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# BMJ Open

## TROG 18.01 Phase III Randomized Clinical Trial of the Novel Integration of New prostate radiation schedules with adJuvant Androgen Deprivation - NINJA

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Manuscripts

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5 2 **prostate radiation schedules with adJuvant Androgen Deprivation - NINJA**  
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3 75 **Abstract**

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5 76 **Introduction:**

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8 77 Stereotactic Body Radiotherapy (SBRT) is a non-invasive alternative to surgery for  
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10 78 the treatment of non-metastatic prostate cancer (PC). The objectives of the NINJA  
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12 79 clinical trial are to compare two emerging SBRT regimens for efficacy with technical  
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14 80 sub-studies focussing on MRI only planning and the use of Knowledge Based  
15  
16 81 Planning (KBP) to assess radiotherapy plan quality.  
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21 83 **Methods and Analysis:**

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24 84 Eligible patients must have biopsy proven unfavourable intermediate or favourable  
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26 85 high risk PC, have an ECOG performance status 0-1, and provide written informed  
27  
28 86 consent. All patients will receive six months in total of Androgen Deprivation  
29  
30 87 Therapy (ADT). Patients will be randomized to one of two SBRT regimens. The first  
31  
32 88 will be 40 Gy in 5 fractions given on alternating days (SBRT monotherapy). The  
33  
34 89 second will be 20 Gy in 2 fractions given one week apart followed 2 weeks later by  
35  
36 90 36 Gy in 12 fractions given 5 times per week (Virtual High Dose Rate Boost [HDRB]).  
37  
38 91 The primary efficacy outcome will be Biochemical Clinical Control (BCC) at five  
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40 92 years. Secondary endpoints look at the transition of centres towards MRI only  
41  
42 93 planning and the impact of KBP on real time plan assessment. Total accrual to 472  
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44 94 patients is planned.  
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51 96 **Ethics and Dissemination:**

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54 97 NINJA is a multicentre cooperative clinical trial comparing two SBRT regimens for  
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56 98 men with PC with novel technical substudies. It builds on promising results from  
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58 99 several single armed studies, and explores radiation dose escalation in the Virtual  
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3 100 HDRB arm. It has HREC approval, and findings will be reported in the peer reviewed  
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5 101 literature.  
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10 103 **Trial Registration:**

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12 104 Australia New Zealand Clinical Trial Registry – ANZCTN 12615000223538.

13  
14 105 Registered prior to opening to accrual 6 November 2018.

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16 106 Full WHO Trial Registration Data Set available on-line via

17  
18 107 <https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375560>  
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24 109 **Article Summary**

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26 110 **Strengths and Limitations of this Study**

- 27  
28 111 • For men with newly diagnosed prostate cancer, will provide data on outcomes for  
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30 112 two emerging approaches to treatment with stereotactic radiotherapy  
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32 113 • Will prospectively explore the implementation of MRI only radiotherapy planning  
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34 114 • Will seek to validate the additional value of automated knowledge based planning  
35  
36 115 • Incorporates novel staging imaging including PSMA-PET and MRI  
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42 117 **Keywords:**

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44 118 Computer Assisted Radiotherapy Planning

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46 119 Image Guided Radiotherapy

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48 120 Intensity Modulated Radiotherapy

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50 121 Prostatic Neoplasms

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52 122 Radiotherapy

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54 123 Radiotherapy Dose Hypofractionation

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56 124 Stereotactic Body Radiotherapy  
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## 125 Introduction

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### 127 *Stereotactic Body Radiotherapy for Prostate Cancer*

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129 Prostate cancer has a major impact on the Australian population with 3500  
130 deaths projected in 2018 and treatment costs to patients and the health system  
131 exceeding \$500 million by 2025.[1 2] The question at the heart of NINJA is to  
132 compare two emerging and practice-changing schedules of radiotherapy that  
133 leverage state-of-the-art technology developments and our Australian clinical trial  
134 experience to make treatments safer, highly efficient and more convenient for  
135 patients. The first schedule is a 5 fraction Stereotactic Body Radiotherapy (SBRT  
136 monotherapy) approach.[3] The alternative regimen is 'Virtual High Dose Rate Boost'  
137 (HDRB), non-invasively delivering brachytherapy-type doses.[4] Superiority of the  
138 latter schedule would validate the utility of dose escalation to improve outcomes.  
139 Similarity of outcomes in the former schedule would allow for major cost savings and  
140 reduced patient burden with reduction of treatment sessions from 40 to 5 (see  
141 **Figure 1**).

142

143 Conventional radiotherapy regimens for prostate cancer are given 5 times per week  
144 for up to 9 consecutive weeks.[5] Recent results from large non-inferiority studies  
145 including substantial Australian input has helped establish a 4-week moderately  
146 hypofractionated schedule as an alternative approach.[6-8] Building on this, large  
147 series are showing excellent outcomes with regimens giving as few as 5  
148 radiotherapy fractions, using higher daily doses of radiotherapy.[9 10] A 477 patient  
149 series with median follow-up of seven years showed 89.6% biochemical disease

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3 150 control with late grade 2 and 3 genitourinary (GU) toxicity low at 9% and 1.7%  
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5 151 respectively.[11 12] Grade 2 gastrointestinal (GI) toxicity was similarly favourable at  
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7 152 4.1%. Our SPARK phase 2 study used a 5-fraction prostate SBRT monotherapy in  
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9 153 conjunction with intrafraction motion management to assess the dosimetric impact of  
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11 154 increasing the accuracy of radiotherapy dose delivery.[3]  
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17 156 Following on from this experience, several randomized studies are currently  
18  
19 157 underway exploring similar stereotactic regimens, where much higher daily doses of  
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21 158 radiotherapy are given in between 5 and 7 visits (**Table 1**). The Scandinavian HYPO-  
22  
23 159 RT-PC study completed accrual in 2015, and presented early toxicity data in 2016  
24  
25 160 showing no significant differences between the control and SBRT arms.[13 14] Initial  
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27 161 efficacy results from this study were presented in 2018, showing no differences  
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29 162 between the two arms. Recent guidelines from ASTRO, AUA and ASCO have  
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31 163 incorporated prostate SBRT monotherapy as a treatment option for centres  
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33 164 experienced in this technique.[15] A 2142 patient SBRT monotherapy experience  
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35 165 has also shown excellent efficacy, and low toxicity.[16] Bringing this together, SBRT  
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37 166 monotherapy is an emerging standard treatment option.  
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45 168 Strong evidence exists for superior disease control through the use of a  
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47 169 brachytherapy boost compared with conventional radiotherapy.[17 18] Despite this,  
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49 170 the use of brachytherapy continues to decline, partly due to concerns regarding  
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51 171 higher risks of significant late GU toxicity.[19] Also, the lack of evidence for improved  
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53 172 disease control translating to improved survival has limited uptake, although the poor  
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55 173 sensitivity of conventional staging investigations may contribute to superior local  
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57 174 control being overwhelmed by undiagnosed micro-metastatic disease. The  
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3 175 emergence of PSMA-PET as a more sensitive and specific staging modality makes  
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5 176 revisiting the radiotherapy dose-escalation question highly relevant.[20 21] An  
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7 177 alternative approach to brachytherapy is a 'virtual HDR boost' where 2-3 large doses  
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9 178 designed to mimic HDRB are delivered via stereotactic techniques with an additional  
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11 179 fractionated External Beam Radiation Therapy (EBRT) component. Relatively small  
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13 180 virtual HDRB series with nearly 4 years follow up have shown this approach to be  
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15 181 feasible, although often using specialised equipment such as the Cyberknife  
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17 182 platform.[22 23] Virtual HDRB has also been proven feasible in the setting of  
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19 183 multicentre phase 2 trial in Australia, with 135 men enrolled on the PROMETHEUS  
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21 184 trial (ACTRN12615000223538) where 2 fractions of 9.5-10Gy are followed by an  
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23 185 EBRT component of either 46Gy in 23 or 36Gy in 12 fractions. Early data from  
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25 186 PROMETHEUS shows no grade 2-3 late GI toxicity after 24 months and grade 2 late  
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27 187 GU toxicity prevalence rates of <7% out to 3 years.[24] Promising efficacy signals  
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29 188 are also becoming evident, with almost ablative PSA levels being observed  
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31 189 consistent with excellent disease response.  
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35 191 Virtual HDRB may represent a significant biological dose escalation compared with  
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37 192 SBRT monotherapy. Assuming prostate cancer has an alpha beta ratio of 1.5 Gy,  
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39 193 40 Gy in 5 fractions and virtual HDRB would be equivalent to 110 and 120 Gy in 2  
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41 194 Gy equivalent fractions respectively. Modelling of RCT data suggests that each  
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43 195 extra Gray in dose translates to ~2% improvement in disease control.[25]  
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45 196 Alternatively, the virtual HDRB approach potentials allows for some variation in  
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47 197 fraction size sensitivity within and between tumours. A reasonable question would  
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49 198 be whether the excellent results seen with HDR brachytherapy boost could be safely  
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3 199 translated into the stereotactic setting on the basis of this increase in biological dose  
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5 200 delivery. This is the fundamental question which drives NINJA.  
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10 202 *Knowledge Based Planning*  
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14 204 Knowledge-Based Planning (KBP) has the potential to simultaneously improve and  
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16 205 automate the radiotherapy planning process. KBP uses previous cases to build a  
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18 206 model of an optimal treatment plan which can then be applied to the current patient.  
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20 207 Previous work suggests that KBP can provide faster and frequently better plans,[26]  
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22 208 but this has not been prospectively assessed in a multicentre fashion. NINJA  
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24 209 provides an ideal opportunity for this.  
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30 211 Radiotherapy plan quality is critically important in achieving optimal treatment  
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32 212 outcomes. The Australia-led TROG 02-02 study for patients with locally advanced  
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34 213 head and neck cancer showed that non-protocol compliant plans had a locoregional  
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36 214 control and overall survival decrement of 24% and 20% respectively.[27] Via TROG,  
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38 215 Australia has become leaders in the use of approaches such as stringent  
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40 216 credentialing and real time review (RTR) of RT contours and plans, with work in  
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42 217 prostate cancer subsequently showing very low rates of protocol deviations both in  
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44 218 the definitive prostate and post-prostatectomy irradiation scenarios.[28 29]  
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50 220 An issue with the current RTR process is that although a plan can be deemed  
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52 221 satisfactory, it is difficult to determine whether it could be improved. As treatment  
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54 222 techniques evolve, satisfying the dose constraints in clinical trial protocols can  
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56 223 become progressively easier. Knowledge-Based Planning (KBP) has emerged as a  
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3 224 promising approach to assess and improve plan quality. In KBP, a model is  
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5 225 developed using a range of patient anatomies and target volumes. This can then be  
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8 226 rapidly applied to a new case to either generate a plan de novo, or to compare with a  
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10 227 conventional plan. The Radiation Therapy Oncology Group (RTOG) 0126 prostate  
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12 228 cohort was selected to study treatment plan quality variations. This work examined  
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14 229 the high-dose Intensity Modulated Radiation Therapy (IMRT) patients using a KBP  
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16 230 model to identify the plans that best met the dosimetric aims of the protocol.[30]  
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18 231 Focusing on Grade 2+ late rectal toxicities with an outcomes-validated normal tissue  
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20 232 complication probability (NTCP) model, the high-dose arm of RTOG 0126 patients  
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22 233 treated with IMRT patients had a 15.1% cumulative incidence of Grade 2+ rectal  
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24 234 complications.[31] KBP plans were predicted to lead to a 4.7% risk reduction in this  
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26 235 rate, which therefore may have cut this incidence by a third. The observed quality  
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28 236 variations in RTOG 0126 give the strongest evidence yet that suboptimal planning is  
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30 237 a critical problem in multi-institutional radiotherapy clinical trials and in the wider  
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32 238 practice of radiotherapy. KBP has yet to be robustly assessed in a multicentre  
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34 239 fashion, where the heterogeneity of planning systems and personnel would be  
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36 240 expected to be greatest.  
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#### 242 *MRI Radiotherapy Planning*

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49 244 Computerised Tomography (CT) is widely used for radiotherapy dosimetry  
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51 245 calculation because of the ability to directly measure electron density. Our team has  
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53 246 validated the use of Magnetic Resonance Imaging (MRI) to create a substitute CT  
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55 247 (sCT) which can then be used for accurate dose calculation.[32] The superior soft  
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57 248 tissue resolution of MRI, absence of radiation dose, and reduction in image artefacts  
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3 249 means that if the dose calculation problem could be solved, standard CT based  
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5 250 planning would be rendered obsolete.[33]  
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10 252 Many centres now acquire both a CT and a MRI scan for each patient, but co-  
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12 253 registration of these datasets introduces significant error mostly under the influence  
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14 254 of bladder filling and varying rectal distension. An attractive alternative would be to  
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16 255 create a substitute CT (sCT) from the MRI dataset to allow RT dose calculation. Our  
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18 256 team has developed a hybrid atlas-voxel based technique of sCT generation which  
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20 257 showed high agreement in both mean monitor units (0.3%+/- sd 0.8%) and dose  
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22 258 delivery (3-dimensional gamma pass rate at 2 mm/2% level of 100% +/- sd 0%.[32] A  
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24 259 group of Swedish centres have shown similar findings in a retrospective, multicentre  
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26 260 study,[34] and our group is prospectively evaluating this approach in 2 centres  
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28 261 (HIPSTER study - ACTRN12616001653459). Given the advantages of MRI for  
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30 262 prostate cancer, and the improving access to MRI in Australia (including  
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32 263 radiotherapy departments with dedicated planning MRI facilities), this is another area  
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34 264 ripe for wider assessment, implementation and eventual broader application.  
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#### 41 42 266 *Summary* 43 44

