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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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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 look at the transition of centres towards MRI only planning and the impact of KBP on real time plan assessment. Total accrual to 472 patients is planned.

Ethics and Dissemination:

NINJA is a multicentre cooperative clinical trial comparing two SBRT regimens for men with PC with novel technical substudies. It builds on promising results from several single armed studies, and explores radiation dose escalation in the Virtual

HDRB arm. It has HREC approval, and findings will be reported in the peer reviewed literature.

Trial Registration:

Australia New Zealand Clinical Trial Registry – ANZCTN 12615000223538.

Registered prior to opening to accrual 6 November 2018.

Full WHO Trial Registration Data Set available on-line via

https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375560

Article Summary

Strengths and Limitations of this Study

- For men with newly diagnosed prostate cancer, will provide data on outcomes for two emerging approaches to treatment with stereotactic radiotherapy
- Will prospectively explore the implementation of MRI only radiotherapy planning
- Will seek to validate the additional value of automated knowledge based planning
- Incorporates novel staging imaging including PSMA-PET and MRI

Keywords:

Computer Assisted Radiotherapy Planning

Image Guided Radiotherapy

Intensity Modulated Radiotherapy

Prostatic Neoplasms

Radiotherapy

Radiotherapy Dose Hypofractionation

Stereotactic Body Radiotherapy

Introduction

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-RT-PC study completed accrual in 2015, and presented early toxicity data in 2016 showing no significant differences between the control and SBRT arms.[13 14] Initial efficacy results from this study were presented in 2018, showing no differences between the two arms. Recent guidelines from ASTRO, AUA and ASCO have incorporated prostate SBRT monotherapy as a treatment option for centres experienced in this technique.[15] A 2142 patient SBRT monotherapy experience has also shown excellent efficacy, and low toxicity.[16] Bringing this together, SBRT monotherapy is an emerging standard treatment option.

Strong evidence exists for superior disease control through the use of a brachytherapy boost compared with conventional radiotherapy.[17 18] Despite this, the use of brachytherapy continues to decline, partly due to concerns regarding higher risks of significant late GU toxicity.[19] Also, the lack of evidence for improved disease control translating to improved survival has limited uptake, although the poor sensitivity of conventional staging investigations may contribute to superior local control being overwhelmed by undiagnosed micro-metastatic disease. The

emergence of PSMA-PET as a more sensitive and specific staging modality makes revisiting the radiotherapy dose-escalation question highly relevant.[20 21] An alternative approach to brachytherapy is a 'virtual HDR boost' where 2-3 large doses designed to mimic HDRB are delivered via stereotactic techniques with an additional fractionated External Beam Radiation Therapy (EBRT) component. Relatively small virtual HDRB series with nearly 4 years follow up have shown this approach to be feasible, although often using specialised equipment such as the Cyberknife platform.[22 23] Virtual HDRB has also been proven feasible in the setting of multicentre phase 2 trial in Australia, with 135 men enrolled on the PROMETHEUS trial (ACTRN12615000223538) where 2 fractions of 9.5-10Gy are followed by an EBRT component of either 46Gy in 23 or 36Gy in 12 fractions. Early data from PROMETHEUS shows no grade 2-3 late GI toxicity after 24 months and grade 2 late GU toxicity prevalence rates of <7% out to 3 years.[24] Promising efficacy signals are also becoming evident, with almost ablative PSA levels being observed consistent with excellent disease response.

Virtual HDRB may represent a significant biological dose escalation compared with SBRT monotherapy. Assuming prostate cancer has an alpha beta ratio of 1.5 Gy, 40 Gy in 5 fractions and virtual HDRB would be equivalent to 110 and 120 Gy in 2 Gy equivalent fractions respectively. Modelling of RCT data suggests that each extra Gray in dose translates to ~2% improvement in disease control.[25] Alternatively, the virtual HDRB approach potentials allows for some variation in fraction size sensitivity within and between tumours. A reasonable question would be whether the excellent results seen with HDR brachytherapy boost could be safely

translated into the stereotactic setting on the basis of this increase in biological dose delivery. This is the fundamental question which drives NINJA.

