10^{-6}$

Size: ___x___ x ___mm (Ax1 > Ax2 x SI)

Location(s) (largest to smallest area involved):

_____,_____,_____,_____

_____,_____,_____,_____

Extraprostatic extension: ❑ No ❑ Yes ❑ Equivocal

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:_____ mm^2/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:_____ mm^2/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

Adenopathy: ❑ No ❑ Yes ❑ Equivocal	**Worst PI-RADS Score: _____**

Other Findings:

_____

_____

Safety:

Was there an immediate reaction to Gd contrast injection: ❑ No ❑ Yes

If yes, please give details:

_____

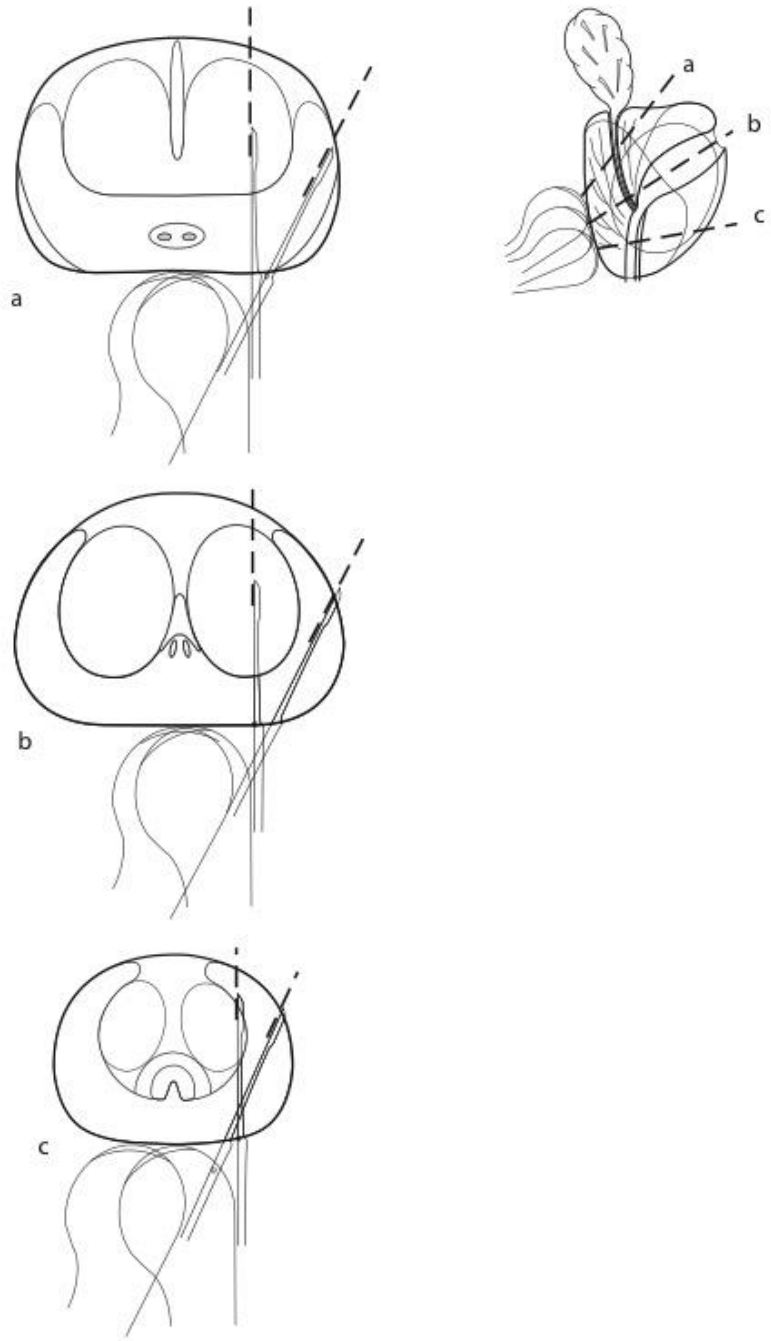
_____

Will subject require an TRUS/MRI-fused biopsy (Pi-Rads >=3)?	**❑No (PI-RADS 1, 2)**	**❑Yes (PI-RADS 3, 4 or 5)**

Appendix 3: Example of systematic TRUS guided biopsy schema

Figure depicting 12-core systematic TRUS guided biopsyschema that sites are recommended to follow. Axial/coronal sections of a prostate gland (left) showing biopsy courses of the 12 biopsies performed under ultrasound guidance with an end fire probe. Upperright: axial planes in the sagittal view. a, base; b, mid-gland; c,

apex.From Haffner *et al* [37].