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47 268 NINJA is a combined phase 3 multicentre study of 472 men randomized to two  
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49 269 novel radiotherapy schedules. The hypotheses are that NINJA will advance 1)  
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51 270 Biochemical Clinical Control (BCC) of prostate cancer, 2) treatment planning via  
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53 271 automation and 3) planning imaging methodology.  
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3 272 **Aim 1: *Radiobiological Dose Escalation*:** The escalated radiation dose delivered  
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5 273 using a virtual HDRB approach achieves superior disease control compared with a  
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7 274 SBRT monotherapy alternative.  
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10 275 **Aim 2: *KBP Advantage*:** The treatment plans using KBP will be dosimetrically  
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12 276 superior to traditional manual planning approaches.  
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15 277 **Aim 3: *MRI only Planning*:** MRI will give dosimetry similar to standard CT planning.  
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3 278 **Methods/Design**  
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8 280 **Study Design:**  
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11  
12 282 The study design is a prospective randomised phase 3 trial available in Australian  
13  
14 283 academic and community Radiation Oncology centres (sites available via Trans-  
15  
16 284 Tasman Radiation Oncology Group) which conforms to the SPIRIT guidelines.  
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18  
19 285 Protocol v2.0 is dated November 2018.  
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24 287 **Key Trial Eligibility Criteria**  
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28 289 Unfavourable intermediate or favourable high risk prostate cancer (any combination  
29  
30 290 of ISUP 3-5 and/or cT2b/T2c/T3aN0 and/or PSA 10-20 in the absence of other high  
31  
32 291 risk factors ie T3b/T4, PSA>20). For high-risk patients, PSMA PET staging prior to  
33  
34 292 study entry showing N0M0 disease. Accruing centres will proactively screen for  
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36 293 potentially eligible patients.  
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42 295 **Pre-Treatment**  
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47 297 All patients will receive a total of six months of Androgen Deprivation Therapy  
48  
49 298 (ADT).[35] Both CT and MRI planning scans will be performed for the first 10  
50  
51 299 patients at each centre and phasing out CT for centres involved in MRI planning  
52  
53 300 aspect of NINJA. Rectal displacement (eg SpaceOAR, Rectafix, Rectal Balloon) is  
54  
55 301 encouraged, but not mandated.[36] Urethral visualization via temporary  
56  
57 302 catheterization or equivalent approaches will be performed. Erectile sparing RT  
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3 303 plans for men with adequate baseline IIEF and desire to maintain erectile function  
4  
5 304 can be used.[37] Centres will be credentialed for MRI planning via their first 5  
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7  
8 305 patients being primarily planned off the CT, but with sCT generation and confirmation  
9  
10 306 of accurate dosimetry. The next ten patients will have planning performed on sCT  
11  
12 307 and confirmed on planning CT. Subsequent patients will omit a planning CT, be  
13  
14 308 planned on sCT, and have confirmation of accurate dosimetry on treatment using a  
15  
16 309 centrally approved approach eg EPID dosimetry[38] or in vivo dosimetry.[39]  
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### 311 ***Time-dose-fractionation planning details***

312  
313 *SBRT Monotherapy arm:* 40 Gy in five fractions delivered 2-3 times per week,  
314 prescribed to CTV D95%.

315 *Virtual HDRB Boost Arm:* 20 Gy in two fractions prescribed to CTV D95% delivered  
316 once a week followed by a two week break and then 36 Gy in 12 fractions delivered  
317 5 times per week prescribed to PTV D95%. See tables 2a-c for dose constraints,  
318 and Figure 2 for an example of the SBRT dosimetry.

### 320 ***Quality Assurance***

321  
322 Centre credentialing will include submission of a 'Virtual HDRB Boost' treatment plan  
323 for a patient to ensure accurate contouring and protocol compliant dose delivery. The  
324 initial KBP model will be generated from phase 2 SPARK and PROMETHEUS trials,  
325 but will be updated as NINJA proceeds. All cases will be submitted for KBP  
326 comparison, and an automated report to be returned within 24 hours. Real-time  
327 review will occur for all patients on trial.

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5 329 ***Treatment Delivery***6  
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8 331 All patients require intra-prostatic markers, and both inter- as well as intra-fraction  
9  
10 332 motion management strategies to ensure accurate treatment delivery. For intra-  
11  
12 333 fraction motion assessment, numerous 'real time' approaches are acceptable (eg  
13  
14 334 KIM, Calypso, Cyber-knife). In all instances, translational movements to be  
15  
16 335 corrected to 0mm threshold prior to commencing treatment.  
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24 337 ***Outcome Reporting***25  
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27  
28 339 Indicators of feasibility, accuracy, impact on replanning, and other qualitative and  
29  
30 340 quantitative markers of KBP and MRI planning will be collected. Patient reported  
31  
32 341 outcomes to include baseline and serial patient reported outcomes (IIEF, EPIC),  
33  
34 342 physician toxicity grading (CTC AE v5), PSA and any sites of confirmed disease  
35  
36 343 relapse or death due to any cause. Participants will have unique identifiers which  
37  
38 344 will protect their confidentiality, and only summary data will be presented after  
39  
40 345 analysis. Participants will be requested to provide this information even if without  
41  
42 346 from study treatment. Any Serious Adverse Events will be reported to the central  
43  
44 347 HREC within 1 working day. Data will be securely electronically stored for at least 15  
45  
46 348 years, and audited to ensure data quality. Any protocol amendments will be  
47  
48 349 reviewed by the HREC, and communicated to all participating centres, investigators  
49  
50 350 and participants. If the prevalence of CTC AE grade 3 GI or GU toxicities exceeds  
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52 351 10% at any stage, the trial will be halted for safety assessment. This oversight will be  
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3 352 provided by the TROG Independent Data Monitoring Committee. A SPIRIT flowchart  
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5 353 is presented in Table 3.  
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10 355 ***Statistical Considerations***  
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12 356  
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14 357 The statistical justification required to achieve the primary efficacy endpoint (Aim 1)  
15  
16 358 is as follows. BCC is a hybrid of biochemical failure via the nadir plus two definition,  
17  
18 359 deployment of salvage treatments, or the detection of local, regional or metastatic  
19  
20 360 relapse via imaging. Using a similar endpoint as well as a short course of ADT, the  
21  
22 361 CHHiP study 60 Gy arm had 90.2% and 84.2% BCC for intermediate and high risk  
23  
24 362 patients respectively.[40] The ASCENDE-RT study also included intermediate and  
25  
26 363 high risk men, managed with 12 months of ADT, and the experimental arm delivered  
27  
28 364 46 Gy in 23 fractions of EBRT alongside a LDR Brachytherapy boost.[18] At 5  
29  
30 365 years, the BCC was 89% in the brachytherapy boost cohort, although with a higher  
31  
32 366 risk patient mix than we are going to accrue on this protocol. Allowing for differences  
33  
34 367 in inter-trial comparisons, we estimate BCC ~86% in the standard SBRT arm. Similar  
35  
36 368 data has been reported for single arm SBRT monotherapy series.[12] For a  
37  
38 369 superiority RCT design, we will aim for a hazard ratio of 0.5 in 5-yr BCC for the  
39  
40 370 virtual HDR arm ie 93%. An HR of 0.5 is chosen because this translates to an  
41  
42 371 absolute improvement of 7%, and any improvements less than this are unlikely to be  
43  
44 372 clinically significant. With alpha 0.05, power of 80%, and drop out of 2% the required  
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46 373 phase 3 sample size is 472 men.  
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56 375 Computer generated randomization will be performed with stratification by centre  
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58 376 and risk grouping via centralized database at the Trial Coordinating Centre in  
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3 377 Newcastle and concealed until intervention assigned. Randomization performed by  
4  
5 378 Data Manager independent of Trial Coordinators who assign interventions and  
6  
7 379 Investigators who enrol participants. Assignment is unblinded, and selected aspects  
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9  
10 380 of the dataset will only be available to appropriately qualified individuals for the  
11  
12 381 relevant analyses.

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17 383 For KBP (Aim 2), we hypothesize that a replanning rate of >15% would be clinically  
18  
19 384 significant. Assuming an error rate of +/-6%, at an alpha of 5%, 136 patients are  
20  
21 385 required. Allow 10% drop-out due to technical issues with a new planning paradigm:  
22  
23 386 total of 150 cases. For MRI planning (Aim 3), having ≥50% of centres involved in  
24  
25 387 this aspect of NINJA completely transition to MRI only planning will be deemed a  
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27 388 success.

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### 32 33 390 ***Patient and Public Involvement***

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37 392 Three patients who had been treated on the phase 2 precursor studies to NINJA  
38  
39 393 were involved as Associate Investigators in the grant application, and subsequent  
40  
41 394 study design through engagement via teleconferences and review of documentation.  
42  
43 395 Given their exposure to the two treatment approaches, they were ideally informed  
44  
45 396 about the potential burden of treatment. These consumers will continue to provide  
46  
47 397 guidance on study recruitment and conduct throughout the duration of the trial.  
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49 398 Study participants will continue with follow-up following treatment, and hence will be  
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51 399 able to be informed about outcomes from the research.

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### 55 56 401 ***Endpoints NINJA Aim 1 – Radiobiological Dose Escalation***

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5 403 For each patient visit, prostate-specific antigen (PSA), GU and GI RTOG physician  
6  
7 404 graded toxicity and patient reported outcomes using the Expanded Prostate Cancer  
8  
9 405 Index Composite (EPIC) instrument will be recorded. The acute toxicity will be  
10  
11 406 measured each week of treatment, and two weeks after treatment completion. As  
12  
13 407 severe acute toxicity is a surrogate for late toxicity, this will be the primary physician  
14  
15 408 reported toxicity outcome for this 3-year study. Patient reported outcomes will be at  
16  
17 409 baseline, then 1, 3 and 5 year marks. Biochemical control will be assessed with PSA  
18  
19 410 testing at baseline, then every six months, with failure defined by the nadir plus 2  
20  
21 411 Phoenix definition. Clinical control consists of any evidence of relapse on imaging,  
22  
23 412 or the initiation of salvage treatments. Biochemical Clinical Control (BCC) is the  
24  
25 413 combination of either biochemical or clinical events. BCC at 5 years will be the  
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27 414 primary endpoint for aim 1.  
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35 416 ***Endpoint NINJA Aim 2 – KBP Advantage***  
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39 418 KBP models will initially be developed for the SBRT monotherapy and virtual HDRB  
40  
41 419 arms. The training sample for the NINJA KBP model will come from the SPARK and  
42  
43 420 PROMETHEUS cohorts, and will be continuously improved during the NINJA trial.  
44  
45 421 As new cases are accepted to the trial they will be incorporated into the knowledge-  
46  
47 422 based dose prediction models to broaden the geometric experience and improve  
48  
49 423 future prediction accuracy. The NINJA KBP automated planning routines'  
50  
51 424 performance will be validated on an independent validation sample of cases (holding  
52  
53 425 back 20% of SPARK/PROMETHEUS cases) to ensure that the final KBP plans are  
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55 426 effecting plans that match the dosimetric goals of the NINJA protocol.  
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6 428 All NINJA patients will have a plan generated as per local standard of care by the  
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8 429 treating centre. If sites are capable of utilizing KBP locally, they will be provided with  
9  
10 430 the NINJA KBP routine. All plans will then be uploaded to TROG to be compared  
11  
12 431 with a KBP generated plan. If the site was submitting a manually generated plan, an  
13  
14 432 automated report will be returned to the treating centre within 24 hours, at which time  
15  
16 433 they can decide whether to proceed with their original manual plan or to replan  
17  
18 434 based on the KBP recommendations. If the site utilizes the NINJA KBP routine, a  
19  
20 435 central quality check will be performed to ensure proper use of the model, but no  
21  
22 436 further recommendation will be made to the submitting site. The utility of KBP will be  
23  
24 437 assessed by recording the rate of replanning following receipt of the KBP plan.  
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### 439 ***Endpoint NINJA Aim 3 – MRI Planning Validation***