Knowledge Based Planning

Knowledge-Based Planning (KBP) has the potential to simultaneously improve and automate the radiotherapy planning process. KBP uses previous cases to build a model of an optimal treatment plan which can then be applied to the current patient. Previous work suggests that KBP can provide faster and frequently better plans,[26] but this has not been prospectively assessed in a multicentre fashion. NINJA provides an ideal opportunity for this.

Radiotherapy plan quality is critically important in achieving optimal treatment outcomes. The Australia-led TROG 02-02 study for patients with locally advanced head and neck cancer showed that non-protocol compliant plans had a locoregional control and overall survival decrement of 24% and 20% respectively.[27] Via TROG, Australia has become leaders in the use of approaches such as stringent credentialing and real time review (RTR) of RT contours and plans, with work in prostate cancer subsequently showing very low rates of protocol deviations both in the definitive prostate and post-prostatectomy irradiation scenarios.[28 29]

An issue with the current RTR process is that although a plan can be deemed satisfactory, it is difficult to determine whether it could be improved. As treatment techniques evolve, satisfying the dose constraints in clinical trial protocols can become progressively easier. Knowledge-Based Planning (KBP) has emerged as a

promising approach to assess and improve plan quality. In KBP, a model is developed using a range of patient anatomies and target volumes. This can then be rapidly applied to a new case to either generate a plan de novo, or to compare with a conventional plan. The Radiation Therapy Oncology Group (RTOG) 0126 prostate cohort was selected to study treatment plan quality variations. This work examined the high-dose Intensity Modulated Radiation Therapy (IMRT) patients using a KBP model to identify the plans that best met the dosimetric aims of the protocol.[30] Focusing on Grade 2+ late rectal toxicities with an outcomes-validated normal tissue complication probability (NTCP) model, the high-dose arm of RTOG 0126 patients treated with IMRT patients had a 15.1% cumulative incidence of Grade 2+ rectal complications.[31] KBP plans were predicted to lead to a 4.7% risk reduction in this rate, which therefore may have cut this incidence by a third. The observed quality variations in RTOG 0126 give the strongest evidence yet that suboptimal planning is a critical problem in multi-institutional radiotherapy clinical trials and in the wider practice of radiotherapy. KBP has yet to be robustly assessed in a multicentre fashion, where the heterogeneity of planning systems and personnel would be expected to be greatest.

MRI Radiotherapy Planning

Computerised Tomography (CT) is widely used for radiotherapy dosimetry calculation because of the ability to directly measure electron density. Our team has validated the use of Magnetic Resonance Imaging (MRI) to create a substitute CT (sCT) which can then be used for accurate dose calculation.[32] The superior soft tissue resolution of MRI, absence of radiation dose, and reduction in image artefacts

means that if the dose calculation problem could be solved, standard CT based planning would be rendered obsolete.[33]

Many centres now acquire both a CT and a MRI scan for each patient, but co-registration of these datasets introduces significant error mostly under the influence of bladder filling and varying rectal distension. An attractive alternative would be to create a substitute CT (sCT) from the MRI dataset to allow RT dose calculation. Our team has developed a hybrid atlas-voxel based technique of sCT generation which showed high agreement in both mean monitor units (0.3%+/- sd 0.8%) and dose delivery (3-dimensional gamma pass rate at 2 mm/2% level of 100% +/- sd 0%.[32] A group of Swedish centres have shown similar findings in a retrospective, multicentre study,[34] and our group is prospectively evaluating this approach in 2 centres (HIPSTER study - ACTRN12616001653459). Given the advantages of MRI for prostate cancer, and the improving access to MRI in Australia (including radiotherapy departments with dedicated planning MRI facilities), this is another area ripe for wider assessment, implementation and eventual broader application.