Appendix 4: 2-page EQ-5D-5L Questionnaire

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑

I have slight problems in walking about ❑

I have moderate problems in walking about ❑

I have severe problems in walking about ❑

I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑

I have slight problems washing or dressing myself ❑

I have moderate problems washing or dressing myself ❑

I have severe problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑

I have slight problems doing my usual activities ❑

I have moderate problems doing my usual activities ❑

I have severe problems doing my usual activities ❑

I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑

I have slight pain or discomfort ❑

I have moderate pain or discomfort ❑

I have severe pain or discomfort ❑

I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑

I am slightly anxious or depressed ❑

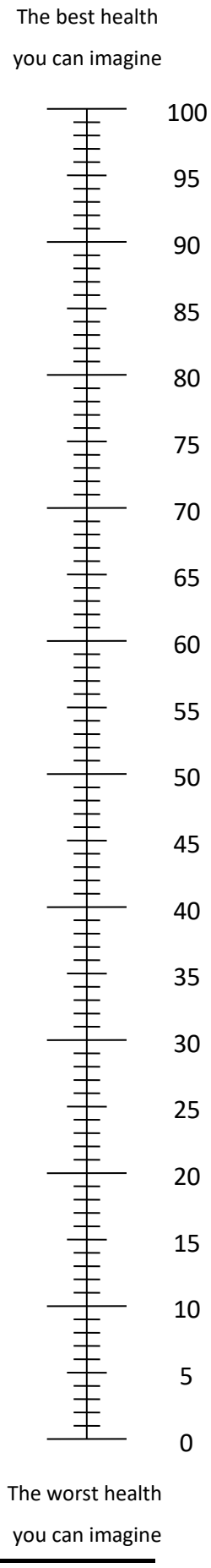
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine. 0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY= ☐



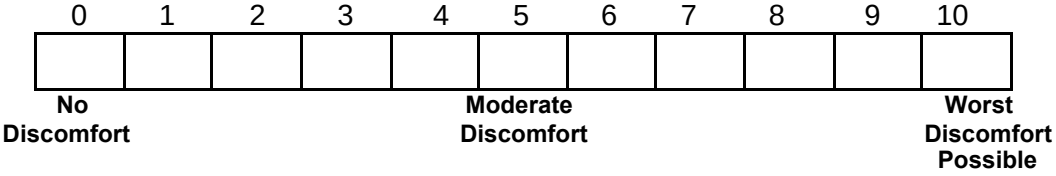
15292 # Appendix 5: Immediate post biopsy questionnaire

Immediate post-biopsy questionnaire

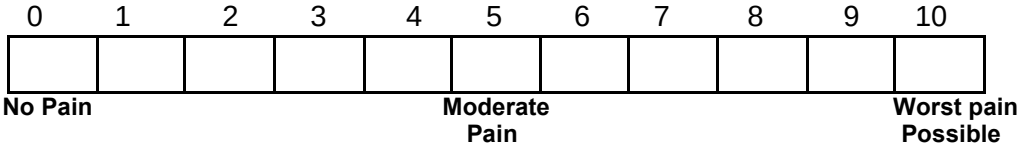
Please ask the patient to fill this out after the biopsy, before they leave the department.

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?



2. Overall, how much pain did the biopsy procedure cause you?



Please complete the next page of questions

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15294

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.

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15296 # 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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 ☐ 1 No ☐ 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

15297

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 ☐ 1 No ☐ 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
	☐ 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 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 ☐ 1 No ☐ 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
	☐ 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 biopsy procedure:

16. Erectile dysfunction, meaning the persistent inability to get and maintain an erection sufficient to allow satisfactory sexual performance

Yes ☐ 1 No ☐ 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
	☐ 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

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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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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 ☐ 1 No ☐ 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
	☐ 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
☐	☐	☐	☐

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
e.g. ciprofloxacin	*500mg*	*2*	*3*

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"):*

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15302

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
	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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	Minor Problem	Moderate Problem	Major Problem
☐ 1	☐ 2	☐ 3	☐ 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.