440

441 This sub-study will be for centres with access to MRI scanning with appropriate  
442 accessories such as a flat top couch. Patients will have a CT and a MRI performed  
443 in the planning position. Clinicians will contour all target volumes and organs at risk  
444 on the MRI. Sites who have not been validated for MRI based planning will go  
445 through a credentialing phase, where the first 5 patients will have the planning  
446 processes assessed.[32] Following credentialing (or evidence of previously fulfilling  
447 this requirement), the MRI will be exported for remote generation of a sCT. A plan  
448 will then be created on the sCT, and copied onto the planning CT. The dosimetry of  
449 these will be compared at points within both the target volume and critical structures.  
450 If the isocentre dose is within 2% and 3D Gamma comparison at 2%/2mm criteria >  
451 90% pass-rate for the entire scanned volume, then the sCT plan will be deemed

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3 452 accurate and used for patient treatment. After ten such patients, centres will have  
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5 453 the option of no longer performing a routine planning scan, but instead using in vivo  
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7 454 dosimetry to confirm accurate dose delivery with the same criteria as for the sCT  
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9  
10 455 and planning CT comparison. The utility of MRI planning will be assessed via:

- 11  
12 456 • Accuracy – The proportion of plans where both the isocentre dose and  
13  
14 457 Gamma comparison are within the stated constraints. Deemed accurate if  
15  
16  
17 458 >95%.
- 18  
19 459 • Feasibility – The proportion of sites who commence accrual who  
20  
21 460 subsequently a) Achieve credentialing and b) Move successfully  
22  
23 461 completely to MR only planning. Deemed feasible is  $\geq 50\%$  of sites.  
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### 30 464 **Other Sub-studies**

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- 32  
33 466 ○ Patient reported outcomes using the IIEF and EPIC questionnaire
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35 467 ○ Physician-reported toxicity using the CTCAE v5 scale
- 36  
37 468 ○ Health economics - the cost effectiveness profiles of the technologies being  
38  
39 469 compared will be assessed in a cost consequence analysis. Resource use  
40  
41 470 implications and impacts have utility both for decision makers and for informing  
42  
43 471 the phase 3 trial-based economic evaluation.
- 44  
45 472 ○ Erectile sparing RT (neurovascular bundles, pudendal arteries, penile bulb) and  
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47 473 impact on patient reported outcomes
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49 474 ○ Performance comparison between intrafraction motion management strategies  
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3 476 **Ethics and Dissemination**  
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8 478 This study has received Ethical approval from the South West Sydney Local Health  
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10 479 District Human Research Ethics Committee (approval number  
11  
12 480 HREC/18/LPOOL/420). After invitation by a credentialed local Investigator, all  
13  
14 481 patients will sign a Participant Information Consent Form prior to being randomized  
15  
16 482 and treated on this study. Participants are free to withdraw from the study at any  
17  
18 483 time. Results will be published in peer reviewed literature, presented at professional  
19  
20 484 meetings, and disseminated through patient facing avenues such as local media.  
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25  
26 486 Prostate SBRT, KBP and MRI planning are all highly promising approaches with the  
27  
28 487 potential to transform patient care far beyond the specific indication of definitive  
29  
30 488 prostate cancer management. A large array of sub-studies will create new scientific  
31  
32 489 knowledge and further inform best practice prostate cancer radiotherapy. The study  
33  
34 490 plan seeks to assess and validate all of these approaches. More importantly, we aim  
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36 491 to increase the capabilities of centres to perform such leading edge treatments. If  
37  
38 492 validated, these approaches can be seamlessly integrated into routine clinical  
39  
40 493 practice.  
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47 495 Conventional prostate cancer radiotherapy currently takes between 20 and 40  
48  
49 496 outpatient visits, so reducing this to between 5 and 14 will assist with access for  
50  
51 497 patients as well as improve resource utilisation. Semi-automation of the planning  
52  
53 498 process via KBP will both streamline processes and reduce variable plan quality.  
54  
55 499 NINJA has been deliberately designed to facilitate treatment at small and larger  
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500 institutes, crossing the divide between public and private as well as metropolitan and  
501 regional.

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3 502 **List of Abbreviations**  
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7  
8 ADT Androgen Deprivation Therapy  
9  
10 ASCO American Society of Clinical Oncology  
11  
12 ASTRO American Society for Therapeutic Radiation Oncology  
13  
14 AUA American Urological Association  
15  
16  
17 BCC Biochemical Clinical Control  
18  
19 CT Computerised Tomography  
20  
21 CTC AE Common Toxicity Criteria Adverse Event  
22  
23 EBRT External Beam Radiation Therapy  
24  
25  
26 ECOG Eastern Cooperative Oncology Group  
27  
28 EPIC Expanded Prostate cancer Index Composite  
29  
30 EPID Electronic Portal Image Device  
31  
32  
33 GI Gastrointestinal  
34  
35 GU Genitourinary  
36  
37 HDRB High Dose Rate Boost  
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39  
40 HREC Human Research Ethics Committee  
41  
42 IIEF International Index of Erectile Function  
43  
44 IMRT Intensity Modulated Radiotherapy  
45  
46  
47 ISUP International Society of Urology  
48  
49 KBP Knowledge Based Planning  
50  
51 KIM Kilovoltage Intrafraction Monitoring  
52  
53  
54 MRI Magnetic Resonance Imaging  
55  
56  
57 NINJA Novel Integration of New prostate radiation schedules with  
58 adJuvant Androgen deprivation  
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3	PC	Prostate Cancer
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5	PSA	Prostate Specific Antigen
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7		
8		Prostate Specific Membrane Antigen Positron Emission
9	PSMA-PET	
10		Tomography
11		
12	RCT	Randomized Controlled Trial
13		
14	RT	Radiation Therapy
15		
16		
17	RTOG	Radiation Therapy Oncology Group
18		
19	RTR	Real Time Review
20		
21	SBRT	Stereotactic Body Radiotherapy
22		
23	sCT	Substitute Computerised Tomography
24		
25		
26		Stereotactic Prostate Adaptive Radiotherapy utilising
27		
28	SPARK	Kilovoltage intrafraction monitoring
29		
30	TROG	Trans Tasman Radiation Oncology Group
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3 505 **Declarations**  
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7 507 *Consent for Publication*  
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11  
12 509 Not applicable, as this manuscript does not include patient information. Trial results,  
13  
14 510 when available, will be widely disseminated via academic meetings, journals, social  
15  
16 511 media and traditional media.  
17

18 512

19 513 *Availability of Data and Materials*  
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23  
24 515 The datasets used and/or analysed during the current study are available from the  
25  
26 516 corresponding author on reasonable request.  
27  
28

29 517  
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32 519  
33 520 *Competing Interests*  
34

35 521

36 522 No competing interests are relevant to the submitted work. J Martin has acted on  
37  
38 523 Advisory Boards for Ferring pharmaceuticals and Janssen, as well as having paid  
39  
40 524 employment with the commercial provider GenesisCare. DC and TL also are  
41  
42 525 employed by Genesis Care. PK is the inventor of a KIM-related patent that has been  
43  
44 526 licensed to Varian Medical Systems by Stanford University and an MLC tracking  
45  
46 527 patent licensed to Leo Cancer Care by the University of Sydney. PK founded Leo but  
47  
48 528 has no ownership interest. PK is the inventor of additional unlicensed KIM-related  
49  
50 529 patents. Other interests include founding and shareholding in Opus Medical and  
51  
52 SeeTreat, unlicensed patents, licenses to Leo Cancer Care, Opus Medical, Standard  
53  
54 Imaging and Varian Medical Systems and research agreements with Siemens  
55  
56  
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3 530 Healthineers and Varian Medical Systems. SS reports grants from Varian Industries,  
4  
5 531 outside the submitted work. KM reports grants from Agency for Healthcare Research  
6  
7 532 and Quality, grants from Padres Pedal the Cause, grants from UC San Diego Office  
8  
9 533 of Innovation, grants, personal fees and non-financial support from Varian Medical  
10  
11 534 Systems; In addition, KM has a patent Knowledge-based prediction of three-  
12  
13 535 dimensional dose distributions with royalties paid to Varian Medical Systems, and a  
14  
15 536 patent Developing Predictive DoseVolume Relationships for a Radiotherapy  
16  
17 537 Treatment licensed to Varian Medical Systems. DM reports personal fees from  
18  
19 538 Ferring, Ipsen, Astra Zeneca, Astellas, and Janssen. CT is an owner of 5D Clinics.  
20  
21 539 Remaining co-authors have no potential competing interests to declare.  
22  
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540

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542

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546 Neither funder has input into elements of study design, conduct or publication.

547

#### 548 *Author Contributions*

549

550 JM and MS conceived of the study. JM, MS, JS and DP were responsible for  
551 protocol drafting and data management plan. All authors were involved in the study  
552 design, acquisition of competitive grant funding and helped to draft this manuscript.  
553 All authors read and approved the final manuscript. No professional writer has been  
554 used.

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7  
8 557  
9

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11  
12 559 have input into study conduct. The full protocol is available through TROG. The trial  
13  
14 560 coordination centre activities are shared between the Radiation Oncology Clinical  
15  
16  
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18  
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20  
21 563 Tillot and Russell Flank.  
22  
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3 708 **Figure 1:** NINJA Trial Schema  
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8 710 **Figure 2** – NINJA Dosimetry example showing very conformal nature of high dose

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10 711 treatment to the Planning Target Volume (PTV). [CTV=Clinical Target Volume,

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12 712 NVB=Neurovascular Bundle, IPA=Internal Pudendal Artery]  
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713 **Table 1:** Selected current and pending randomized trials investigating SBRT for  
 714 prostate cancer

<i><b>Trial</b></i>	<i><b>Control Arm(s)</b></i>	<i><b>Experimental Arm</b></i>	<i><b>n</b></i>	<i><b>Progress</b></i>
HYPO-RT-PC (ISRCTN45905321)	78Gy/39	42.7Gy/7	1400	Results presented 2018
PACE (NCT01584258)	78Gy/39 or 62Gy/20	36.25Gy/5	858	Completed accrual
HEAT (NCT01794403)	70.2Gy/26	36.25Gy/5	456	Accruing
NRG GU005 (NCT03367702)	70Gy/28	36.25Gy/5	622	Accruing

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716 **Table 2a:** Target Volume Objectives and Organs at Risk Constraints – 40 Gy in 5#

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Objective	Protocol	Minor Variation	Major Variation
CTVp D95%	≥40.0	38 - <40 Gy	<38 Gy
PTV_4000 D95%	≥36 Gy	34.44 - <36 Gy	<34.44 Gy
PTV_4000 D98%	≥34.44 Gy (95% of 36.25 Gy)	32.72 - <34.44 Gy	<32.72 Gy
PTV_4000 D2%	≤42 Gy	42 – 42.8 Gy	>42.8 Gy
Dmax (0.1cc)	≤42.8 Gy	42.8 – 44 Gy	>44 Gy
Dmax (0.1cc)	Not in OAR	NA	In OAR

718

Constraint	Protocol	Minor Variation	Major Variation
RECTUM V40 Gy	≤0.1cc	NA	>0.1cc
RECTUM V36 Gy	≤1cc	>1 - 2cc	>2cc
RECTUM V32 Gy	≤10%	>10 - 20%	>20%
RECTUM V20 Gy	≤40%	>40 - 50%	>50%
URETHRA_PRV V42 Gy	≤0.1cc	NA	>0.1cc
BLADDER V40 Gy	≤2cc	>2 - 3cc	>3cc
BLADDER V36 Gy	≤10cc	>10 - 20cc	>20cc
BLADDER V32 Gy	≤10%	>5 - 10%	>10%
BLADDER V20 Gy	≤40%	>40 - 50%	>50%
PENILE BULB V36 Gy	≤0.1cc	NA	>0.1cc

Constraint	Protocol	Minor Variation	Major Variation
PENILE BULB V20			
Gy	≤3cc	>3 - 5cc	>5cc
FEM HEAD V30 Gy	≤0.1cc	NA	>0.1cc
FEM HEAD V20 Gy	≤10cc	>10 - 15cc	>15cc
SIGMOID V40 Gy	≤0.1cc	NA	>0.1cc
SIGMOID V36 Gy	≤2cc	>2 - 3cc	>3cc
SMALL BOWEL V30			
Gy	≤1cc	NA	>1cc
SMALL BOWEL V25			
Gy	≤20cc	>20 - 40cc	>40cc
Conformity index*	≤1.1	>1.1 - 1.2	>1.2
Int. dose spillage**	≤4	>4 - 5	>5
MU/cGy ratio***	≤3	>3 - 4	>4

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720 \* Optional - Volume receiving 36.25 Gy/volume of PTV

721 \*\* Optional - Ratio of volume receiving 36.25 Gy: 18.13 Gy

722 \*\*\* Optional - Ratio of MU delivered per fraction divided by 800 (the number of cGy  
723 prescribed/fraction)

724

725 **Table 2b:** Target Volume Objectives and Organs at Risk Constraints – Virtual HDRB