Summary

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

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

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

Aim 3: ***MRI only Planning***: MRI will give dosimetry similar to standard CT planning.

Methods/Design

Study Design:

The study design is a prospective randomised phase 3 trial available in Australian academic and community Radiation Oncology centres (sites available via Trans-Tasman Radiation Oncology Group) which conforms to the SPIRIT guidelines. Protocol v2.0 is dated November 2018.

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. Accruing centres will proactively screen for potentially eligible patients.

Pre-Treatment

All patients will receive a total of six months of Androgen Deprivation Therapy (ADT).[35] 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 visualization via temporary catheterization or equivalent approaches will be performed. Erectile sparing RT

plans for men with adequate baseline IIEF and desire to maintain erectile function can be used.[37] Centres will be credentialed for MRI planning via their first 5 patients being primarily planned off the CT, but with sCT generation and confirmation of accurate dosimetry. The next ten patients will have planning performed on sCT and confirmed on planning CT. Subsequent patients will omit a planning CT, be planned on sCT, and have confirmation of accurate dosimetry on treatment using a centrally approved approach eg EPID dosimetry[38] or in vivo dosimetry.[39]

Time-dose-fractionation planning details

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

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

Quality Assurance

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

Treatment Delivery

All patients require intra-prostatic markers, and both inter- as well as intra-fraction motion management strategies to ensure accurate treatment delivery. For intra-fraction motion assessment, numerous 'real time' approaches are acceptable (eg KIM, Calypso, Cyber-knife). In all instances, translational movements to be corrected to 0mm threshold prior to commencing treatment.

Outcome Reporting

Indicators of feasibility, accuracy, impact on replanning, and other qualitative and quantitative markers of KBP and MRI planning will be collected. Patient reported outcomes to include baseline and serial patient reported outcomes (IIEF, EPIC), physician toxicity grading (CTC AE v5), PSA and any sites of confirmed disease relapse or death due to any cause. Participants will have unique identifiers which will protect their confidentiality, and only summary data will be presented after analysis. Participants will be requested to provide this information even if without from study treatment. Any Serious Adverse Events will be reported to the central HREC within 1 working day. Data will be securely electronically stored for at least 15 years, and audited to ensure data quality. Any protocol amendments will be reviewed by the HREC, and communicated to all participating centres, investigators and participants. If the prevalence of CTC AE grade 3 GI or GU toxicities exceeds 10% at any stage, the trial will be halted for safety assessment. This oversight will be

provided by the TROG Independent Data Monitoring Committee. A SPIRIT flowchart is presented in Table 3.

Statistical Considerations

The statistical justification required to achieve the primary efficacy endpoint (Aim 1) is as follows. BCC is a hybrid of biochemical failure via the nadir plus two definition, deployment of salvage treatments, or the detection of local, regional or metastatic relapse via imaging. Using a similar endpoint as well as a short course of ADT, the CHHiP study 60 Gy arm had 90.2% and 84.2% BCC for intermediate and high risk patients respectively.[40] The ASCENDE-RT study also included intermediate and high risk men, managed with 12 months of ADT, and the experimental arm delivered 46 Gy in 23 fractions of EBRT alongside a LDR Brachytherapy boost.[18] At 5 years, the BCC was 89% in the brachytherapy boost cohort, although with a higher risk patient mix than we are going to accrue on this protocol. Allowing for differences in inter-trial comparisons, we estimate BCC ~86% in the standard SBRT arm. Similar data has been reported for single arm SBRT monotherapy series.[12] For a superiority RCT design, we will aim for a hazard ratio of 0.5 in 5-yr BCC for the virtual HDR arm ie 93%. An HR of 0.5 is chosen because this translates to an absolute improvement of 7%, and any improvements less than this are unlikely to be clinically significant. With alpha 0.05, power of 80%, and drop out of 2% the required phase 3 sample size is 472 men.