726 Boost, SBRT component 20 Gy in 2 fractions

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Objective	Protocol	Minor Variation	Major Variation
CTVp D95%	≥20 Gy	18 - <20 Gy	<18 Gy
PTV_2000 D95%	≥18 Gy	17 – <18 Gy	<17 Gy
PTV_2000 D98%	≥17 Gy	16 - <17 Gy	<16 Gy
PTV_2000 D2%	≤21 Gy	>21 - 21.4 Gy	>21.4 Gy
Dmax (0.1cc)	≤21.4 Gy	>21.4 – 22 Gy	>22 Gy
Dmax (0.1cc)	Not in OAR	NA	In OAR

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Constraint	Protocol	Minor Variation	Major Variation
RECTUM V20 Gy	≤0.1cc	NA	>0.1cc
RECTUM V16 Gy	≤1cc	>1 - 2cc	>2cc
RECTUM V14 Gy	≤10%	>10 - 20%	>20%
RECTUM V10 Gy	≤40%	>40 - 50%	>50%
URETHRA_PRV V21 Gy	≤0.1cc	NA	>0.1cc
BLADDER V20 Gy	≤2cc	>2 - 3cc	>3cc
BLADDER V18 Gy	≤10cc	>10 - 20cc	>20cc
BLADDER V16 Gy	≤10%	>5 - 10%	>10%
BLADDER V10 Gy	≤40%	>40 - 50%	>50%
PENILE BULB V18 Gy	≤0.1cc	NA	>0.1cc

PENILE BULB V10			
Gy	≤3cc	>3 - 5cc	>5cc
FEM HEAD V15 Gy	≤0.1cc	NA	>0.1cc
FEM HEAD V10 Gy	≤10cc	>10 - 15cc	>15cc
SIGMOID V20 Gy	≤0.1cc	NA	>0.1cc
SIGMOID V18 Gy	≤2cc	>2 - 3cc	>3cc
SMALL BOWEL V15			
Gy	≤1cc	NA	>1cc
SMALL BOWEL V10			
Gy	≤20cc	>20 - 40cc	>40cc
Conformity index*	≤1.1	>1.1 - 1.2	>1.2
Int. dose spillage**	≤4	>4 - 5	>5
MU/cGy ratio***	≤3	>3 - 4	>4

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730 \* Optional - Volume receiving 18 Gy/volume of PTV

731 \*\* Optional - Ratio of volume receiving 18 Gy: 9 Gy

732 \*\*\* Optional - Ratio of MU delivered per fraction divided by 1000 (the number of cGy  
733 prescribed/fraction)

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739 **Table 2c:** Target Volume Objectives and Organs at Risk Constraints – Virtual HDRB

740 Boost, EBRT component 36 Gy in 12 fractions

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Objectives	Protocol	Minor Variation	Major Variation
PTV_3600 D95%	≥36 Gy	34.2 - <36 Gy	<34.2 Gy
PTV_3600 D98%	≥34.2 Gy	32.4 - <34.2 Gy	<32.4 Gy
PTV_3600 D2%	≤37.8 Gy	>37.8 - 38.5 Gy	>38.5 Gy
PTV_3600 (0.1cc)	≤38.5 Gy	>38.5 – 39.6 Gy	>39.6 Gy

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Constraint	Protocol	Minor Variation	Major Variation
Small Bowel Dmax (0.1cc)	≤36 Gy	>36-38 Gy	>38 Gy
Fem Head Dmax (0.1cc)	≤25 Gy	>25-35 Gy	>35 Gy
Rectum V30 Gy	≤25%	>25%-35%	>35%
Bladder V32 Gy	≤25%	>25%-35%	>35%

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745 **Table 1:** Schedule of Assessments as per SPIRIT Guidelines.

Assessment	Pre Treatment		Treatment	Follow-up		
	Pre-Registration <sup>1</sup>	Baseline <sup>2</sup>		Post SBRT <sup>3</sup>	Every 6 mths <sup>4</sup>	24, 60 mths <sup>4</sup>
Informed Consent	✓					
Eligibility assessment	✓					
Staging investigations <sup>5</sup>	✓					
Clinical examination		✓		✓	✓	
Adverse event		✓	✓	✓	✓	
PSA		✓		✓	✓	
PRO EPIC 26 +/- IIEF 25		✓		✓		✓

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<sup>1</sup> To be done within 60 days of registration.

<sup>2</sup> To be done no more than 2 weeks post registration and within 4 weeks of starting treatment.

<sup>3</sup> To be performed between 6 weeks post SBRT treatment completion.

<sup>4</sup> From commencement of ADT.

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3 Note that PSMA-PET is mandated for favourable high risk patients. Whole  
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5 <sup>5</sup> Body Bone Scan with CT or MRI of the pelvis +/- abdomen are acceptable for  
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7 unfavourable intermediate risk patients.  
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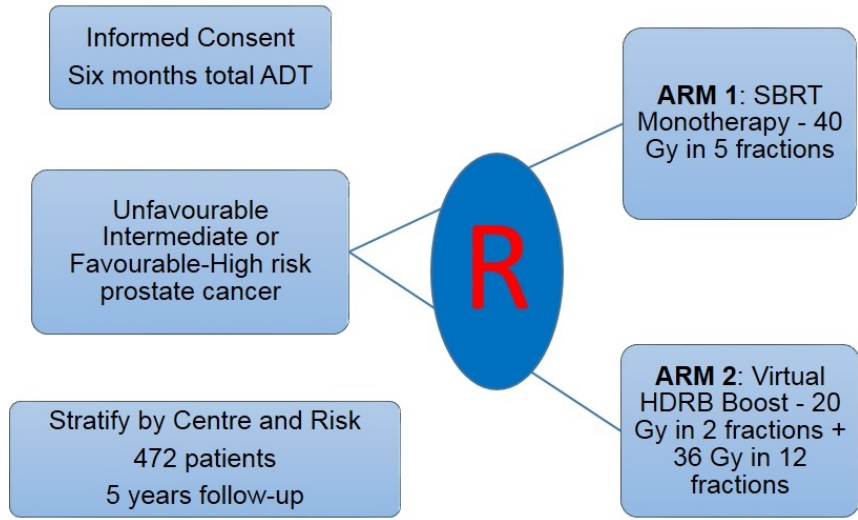
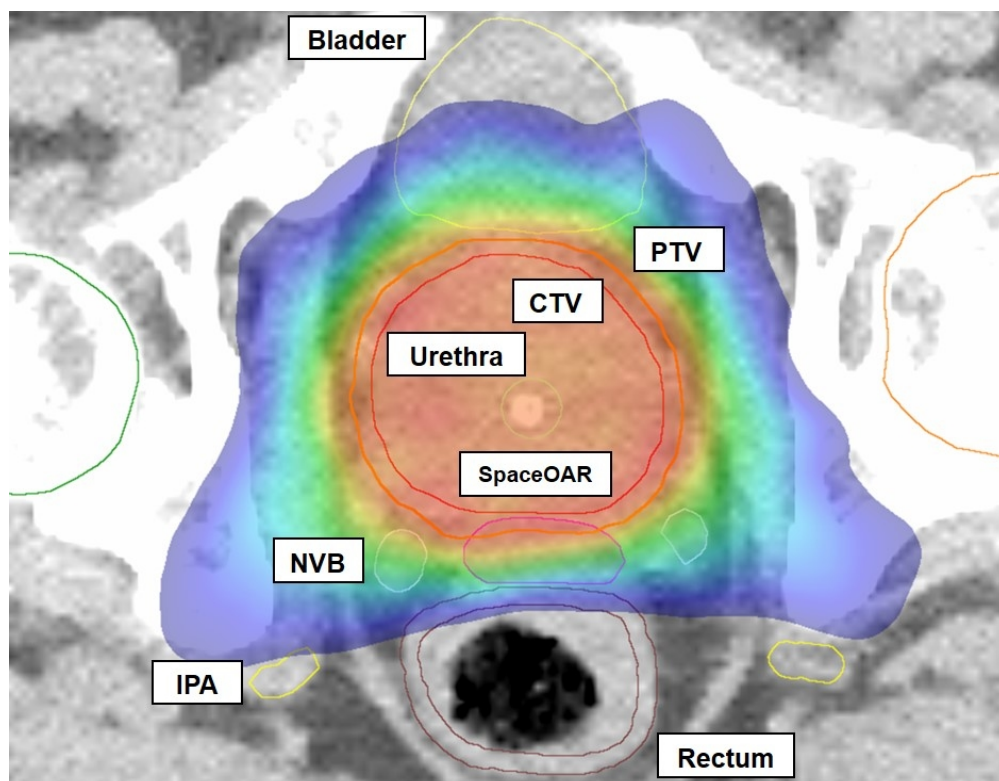


Figure 1: NINJA Trial Schema

161x84mm (150 x 150 DPI)



32 Figure 2 – NINJA Dosimetry example showing very conformal nature of high dose treatment to the Planning  
33 Target Volume (PTV). [CTV=Clinical Target Volume, NVB=Neurovascular Bundle, IPA=Internal Pudendal  
34 Artery]

35 159x123mm (150 x 150 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <b>p1 Title page Heading</b>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <b>p5 Trial Registration</b>
	2b	All items from the World Health Organization Trial Registration Data Set <b>p5 Trial Registration</b>
Protocol version	3	Date and version identifier <b>p13 Methods, Study Design</b>
Funding	4	Sources and types of financial, material, and other support <b>p25 Declarations, Funding</b>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <b>p1-2 Title page</b>
	5b	Name and contact information for the trial sponsor <b>p3 Trial Sponsor</b>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <b>p26 Funding and Acknowledgement sections</b>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <b>p26 Acknowledgements</b>
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <b>p6-11 Background</b>
	6b	Explanation for choice of comparators <b>p6-11 Background and p16-19 Statistical Considerations</b>

1			
2	Objectives	7	Specific objectives or hypotheses <a href="#">p11 Final paragraphs of Background</a>
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5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <a href="#">p11-12 Background, Summary</a>
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11	<b>Methods: Participants, interventions, and outcomes</b>		
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13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <a href="#">p13 Methods/Design, Study Design</a>
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17	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <a href="#">p13-14 Key Trial Eligibility Criteria</a>
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23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <a href="#">p14-19 especially sections Pre-treatment, Time-dose-fractionation planning details, Treatment Delivery, Endpoint NINJA Aim 2 – KBP Advantage, Endpoint NINJA Aim 3 – MRI Planning Validation.</a>
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30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <a href="#">p25 Declarations, Ethics Approval and Consent to Participate</a>
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36		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <a href="#">Not Applicable – it is exceedingly rare for a patient on a Radiation Oncology Clinical trial to not adhere with their cancer treatment</a>
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43		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <a href="#">Not Applicable</a>
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46	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <a href="#">p17-19 Endpoints NINJA Aim 1-3 and Other Sub-studies</a>
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55	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <a href="#">p40 Table 3</a>
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1 2 3 4 5 6	Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations <b>p16-19 Statistical Considerations</b>
7 8 9	Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size <b>p13-14 Key Trial Eligibility Criteria</b>

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

14 15 16 17 18 19 20 21 22	Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
23 24 25 26 27	Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
28 29 30 31 32	Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
33 34 35 36 37 38 39 40 41	Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
		17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial <b>Not Applicable</b>

### Methods: Data collection, management, and analysis

44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60	Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol <b>p15-16 Outcome Reporting</b>
		18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols <b>p15-16 Outcome Reporting</b>

1			
2	Data	19	Plans for data entry, coding, security, and storage, including any
3	management		related processes to promote data quality (eg, double data entry;
4			range checks for data values). Reference to where details of data
5			management procedures can be found, if not in the protocol <a href="#">p15-16</a>
6			<a href="#">Outcome Reporting</a>
7			
8	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
9	methods		Reference to where other details of the statistical analysis plan can be
10			found, if not in the protocol <a href="#">p16-19</a> <a href="#">Statistical Considerations</a>
11			
12		20b	Methods for any additional analyses (eg, subgroup and adjusted
13			analyses) <a href="#">p16-19</a> <a href="#">Statistical Considerations</a>
14			
15		20c	Definition of analysis population relating to protocol non-adherence
16			(eg, as randomised analysis), and any statistical methods to handle
17			missing data (eg, multiple imputation) <a href="#">p16-19</a> <a href="#">Statistical</a>
18			<a href="#">Considerations</a>
19			
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22	<b>Methods: Monitoring</b>		
23			
24	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
25			and reporting structure; statement of whether it is independent from
26			the sponsor and competing interests; and reference to where further
27			details about its charter can be found, if not in the protocol.
28			Alternatively, an explanation of why a DMC is not needed <a href="#">p15-16</a>
29			<a href="#">Outcome Reporting</a>
30			
31		21b	Description of any interim analyses and stopping guidelines, including
32			who will have access to these interim results and make the final
33			decision to terminate the trial <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
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35			
36	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
37			spontaneously reported adverse events and other unintended effects
38			of trial interventions or trial conduct <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
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41	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
42			whether the process will be independent from investigators and the
43			sponsor <a href="#">Not Applicable</a>
44			
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46	<b>Ethics and dissemination</b>		
47			
48	Research ethics	24	Plans for seeking research ethics committee/institutional review board
49	approval		(REC/IRB) approval <a href="#">p25</a> <a href="#">Declarations, Ethics Approval and Consent</a>
50			<a href="#">to Participate</a>
51			
52	Protocol	25	Plans for communicating important protocol modifications (eg,
53	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
54			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
55			regulators) <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
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2	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) <b>p25 Declarations, Ethics Approval and Consent to Participate</b>
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6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable <b>Not applicable</b>
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10	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial <b>p15-16 Outcome Reporting</b>
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site <b>p25 Competing Interests</b>
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18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators <b>p17 Statistical Considerations, paragraph 2</b>
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23	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation <b>Not applicable</b>
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27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <b>p25 Consent for Publication</b>
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34		31b	Authorship eligibility guidelines and any intended use of professional writers <b>p26 Authors Contributions</b>
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38		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <b>Not Applicable</b>
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41	<b>Appendices</b>		
42			
43	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <b>Provided as supplementary material</b>
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47	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable <b>Not applicable</b>
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.

# BMJ Open

## TROG 18.01 Phase III Randomized Clinical Trial of the Novel Integration of New prostate radiation schedules with adJuvant Androgen Deprivation - The NINJA Study Protocol

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<b>Primary Subject Heading</b>:	Oncology

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Secondary Subject Heading:	Urology
Keywords:	Prostate disease < UROLOGY, RADIOTHERAPY, Radiation oncology < RADIOLOGY & IMAGING, ONCOLOGY, Clinical trials < THERAPEUTICS



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3 **TROG 18.01 Phase III Randomized Clinical Trial of the Novel Integration of New**  
4 **prostate radiation schedules with adJuvant Androgen Deprivation – The NINJA**  
5 **Study Protocol**  
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For peer review only

## Abstract

### Introduction:

Stereotactic Body Radiotherapy (SBRT) is a non-invasive alternative to surgery for the treatment of non-metastatic prostate cancer (PC). The objectives of the NINJA clinical trial are to compare two emerging SBRT regimens for efficacy with technical sub-studies focussing on MRI only planning and the use of Knowledge Based Planning (KBP) to assess radiotherapy plan quality.

### Methods and Analysis:

Eligible patients must have biopsy proven unfavourable intermediate or favourable high risk PC, have an ECOG performance status 0-1, and provide written informed consent. All patients will receive six months in total of Androgen Deprivation Therapy (ADT). Patients will be randomized to one of two SBRT regimens. The first will be 40 Gy in 5 fractions given on alternating days (SBRT monotherapy). The second will be 20 Gy in 2 fractions given one week apart followed 2 weeks later by 36 Gy in 12 fractions given 5 times per week (Virtual High Dose Rate Boost [HDRB]). The primary efficacy outcome will be Biochemical Clinical Control (BCC) at five years. Secondary endpoints for the initial portion of NINJA look at the transition of centres towards MRI only planning and the impact of KBP on real time plan assessment. The first 150 men will demonstrate accrual feasibility as well as addressing the KBP and MRI planning aims, prior to proceeding with total accrual to 472 patients as a phase 3 randomized controlled trial.

### Ethics and Dissemination:

NINJA is a multicentre cooperative clinical trial comparing two SBRT regimens for men with PC. It builds on promising results from several single armed studies, and explores radiation dose escalation in the Virtual HDRB arm. The initial component includes novel technical elements, and will form an important platform set for a definitive phase 3 study.

### Trial Registration:

Australia New Zealand Clinical Trial Registry – ANZCTN 12615000223538.  
Registered prior to opening to accrual 6 November 2018.

**Strengths and Limitations:**

- Randomized trial comparing two emerging radiotherapy regimens for prostate cancer
- Technological sub-study seeking to implement MRI only planning
- Use of novel approaches such as automated plan assessment to ensure high quality treatment
- Limitation is the use of a biochemical surrogate endpoint at 5 years rather than longer term survival endpoints

**Keywords:**

Computer Assisted Radiotherapy Planning

Image Guided Radiotherapy

Intensity Modulated Radiotherapy

Prostatic Neoplasms

Radiotherapy

Radiotherapy Dose Hypofractionation

Stereotactic Body Radiotherapy



## Background

### *Stereotactic Body Radiotherapy for Prostate Cancer*

Prostate cancer has a major impact on the Australian population with 3500 deaths projected in 2018 and treatment costs to patients and the health system exceeding \$500 million by 2025.(1, 2) The question at the heart of NINJA is to compare two emerging and practice-changing schedules of radiotherapy that leverage state-of-the-art technology developments and our Australian clinical trial experience to make treatments safer, highly efficient and more convenient for patients. The first schedule is a 5 fraction Stereotactic Body Radiotherapy (SBRT monotherapy) approach.(3) The alternative regimen is 'Virtual High Dose Rate Boost' (HDRB), non-invasively delivering brachytherapy-type doses.(4) Superiority of the latter schedule would validate the utility of dose escalation to improve outcomes. Similarity of outcomes in the former schedule would allow for major cost savings and reduced patient burden with reduction of treatment sessions from 40 to 5 (see **Figure 1**).

Conventional radiotherapy regimens for prostate cancer are given 5 times per week for up to 9 consecutive weeks.(5) Recent results from large non-inferiority studies including substantial Australian input has helped establish a 4-week moderately hypofractionated schedule as an alternative approach.(6-8) Building on this, large series are showing excellent outcomes with regimens giving as few as 5 radiotherapy fractions, using higher daily doses of radiotherapy.(9, 10) A 477 patient series with median follow-up of seven years showed 89.6% biochemical disease control with late grade 2 and 3 genitourinary (GU) toxicity low at 9% and 1.7% respectively.(11, 12) Grade 2 gastrointestinal (GI) toxicity was similarly favourable at 4.1%. Our SPARK phase 2 study used a 5-fraction prostate SBRT monotherapy in conjunction with intrafraction motion management to assess the dosimetric impact of increasing the accuracy of radiotherapy dose delivery.(3)

Following on from this experience, several randomized studies are currently underway exploring similar stereotactic regimens, where much higher daily doses of radiotherapy are given in between 5 and 7 visits (**Table 1**). The Scandinavian HYPO-

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3 RT-PC study completed accrual in 2015, and presented early toxicity data in 2016  
4 showing no significant differences between the control and SBRT arms.(13, 14)  
5 Initial efficacy results from this study were presented in 2018, showing no differences  
6 between the two arms. Recent guidelines from ASTRO, AUA and ASCO have  
7 incorporated prostate SBRT monotherapy as a treatment option for centres  
8 experienced in this technique.(15) Bringing this together, although SBRT  
9 monotherapy can currently be considered investigational, it is likely to gain wider  
10 acceptance as a standard treatment option in the near future. Hence our plan is to  
11 commence NINJA as a randomized phase 2 study, but to convert to a fully powered  
12 phase 3 study with SBRT monotherapy as the control arm as the evidence base  
13 continues to mature.  
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24 Strong evidence exists for superior disease control through the use of a  
25 brachytherapy boost compared with conventional radiotherapy.(16, 17) Despite this,  
26 the use of brachytherapy continues to decline, partly due to concerns regarding  
27 higher risks of significant late GU toxicity.(18) Also, the lack of evidence for improved  
28 disease control translating to improved survival has limited uptake, although the poor  
29 sensitivity of conventional staging investigations may contribute to superior local  
30 control being overwhelmed by undiagnosed micro-metastatic disease. The  
31 emergence of PSMA-PET as a more sensitive and specific staging modality makes  
32 revisiting the radiotherapy dose-escalation question highly relevant.(19, 20) An  
33 alternative approach to brachytherapy is a 'virtual HDR boost' where 2-3 large doses  
34 designed to mimic HDRB are delivered via stereotactic techniques with an additional  
35 fractionated External Beam Radiation Therapy (EBRT) component. Relatively small  
36 virtual HDRB series with nearly 4 years follow up have shown this approach to be  
37 feasible, although often using specialised equipment such as the Cyberknife  
38 platform.(21, 22) Virtual HDRB has also been proven feasible in the setting of  
39 multicentre phase 2 trial in Australia, with 135 men enrolled on the PROMETHEUS  
40 trial (ACTRN12615000223538) where 2 fractions of 9.5-10Gy are followed by an  
41 EBRT component of either 46Gy in 23 or 36Gy in 12 fractions. Early data from  
42 PROMETHEUS shows no grade 2-3 late GI toxicity after 24 months and grade 2 late  
43 GU toxicity prevalence rates of <7% out to 3 years. Promising efficacy signals are  
44 also becoming evident, with almost ablative PSA levels being observed consistent  
45 with excellent disease response.(23)  
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5 Virtual HDRB may represent a significant biological dose escalation compared with  
6 SBRT monotherapy. Assuming prostate cancer has an alpha beta ratio of 1.5 Gy,  
7 40 Gy in 5 fractions and virtual HDRB would be equivalent to 110 and 120 Gy in 2  
8 Gy equivalent fractions respectively. Modelling of RCT data suggests that each  
9 extra Gray in dose translates to ~2% improvement in disease control.(24) The virtual  
10 HDRB approach also acknowledges the possibility of heterogeneity in the alpha-beta  
11 ratio, and therefore potentially allows for some variation in fraction size sensitivity  
12 within and between tumours. A reasonable question would be whether the excellent  
13 results seen with HDR brachytherapy boost could be safely translated into the  
14 stereotactic setting on the basis of this increase in biological dose delivery. This is  
15 the fundamental question which drives NINJA.  
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### 25 *Knowledge Based Planning*

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29 Knowledge-Based Planning (KBP) has the potential to simultaneously improve and  
30 automate the radiotherapy planning process. KBP uses previous cases to build a  
31 model of an optimal treatment plan which can then be applied to the current patient.  
32 Previous work suggests that KBP can provide faster and frequently better plans,(25)  
33 but this has not been prospectively assessed in a multicentre fashion. NINJA  
34 provides an ideal opportunity for this.  
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41 Radiotherapy plan quality is critically important in achieving optimal treatment  
42 outcomes. The Australia-led TROG 02-02 study for patients with locally advanced  
43 head and neck cancer showed that non-protocol compliant plans had a locoregional  
44 control and overall survival decrement of 24% and 20% respectively.(26) Via TROG,  
45 Australia has become leaders in the use of approaches such as stringent  
46 credentialing and real time review (RTR) of RT contours and plans, with work in  
47 prostate cancer subsequently showing very low rates of protocol deviations both in  
48 the definitive prostate and post-prostatectomy irradiation scenarios.(27, 28)  
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56 An issue with the current RTR process is that although a plan can be deemed  
57 satisfactory, it is difficult to determine whether it could be improved. As treatment  
58 techniques evolve, satisfying the dose constraints in clinical trial protocols can  
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3 become progressively easier. Knowledge-Based Planning (KBP) has emerged as a  
4 promising approach to assess and improve plan quality. In KBP, a model is  
5 developed using a range of patient anatomies and target volumes. This can then be  
6 rapidly applied to a new case to either generate a plan de novo, or to compare with a  
7 conventional plan. The Radiation Therapy Oncology Group (RTOG) 0126 prostate  
8 cohort was selected to study treatment plan quality variations. This work examined  
9 the high-dose Intensity Modulated Radiation Therapy (IMRT) patients using a KBP  
10 model to identify the plans that best met the dosimetric aims of the protocol.(29)  
11 Focusing on Grade 2+ late rectal toxicities with an outcomes-validated normal tissue  
12 complication probability (NTCP) model, the high-dose arm of RTOG 0126 patients  
13 treated with IMRT patients had a 15.1% cumulative incidence of Grade 2+ rectal  
14 complications.(30) KBP plans were predicted to lead to a 4.7% risk reduction in this  
15 rate, which therefore may have cut this incidence by a third. The observed quality  
16 variations in RTOG 0126 give the strongest evidence yet that suboptimal planning is  
17 a critical problem in multi-institutional radiotherapy clinical trials and in the wider  
18 practice of radiotherapy. KBP has yet to be robustly assessed in a multicentre  
19 fashion, where the heterogeneity of planning systems and personnel would be  
20 expected to be greatest.

### 31 32 33 34 35 36 *MRI Radiotherapy Planning*

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39 Computerised Tomography (CT) is widely used for radiotherapy dosimetry  
40 calculation because of the ability to directly measure electron density. Our team has  
41 validated the use of Magnetic Resonance Imaging (MRI) to create a substitute CT  
42 (sCT) which can then be used for accurate dose calculation.(31) The superior soft  
43 tissue resolution of MRI, absence of radiation dose, and reduction in image artefacts  
44 means that if the dose calculation problem could be solved, standard CT based  
45 planning would be rendered obsolete.(32)

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53 Many centres now acquire both a CT and a MRI scan for each patient, but co-  
54 registration of these datasets introduces significant error mostly under the influence  
55 of bladder filling and varying rectal distension. An attractive alternative would be to  
56 create a substitute CT (sCT) from the MRI dataset to allow RT dose calculation. Our  
57 team has developed a hybrid atlas-voxel based technique of sCT generation which  
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3 showed high agreement in both mean monitor units (0.3%+/- sd 0.8%) and dose  
4 delivery (3-dimensional gamma pass rate at 2 mm/2% level of 100% +/- sd 0%.(31)  
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6 A group of Swedish centres have shown similar findings in a retrospective,  
7  
8 multicentre study,(33) and our group is prospectively evaluating this approach in 2  
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10 centres (HIPSTER study - ACTRN12616001653459). Given the advantages of MRI  
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12 for prostate cancer, and the improving access to MRI in Australia (including  
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14 radiotherapy departments with dedicated planning MRI facilities), this is another area  
15  
16 ripe for wider assessment, implementation and eventual broader application.  
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### 18 19 *Summary*

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22 NINJA is a combined phase 2/3 multicentre study of 472 men randomized to two  
23  
24 novel radiotherapy schedules. The hypotheses are that NINJA will advance 1)  
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26 Biochemical Clinical Control (BCC) of prostate cancer, 2) treatment planning via  
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28 automation and 3) planning imaging methodology.

29 **Aim 1: *Radiobiological Dose Escalation*:** The escalated radiation dose delivered  
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31 using a virtual HDRB approach achieves superior disease control compared with a  
32  
33 SBRT monotherapy alternative.

34 **Aim 2: *KBP Advantage*:** The treatment plans using KBP will be dosimetrically  
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36 superior to traditional manual planning approaches.

37 **Aim 3: *MRI only Planning*:** MRI will give dosimetry similar to standard CT planning.  
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## Methods/Design

### **Study Design:**

The study design is a prospective randomised phase 3 trial which conforms to the SPIRIT guidelines. We will initially enrol 150 men to demonstrate accrual feasibility as well as addressing the KBP and MRI planning aims, prior to proceeding with total accrual as a randomized phase 3 controlled trial.

- *Stage one:* Feasibility indicators – activate at least 10 centres, and accrue 50 patients within 18 months of central HREC approval.
- *Stage two:* Accrue total of 150 patients for randomized phase 2 component within 36 months of approval. Analyses of KBP and MRI planning components.
- *Stage three:* Complete accrual of 472 patients to the two SBRT arms.

### **Key Trial Eligibility Criteria**

Unfavourable intermediate or favourable high risk prostate cancer (any combination of ISUP 3-5 and/or cT2b/T2c/T3aN0 and/or PSA 10-20 in the absence of other high risk factors ie T3b/T4, PSA>20). For high-risk patients, PSMA PET staging prior to study entry showing N0M0 disease. Prostate volume <100cc, and patients can only be randomized after a plan has been generated showing that protocol compliant treatment can be performed.

### **Pre-Treatment**

All patients will receive a total of six months of Androgen Deprivation Therapy (ADT).(34, 35) The use of PSMA PET staging for high risk men, and criteria to exclude very high risk features should minimize any potential additive benefits of longer course ADT in this population. Both CT and MRI planning scans will be performed for the first 10 patients at each centre and phasing out CT for centres involved in MRI planning aspect of NINJA. Rectal displacement (eg SpaceOAR, Rectafix, Rectal Balloon) is encouraged, but not mandated.(36) Urethral positional estimation via temporary catheterization or equivalent approaches such as high-

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3 resolution sagittal MRI can be performed. Erectile sparing RT plans for men with  
4 adequate baseline IIEF and desire to maintain erectile function can be used.(37)  
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6 Centres will be credentialed for MRI planning via their first 5 patients being primarily  
7 planned off the CT, but with sCT generation and confirmation of accurate dosimetry.  
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9 The next ten patients will have planning performed on sCT and confirmed on  
10 planning CT. Subsequent patients will omit a planning CT, be planned on sCT, and  
11 have confirmation of accurate dosimetry on treatment using a centrally approved  
12 approach eg EPID dosimetry(38) or in vivo dosimetry.(39)  
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### 19 ***Time-dose-fractionation planning details***

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22 Clinical Target Volume (CTV): Entire prostate and proximal 10mm of seminal  
23 vesicles. No elective nodal irradiation permitted.

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25 Planning Target Volume (PTV): For SBRT treatments, 3mm uniform expansion from  
26 CTV. For Virtual HDRB 36 Gy in 12 fraction component, 7mm uniform expansion  
27 from CTV.  
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30 ***SBRT Monotherapy arm:*** 40 Gy in five fractions delivered 2-3 times per week,  
31 prescribed to CTV D95%.  
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34 ***Virtual HDRB Boost Arm:*** 20 Gy in two fractions prescribed to CTV D95% delivered  
35 once a week followed by a two week break and then 36 Gy in 12 fractions delivered  
36 5 times per week prescribed to PTV D95%. See tables 2a-c for dose constraints,  
37 and Figure 2 for an example of the SBRT dosimetry.  
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### 42 ***Quality Assurance***

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45 Centre credentialing will include submission of a 'Virtual HDRB Boost' treatment plan  
46 for a patient to ensure accurate contouring and protocol compliant dose delivery. The  
47 initial KBP model will be generated from phase 2 SPARK and PROMETHEUS trials,  
48 but will be updated as NINJA proceeds. All cases will be submitted for KBP  
49 comparison, and an automated report to be returned within 24 hours. Real-time  
50 review will occur for all patients on trial.  
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### 58 ***Treatment Delivery***

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3 All patients require intra-prostatic markers, and both inter- as well as intra-fraction  
4 motion management strategies to ensure accurate treatment delivery. For intra-  
5 fraction motion assessment, numerous 'real time' approaches are acceptable (eg  
6 KIM, Calypso, Cyber-knife). In all instances, translational movements to be  
7 corrected to 0mm threshold prior to commencing treatment. Rotational corrections  
8 do not need to be applied due to minimal dosimetric impact from such motion.(40)  
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### 15 ***Outcome Reporting***

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18 Indicators of feasibility, accuracy, impact on replanning, and other qualitative and  
19 quantitative markers of KBP and MRI planning will be collected. Patient reported  
20 outcomes to include baseline and serial patient reported outcomes (IIEF, EPIC),  
21 physician toxicity grading (CTC AE v5), PSA and any sites of confirmed disease  
22 relapse or death due to any cause. If the prevalence of CTC AE grade 3 GI or GU  
23 toxicities exceeds 10% at any stage, the trial will be halted for safety assessment. A  
24 SPIRIT flowchart is presented in Table 3.  
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### 32 ***Statistical Considerations***

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35 The statistical justification required to achieve the primary efficacy endpoint (Aim 1)  
36 is as follows. BCC is a hybrid of biochemical failure via the nadir plus two definition,  
37 deployment of salvage treatments, or the detection of local, regional or metastatic  
38 relapse via imaging. Using a similar endpoint as well as a short course of ADT, the  
39 CHHiP study 60 Gy arm had 90.2% and 84.2% BCC for intermediate and high risk  
40 patients respectively.(41) The ASCENDE-RT study also included intermediate and  
41 high risk men, managed with 12 months of ADT, and the experimental arm delivered  
42 46 Gy in 23 fractions of EBRT alongside a LDR Brachytherapy boost.(17) At 5  
43 years, the BCC was 89% in the brachytherapy boost cohort, although with a higher  
44 risk patient mix than we are going to accrue on this protocol. Allowing for differences  
45 in inter-trial comparisons, we estimate BCC ~86% in the standard SBRT arm. Similar  
46 data has been reported for single arm SBRT monotherapy series.(12) For a  
47 superiority RCT design, we will aim for a hazard ratio of 0.5 in 5-yr BCC for the  
48 virtual HDR arm ie 93%. An HR of 0.5 is chosen because this translates to an  
49 absolute improvement of 7%, and any improvements less than this are unlikely to be  
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3 clinically significant. With alpha 0.05, power of 80%, and drop out of 2% the required  
4 phase 3 sample size is 472 men.  
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8 For KBP (Aim 2), we hypothesize that a replanning rate of >15% would be clinically  
9 significant. Assuming an error rate of +/-6%, at an alpha of 5%, 136 patients are  
10 required. Allow 10% drop-out due to technical issues with a new planning paradigm:  
11 total of 150 cases. For MRI planning (Aim 3), having  $\geq 50\%$  of centres involved in  
12 this aspect of NINJA completely transition to MRI only planning will be deemed a  
13 success.  
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### 20 ***Endpoints NINJA Aim 1 – Radiobiological Dose Escalation***

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23 For each patient visit, prostate-specific antigen (PSA), GU and GI RTOG physician  
24 graded toxicity and patient reported outcomes using the Expanded Prostate Cancer  
25 Index Composite (EPIC) instrument will be recorded. The acute toxicity will be  
26 measured each week of treatment, and two weeks after treatment completion. As  
27 severe acute toxicity is a surrogate for late toxicity, this will be the primary physician  
28 reported toxicity outcome for this 3-year study. Patient reported outcomes will be at  
29 baseline, then 1, 3 and 5 year marks. Biochemical control will be assessed with PSA  
30 testing at baseline, then every six months, with failure defined by the nadir plus 2  
31 Phoenix definition. Clinical control consists of any evidence of relapse on imaging,  
32 or the initiation of salvage treatments. Biochemical Clinical Control (BCC) is the  
33 combination of either biochemical or clinical events. BCC at 5 years will be the  
34 primary endpoint for aim 1.  
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### 46 ***Endpoint NINJA Aim 2 – KBP Advantage***

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49 KBP models will initially be developed for the SBRT monotherapy and virtual HDRB  
50 arms. The training sample for the NINJA KBP model will come from the SPARK and  
51 PROMETHEUS cohorts, and will be continuously improved during the NINJA trial.  
52 As new cases are accepted to the trial they will be incorporated into the knowledge-  
53 based dose prediction models to broaden the geometric experience and improve  
54 future prediction accuracy. The NINJA KBP automated planning routines'  
55 performance will be validated on an independent validation sample of cases (holding  
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3 back 20% of SPARK/PROMETHEUS cases) to ensure that the final KBP plans are  
4 effecting plans that match the dosimetric goals of the NINJA protocol.  
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8 All NINJA patients will have a plan generated as per local standard of care by the  
9 treating centre. If sites are capable of utilizing KBP locally, they will be provided with  
10 the NINJA KBP routine. All plans will then be uploaded to TROG to be compared  
11 with a KBP generated plan. All plans will then be uploaded to TROG to be compared  
12 with a KBP generated plan. If the site was submitting a manually generated plan, an  
13 automated report will be returned to the treating centre within 24 hours, at which time  
14 they can decide whether to proceed with their original manual plan or to replan  
15 based on the KBP recommendations. If the site utilizes the NINJA KBP routine, a  
16 central quality check will be performed to ensure proper use of the model, but no  
17 further recommendation will be made to the submitting site. The utility of KBP will be  
18 assessed by recording the rate of replanning following receipt of the KBP plan.  
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### 27 ***Endpoint NINJA Aim 3 – MRI Planning Validation***

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30 This sub-study will be for centres with access to MRI scanning with appropriate  
31 accessories such as a flat top couch. Patients will have a CT and a MRI performed  
32 in the planning position. Clinicians will contour all target volumes and organs at risk  
33 on the MRI. Sites who have not been validated for MRI based planning will go  
34 through a credentialing phase, where the first 5 patients will have the planning  
35 processes assessed.<sup>(31)</sup> Following credentialing (or evidence of previously fulfilling  
36 this requirement), the MRI will be exported for remote generation of a sCT. A plan  
37 will then be created on the sCT, and copied onto the planning CT. The dosimetry of  
38 these will be compared at points within both the target volume and critical structures.  
39 If the isocentre dose is within 2% and 3D Gamma comparison at 2%/2mm criteria >  
40 90% pass-rate for the entire scanned volume, then the sCT plan will be deemed  
41 accurate and used for patient treatment. After ten such patients, centres will have  
42 the option of no longer performing a routine planning scan, but instead using in vivo  
43 dosimetry to confirm accurate dose delivery with the same criteria as for the sCT  
44 and planning CT comparison. The utility of MRI planning will be assessed via:  
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- 56 • Accuracy – The proportion of plans where both the isocentre dose and  
57 Gamma comparison are within the stated constraints. Deemed accurate if  
58 >95%.  
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- Feasibility – The proportion of sites who commence accrual who subsequently a) Achieve credentialing and b) Move successfully completely to MR only planning. Deemed feasible is  $\geq 50\%$  of sites.

### ***Other Sub-studies***

- Patient reported outcomes using the IIEF and EPIC questionnaire
- Physician-reported toxicity using the CTCAE v5 scale
- Health economics - the cost effectiveness profiles of the technologies being compared will be assessed in a cost consequence analysis. Resource use implications and impacts have utility both for decision makers and for informing the phase 3 trial-based economic evaluation.
- Erectile sparing RT (neurovascular bundles, pudendal arteries, penile bulb) and impact on patient reported outcomes
- Performance comparison between intrafraction motion management strategies

### ***Patient and Public Involvement***

Many of the baseline requirements for NINJA has been informed by consumer feedback. The concept of improved treatment accuracy resonated with our consumer advisors, and as such is mandated for all patients in NINJA. Improved pre-treatment imaging with PSMA PET will help define those most likely to benefit from aggressive management of their primary prostate cancer, an approach which our consumer advisors found essential for men with higher risk disease. Our consumer advisors also prioritise patient reported outcomes (PROs), and as such, PROs are one of our key endpoints. Our focus on assessing shorter, non-invasive radiotherapy treatment regimens which can be delivered on an outpatient basis also resonated with our consumer advisors.

Our consumer advisors will engage with consumer groups through organisations such as TROG (Trans-Tasman Radiation Oncology Group), ANZUP (Australia New Zealand Urogenital Program) and PCFA (Prostate Cancer Foundation of Australia)

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3 to ensure broad consumer awareness of NINJA. The Trial Management Committee  
4 will continue to include our consumer advisors in ongoing discussions regarding  
5 accrual and toxicities to gain their perspective on any changes to the conduct of the  
6 trial which might be advisable.  
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11 NINJA is designed with numerous potentially practice changing outcomes;  
12 consumers will remain critical throughout the trial to maximise integration of these  
13 into wider clinical practice. Several of our team are very active on social media,  
14 which can make direct connections with consumers about our findings. Many of our  
15 clinician CIs and AIs are regular speakers for local prostate cancer support groups.  
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## Discussion

Prostate SBRT, KBP and MRI planning are all highly promising approaches with the potential to transform patient care far beyond the specific indication of definitive prostate cancer management. A large array of sub-studies will create new scientific knowledge and further inform best practice prostate cancer radiotherapy. The study plan seeks to assess and validate all of these approaches. More importantly, we aim to increase the capabilities of centres to perform such leading edge treatments. If validated, these approaches can be seamlessly integrated into routine clinical practice.

Conventional prostate cancer radiotherapy currently takes between 20 and 40 outpatient visits, so reducing this to between 5 and 14 will assist with access for patients as well as improve resource utilisation. Semi-automation of the planning process via KBP will both streamline processes and reduce variable plan quality. NINJA has been deliberately designed to facilitate treatment at small and larger institutes, crossing the divide between public and private as well as metropolitan and regional.

NINJA seeks to prospectively assess and validate promising new technologies as part of a randomized study comparing two novel prostate RT regimens. The research pathway established can serve as a template for future attempts to explore promising technological innovations in a cost-effective manner. Beyond the geographic, sector and regional collaborations, NINJA brings together multiple states, as well as disciplines in clinical, technical and research fields.

## List of Abbreviations

ADT	Androgen Deprivation Therapy
ASCO	American Society of Clinical Oncology
ASTRO	American Society for Therapeutic Radiation Oncology
AUA	American Urological Association
BCC	Biochemical Clinical Control
CT	Computerised Tomography
CTC AE	Common Toxicity Criteria Adverse Event
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
EPIC	Expanded Prostate cancer Index Composite
EPID	Electronic Portal Image Device
GI	Gastrointestinal
GU	Genitourinary
HDRB	High Dose Rate Boost
HREC	Human Research Ethics Committee
IIEF	International Index of Erectile Function
IMRT	Intensity Modulated Radiotherapy
ISUP	International Society of Uro pathology
KBP	Knowledge Based Planning
KIM	Kilovoltage Intrafraction Monitoring
MRI	Magnetic Resonance Imaging
NINJA	Novel Integration of New prostate radiation schedules with adJuvant Androgen deprivation
PC	Prostate Cancer
PSA	Prostate Specific Antigen
PSMA-PET	Prostate Specific Membrane Antigen Positron Emission Tomography
RCT	Randomized Controlled Trial
RT	Radiation Therapy
RTOG	Radiation Therapy Oncology Group
RTR	Real Time Review

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SBRT	Stereotactic Body Radiotherapy
sCT	Substitute Computerised Tomography
	Stereotactic Prostate Adaptive Radiotherapy utilising
SPARK	Kilovoltage intrafraction monitoring
TROG	Trans Tasman Radiation Oncology Group

For peer review only

## Declarations

### *Ethics Approval and Consent to Participate*

This study has received Ethical approval from the South West Sydney Local Health District Human Research Ethics Committee (approval number HREC/18/LPOOL/420). All patients will sign a Participant Information Consent Form prior to being randomized and treated on this study.

### *Consent for Publication*

Not applicable, as this manuscript does not include patient information.

### *Availability of Data and Materials*

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

### *Competing Interests*

The author(s) declare that they have no competing interests

### *Funding*

This study underwent competitive peer review by the National Health and Medical Research Council (NHMRC) and was awarded governmental Cancer Australia funding (APP1158455). Additional seed funding was provided by mundipharma.

### *Authors Contributions*

JM and MS conceived of the study. JM, MS, JS and DP were responsible for protocol drafting and data management plan. JM, PK, SS, PG, DC, KM, JD, DP, PC, NM, AR, JL, JS, CO, CT, DM, JMi, KHT, LH, PR, AH, TL, TH and MS were involved in the study design, acquisition of competitive grant funding and helped to draft this



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3 manuscript. JM, PK, SS, PG, DC, KM, JD, DP, PC, NM, AR, JL, JS, CO, CT, DM,  
4 JMi, KHT, LH, PR, AH, TL, TH and MS will remain involved in the conduct and  
5 reporting of the study, and have read and approved the final manuscript.  
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11  
12  
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16 clinical trial design.  
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3 **Figure Captions:**  
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6 **Figure 1:** NINJA Trial Schema  
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10 **Figure 2** – NINJA Dosimetry example showing very conformal nature of high dose  
11 treatment to the Planning Target Volume (PTV). [CTV=Clinical Target Volume,  
12 NVB=Neurovascular Bundle, IPA=Internal Pudendal Artery]  
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**Table 1:** Selected current and pending randomized trials investigating SBRT for prostate cancer

<i><b>Trial</b></i>	<i><b>Control Arm(s)</b></i>	<i><b>Experimental Arm</b></i>	<i><b>n</b></i>	<i><b>Progress</b></i>
HYPO-RT-PC (ISRCTN45905321)	78Gy/39	42.7Gy/7	1400	Results presented 2018
PACE (NCT01584258)	78Gy/39 or 62Gy/20	36.25Gy/5	858	Completed accrual
HEAT (NCT01794403)	70.2Gy/26	36.25Gy/5	456	Accruing
NRG GU005 (NCT03367702)	70Gy/28	36.25Gy/5	622	Accruing

**Table 2a:** Target Volume Objectives and Organs at Risk Constraints – 40 Gy in 5#

Objective	Protocol	Minor Variation	Major Variation
CTVp D95%	≥40.0	38 - <40 Gy	<38 Gy
PTV_4000 D95%	≥36 Gy	34.44 - <36 Gy	<34.44 Gy
PTV_4000 D98%	≥34.44 Gy (95% of 36.25 Gy)	32.72 - <34.44 Gy	<32.72 Gy
PTV_4000 D2%	≤42 Gy	42 – 42.8 Gy	>42.8 Gy
Dmax (0.1cc)	≤42.8 Gy	42.8 – 44 Gy	>44 Gy
Dmax (0.1cc)	Not in OAR	NA	In OAR

Constraint	Protocol	Minor Variation	Major Variation
RECTUM V40 Gy	≤0.1cc	NA	>0.1cc
RECTUM V36 Gy	≤1cc	>1 - 2cc	>2cc
RECTUM V32 Gy	≤10%	>10 - 20%	>20%
RECTUM V20 Gy	≤40%	>40 - 50%	>50%
URETHRA_PRV V42 Gy	≤0.1cc	NA	>0.1cc
BLADDER V40 Gy	≤2cc	>2 - 3cc	>3cc
BLADDER V36 Gy	≤10cc	>10 - 20cc	>20cc
BLADDER V32 Gy	≤10%	>5 - 10%	>10%
BLADDER V20 Gy	≤40%	>40 - 50%	>50%
PENILE BULB V36 Gy	≤0.1cc	NA	>0.1cc
PENILE BULB V20 Gy	≤3cc	>3 - 5cc	>5cc
FEM HEAD V30 Gy	≤0.1cc	NA	>0.1cc
FEM HEAD V20 Gy	≤10cc	>10 - 15cc	>15cc
SIGMOID V40 Gy	≤0.1cc	NA	>0.1cc
SIGMOID V36 Gy	≤2cc	>2 - 3cc	>3cc

Constraint	Protocol	Minor Variation	Major Variation
SMALL BOWEL V30 Gy	≤1cc	NA	>1cc
SMALL BOWEL V25 Gy	≤20cc	>20 - 40cc	>40cc
Conformity index*	≤1.1	>1.1 - 1.2	>1.2
Int. dose spillage**	≤4	>4 - 5	>5
MU/cGy ratio***	≤3	>3 - 4	>4

\* Optional - Volume receiving 36.25 Gy/volume of PTV

\*\* Optional - Ratio of volume receiving 36.25 Gy: 18.13 Gy

\*\*\* Optional - Ratio of MU delivered per fraction divided by 800 (the number of cGy prescribed/fraction)



**Table 2b:** Target Volume Objectives and Organs at Risk Constraints – Virtual HDRB  
Boost, SBRT component 20 Gy in 2 fractions

Objective	Protocol	Minor Variation	Major Variation
CTVp D95%	≥20 Gy	18 - <20 Gy	<18 Gy
PTV_2000 D95%	≥18 Gy	17 – <18 Gy	<17 Gy
PTV_2000 D98%	≥17 Gy	16 - <17 Gy	<16 Gy
PTV_2000 D2%	≤21 Gy	>21 - 21.4 Gy	>21.4 Gy
Dmax (0.1cc)	≤21.4 Gy	>21.4 – 22 Gy	>22 Gy
Dmax (0.1cc)	Not in OAR	NA	In OAR

Constraint	Protocol	Minor Variation	Major Variation
RECTUM V20 Gy	≤0.1cc	NA	>0.1cc
RECTUM V16 Gy	≤1cc	>1 - 2cc	>2cc
RECTUM V14 Gy	≤10%	>10 - 20%	>20%
RECTUM V10 Gy	≤40%	>40 - 50%	>50%
URETHRA_PRV V21 Gy	≤0.1cc	NA	>0.1cc
BLADDER V20 Gy	≤2cc	>2 - 3cc	>3cc
BLADDER V18 Gy	≤10cc	>10 - 20cc	>20cc
BLADDER V16 Gy	≤10%	>5 - 10%	>10%
BLADDER V10 Gy	≤40%	>40 - 50%	>50%
PENILE BULB V18 Gy	≤0.1cc	NA	>0.1cc
PENILE BULB V10 Gy	≤3cc	>3 - 5cc	>5cc
FEM HEAD V15 Gy	≤0.1cc	NA	>0.1cc
FEM HEAD V10 Gy	≤10cc	>10 - 15cc	>15cc
SIGMOID V20 Gy	≤0.1cc	NA	>0.1cc
SIGMOID V18 Gy	≤2cc	>2 - 3cc	>3cc
SMALL BOWEL V15 Gy	≤1cc	NA	>1cc

SMALL BOWEL V10 Gy	≤20cc	>20 - 40cc	>40cc
Conformity index*	≤1.1	>1.1 - 1.2	>1.2
Int. dose spillage**	≤4	>4 - 5	>5
MU/cGy ratio***	≤3	>3 - 4	>4

\* Optional - Volume receiving 18 Gy/volume of PTV

\*\* Optional - Ratio of volume receiving 18 Gy: 9 Gy

\*\*\* Optional - Ratio of MU delivered per fraction divided by 1000 (the number of cGy prescribed/fraction)

**Table 2c:** Target Volume Objectives and Organs at Risk Constraints – Virtual HDRB Boost, EBRT component 36 Gy in 12 fractions

Objectives	Protocol	Minor Variation	Major Variation
PTV_3600 D95%	≥36 Gy	34.2 - <36 Gy	<34.2 Gy
PTV_3600 D98%	≥34.2 Gy	32.4 - <34.2 Gy	<32.4 Gy
PTV_3600 D2%	≤37.8 Gy	>37.8 - 38.5 Gy	>38.5 Gy
PTV_3600 (0.1cc)	≤38.5 Gy	>38.5 – 39.6 Gy	>39.6 Gy

Constraint	Protocol	Minor Variation	Major Variation
Small Bowel Dmax (0.1cc)	≤36 Gy	>36-38 Gy	>38 Gy
Fem Head Dmax (0.1cc)	≤25 Gy	>25-35 Gy	>35 Gy
Rectum V30 Gy	≤25%	>25%-35%	>35%
Bladder V32 Gy	≤25%	>25%-35%	>35%

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**Table 1:** Schedule of Assessments as per SPIRIT Guidelines.

Assessment	Pre Treatment		Treatment	Follow-up		
	Pre-Registration <sup>1</sup>	Baseline <sup>2</sup>		Post SBRT <sup>3</sup>	Every 6 mths <sup>4</sup>	24, 60 mths <sup>4</sup>
Informed Consent	✓					
Eligibility assessment	✓					
Staging investigations <sup>5</sup>	✓					
Clinical examination		✓		✓	✓	
Adverse event		✓	✓	✓	✓	
PSA		✓		✓	✓	
PRO EPIC 26 +/- IIEF 25		✓		✓		✓

<sup>1</sup> To be done within 60 days of registration.

<sup>2</sup> To be done no more than 2 weeks post registration and within 4 weeks of starting treatment.

<sup>3</sup> To be performed between 6 weeks post SBRT treatment completion.

<sup>4</sup> From commencement of ADT.

Note that PSMA-PET is mandated for high risk patients. Whole Body Bone

<sup>5</sup> Scan with CT or MRI of the pelvis +/- abdomen are acceptable for unfavourable intermediate risk patients.

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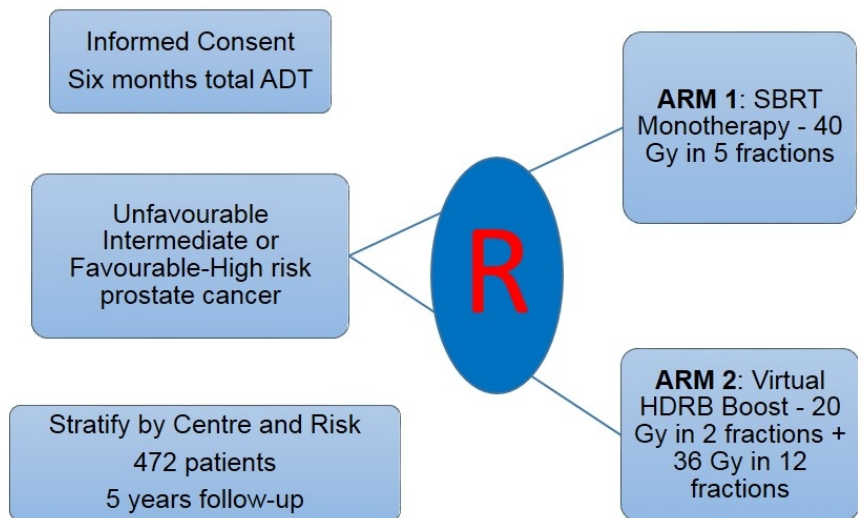


Figure 1: NINJA Trial Schema

161x84mm (150 x 150 DPI)

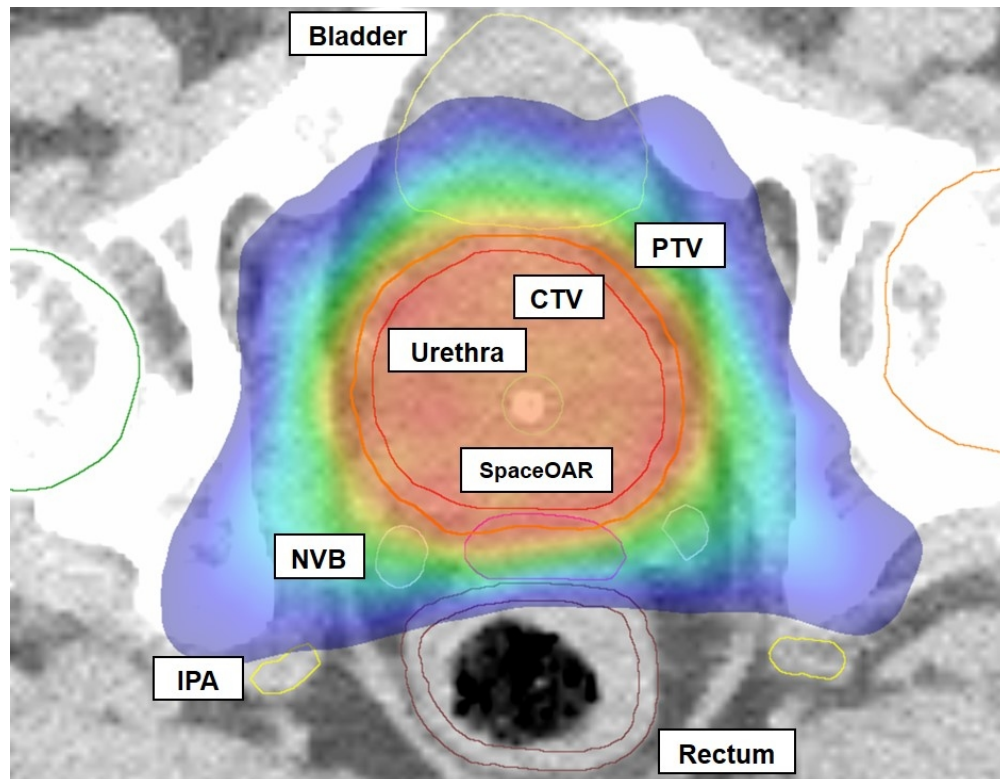


Figure 2 – NINJA Dosimetry example showing very conformal nature of high dose treatment to the Planning Target Volume (PTV). [CTV=Clinical Target Volume, NVB=Neurovascular Bundle, IPA=Internal Pudendal Artery]

159x123mm (150 x 150 DPI)



SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents\*

Section/item	Item No	Description
<b>Administrative information</b>		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym <a href="#">p1 Title page Heading</a>
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry <a href="#">p5 Trial Registration</a>
	2b	All items from the World Health Organization Trial Registration Data Set <a href="#">p5 Trial Registration</a>
Protocol version	3	Date and version identifier <a href="#">p13 Methods, Study Design</a>
Funding	4	Sources and types of financial, material, and other support <a href="#">p25 Declarations, Funding</a>
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors <a href="#">p1-2 Title page</a>
	5b	Name and contact information for the trial sponsor <a href="#">p3 Trial Sponsor</a>
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities <a href="#">p26 Funding and Acknowledgement sections</a>
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee) <a href="#">p26 Acknowledgements</a>
<b>Introduction</b>		
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention <a href="#">p6-11 Background</a>
	6b	Explanation for choice of comparators <a href="#">p6-11 Background and p16-19 Statistical Considerations</a>



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2	Objectives	7	Specific objectives or hypotheses <b>p11 Final paragraphs of Background</b>
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5	Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) <b>p11-12 Background, Summary</b>
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11	<b>Methods: Participants, interventions, and outcomes</b>		
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13	Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained <b>p13 Methods/Design, Study Design</b>
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17	Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) <b>p13-14 Key Trial Eligibility Criteria</b>
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23	Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered <b>p14-19 especially sections Pre-treatment, Time-dose-fractionation planning details, Treatment Delivery, Endpoint NINJA Aim 2 – KBP Advantage, Endpoint NINJA Aim 3 – MRI Planning Validation.</b>
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30		11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease) <b>p25 Declarations, Ethics Approval and Consent to Participate</b>
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36		11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) <b>Not Applicable – it is exceedingly rare for a patient on a Radiation Oncology Clinical trial to not adhere with their cancer treatment</b>
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43		11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial <b>Not Applicable</b>
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46	Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended <b>p17-19 Endpoints NINJA Aim 1-3 and Other Sub-studies</b>
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55	Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) <b>p40 Table 3</b>
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2	Sample size	14	Estimated number of participants needed to achieve study objectives
3			and how it was determined, including clinical and statistical
4			assumptions supporting any sample size calculations <b>p16-19</b>
5			<b>Statistical Considerations</b>
6			
7	Recruitment	15	Strategies for achieving adequate participant enrolment to reach
8			target sample size <b>p13-14 Key Trial Eligibility Criteria</b>
9			

### Methods: Assignment of interventions (for controlled trials)

#### Allocation:

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15	Sequence	16a	Method of generating the allocation sequence (eg, computer-
16	generation		generated random numbers), and list of any factors for stratification.
17			To reduce predictability of a random sequence, details of any planned
18			restriction (eg, blocking) should be provided in a separate document
19			that is unavailable to those who enrol participants or assign
20			interventions <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
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23	Allocation	16b	Mechanism of implementing the allocation sequence (eg, central
24	concealment		telephone; sequentially numbered, opaque, sealed envelopes),
25	mechanism		describing any steps to conceal the sequence until interventions are
26			assigned <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
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29	Implementation	16c	Who will generate the allocation sequence, who will enrol participants,
30			and who will assign participants to interventions <b>p16-17 Statistical</b>
31			<b>Considerations, 2<sup>nd</sup> paragraph</b>
32			
33	Blinding	17a	Who will be blinded after assignment to interventions (eg, trial
34	(masking)		participants, care providers, outcome assessors, data analysts), and
35			how <b>p16-17 Statistical Considerations, 2<sup>nd</sup> paragraph</b>
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38		17b	If blinded, circumstances under which unblinding is permissible, and
39			procedure for revealing a participant's allocated intervention during
40			the trial <b>Not Applicable</b>
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### Methods: Data collection, management, and analysis

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44	Data collection	18a	Plans for assessment and collection of outcome, baseline, and other
45	methods		trial data, including any related processes to promote data quality (eg,
46			duplicate measurements, training of assessors) and a description of
47			study instruments (eg, questionnaires, laboratory tests) along with
48			their reliability and validity, if known. Reference to where data
49			collection forms can be found, if not in the protocol <b>p15-16 Outcome</b>
50			<b>Reporting</b>
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53		18b	Plans to promote participant retention and complete follow-up,
54			including list of any outcome data to be collected for participants who
55			discontinue or deviate from intervention protocols <b>p15-16 Outcome</b>
56			<b>Reporting</b>
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2	Data	19	Plans for data entry, coding, security, and storage, including any
3	management		related processes to promote data quality (eg, double data entry;
4			range checks for data values). Reference to where details of data
5			management procedures can be found, if not in the protocol <a href="#">p15-16</a>
6			<a href="#">Outcome Reporting</a>
7			
8	Statistical	20a	Statistical methods for analysing primary and secondary outcomes.
9	methods		Reference to where other details of the statistical analysis plan can be
10			found, if not in the protocol <a href="#">p16-19</a> <a href="#">Statistical Considerations</a>
11			
12		20b	Methods for any additional analyses (eg, subgroup and adjusted
13			analyses) <a href="#">p16-19</a> <a href="#">Statistical Considerations</a>
14			
15		20c	Definition of analysis population relating to protocol non-adherence
16			(eg, as randomised analysis), and any statistical methods to handle
17			missing data (eg, multiple imputation) <a href="#">p16-19</a> <a href="#">Statistical</a>
18			<a href="#">Considerations</a>
19			
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21			
22	<b>Methods: Monitoring</b>		
23			
24	Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role
25			and reporting structure; statement of whether it is independent from
26			the sponsor and competing interests; and reference to where further
27			details about its charter can be found, if not in the protocol.
28			Alternatively, an explanation of why a DMC is not needed <a href="#">p15-16</a>
29			<a href="#">Outcome Reporting</a>
30			
31		21b	Description of any interim analyses and stopping guidelines, including
32			who will have access to these interim results and make the final
33			decision to terminate the trial <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
34			
35			
36	Harms	22	Plans for collecting, assessing, reporting, and managing solicited and
37			spontaneously reported adverse events and other unintended effects
38			of trial interventions or trial conduct <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
39			
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41	Auditing	23	Frequency and procedures for auditing trial conduct, if any, and
42			whether the process will be independent from investigators and the
43			sponsor <a href="#">Not Applicable</a>
44			
45			
46	<b>Ethics and dissemination</b>		
47			
48	Research ethics	24	Plans for seeking research ethics committee/institutional review board
49	approval		(REC/IRB) approval <a href="#">p25</a> <a href="#">Declarations, Ethics Approval and Consent</a>
50			<a href="#">to Participate</a>
51			
52	Protocol	25	Plans for communicating important protocol modifications (eg,
53	amendments		changes to eligibility criteria, outcomes, analyses) to relevant parties
54			(eg, investigators, REC/IRBs, trial participants, trial registries, journals,
55			regulators) <a href="#">p15-16</a> <a href="#">Outcome Reporting</a>
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2	Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) <b>p25</b>
3			<b>Declarations, Ethics Approval and Consent to Participate</b>
4			
5			
6		26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable <b>Not</b>
7			<b>applicable</b>
8			
9			
10	Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial <b>p15-16 Outcome Reporting</b>
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15	Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site <b>p25 Competing Interests</b>
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18	Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators <b>p17 Statistical Considerations, paragraph 2</b>
19			
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23	Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation <b>Not applicable</b>
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27	Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions <b>p25 Consent for Publication</b>
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34		31b	Authorship eligibility guidelines and any intended use of professional writers <b>p26 Authors Contributions</b>
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38		31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code <b>Not Applicable</b>
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41	<b>Appendices</b>		
42			
43	Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates <b>Provided as supplementary material</b>
44			
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47	Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable <b>Not applicable</b>
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\*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "[Attribution-NonCommercial-NoDerivs 3.0 Unported](https://creativecommons.org/licenses/by-nc-nd/3.0/)" license.