Computer generated randomization will be performed with stratification by centre and risk grouping via centralized database at the Trial Coordinating Centre in

Newcastle and concealed until intervention assigned. Randomization performed by Data Manager independent of Trial Coordinators who assign interventions and Investigators who enrol participants. Assignment is unblinded, and selected aspects of the dataset will only be available to appropriately qualified individuals for the relevant analyses.

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

Patient and Public Involvement

Three patients who had been treated on the phase 2 precursor studies to NINJA were involved as Associate Investigators in the grant application, and subsequent study design through engagement via teleconferences and review of documentation. Given their exposure to the two treatment approaches, they were ideally informed about the potential burden of treatment. These consumers will continue to provide guidance on study recruitment and conduct throughout the duration of the trial. Study participants will continue with follow-up following treatment, and hence will be able to be informed about outcomes from the research.

Endpoints NINJA Aim 1 – Radiobiological Dose Escalation

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

Endpoint NINJA Aim 2 – KBP Advantage

KBP models will initially be developed for the SBRT monotherapy and virtual HDRB arms. The training sample for the NINJA KBP model will come from the SPARK and PROMETHEUS cohorts, and will be continuously improved during the NINJA trial. As new cases are accepted to the trial they will be incorporated into the knowledge-based dose prediction models to broaden the geometric experience and improve future prediction accuracy. The NINJA KBP automated planning routines' performance will be validated on an independent validation sample of cases (holding back 20% of SPARK/PROMETHEUS cases) to ensure that the final KBP plans are effecting plans that match the dosimetric goals of the NINJA protocol.

All NINJA patients will have a plan generated as per local standard of care by the treating centre. If sites are capable of utilizing KBP locally, they will be provided with the NINJA KBP routine. All plans will then be uploaded to TROG to be compared with a KBP generated plan. If the site was submitting a manually generated plan, an automated report will be returned to the treating centre within 24 hours, at which time they can decide whether to proceed with their original manual plan or to replan based on the KBP recommendations. If the site utilizes the NINJA KBP routine, a central quality check will be performed to ensure proper use of the model, but no further recommendation will be made to the submitting site. The utility of KBP will be assessed by recording the rate of replanning following receipt of the KBP plan.

Endpoint NINJA Aim 3 – MRI Planning Validation

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

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

- Accuracy – The proportion of plans where both the isocentre dose and Gamma comparison are within the stated constraints. Deemed accurate if >95%.
- 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 ≥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

Ethics and Dissemination

This study has received Ethical approval from the South West Sydney Local Health District Human Research Ethics Committee (approval number HREC/18/LPOOL/420). After invitation by a credentialed local Investigator, all patients will sign a Participant Information Consent Form prior to being randomized and treated on this study. Participants are free to withdraw from the study at any time. Results will be published in peer reviewed literature, presented at professional meetings, and disseminated through patient facing avenues such as local media.

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.

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

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Declarations

Consent for Publication

Not applicable, as this manuscript does not include patient information. Trial results, when available, will be widely disseminated via academic meetings, journals, social media and traditional media.

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

No competing interests are relevant to the submitted work. J Martin has acted on Advisory Boards for Ferring pharmaceuticals and Janssen, as well as having paid employment with the commercial provider GenesisCare. DC and TL also are employed by Genesis Care. PK is the inventor of a KIM-related patent that has been licensed to Varian Medical Systems by Stanford University and an MLC tracking patent licensed to Leo Cancer Care by the University of Sydney. PK founded Leo but has no ownership interest. PK is the inventor of additional unlicensed KIM-related patents. Other interests include founding and shareholding in Opus Medical and SeeTreat, unlicensed patents, licenses to Leo Cancer Care, Opus Medical, Standard Imaging and Varian Medical Systems and research agreements with Siemens

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Author Contributions

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

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Figure 1: NINJA Trial Schema

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]

Table 1: Selected current and pending randomized trials investigating SBRT for prostate cancer

Trial	***Control Arm(s)***	***Experimental Arm***	***n***	***Progress***
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

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

* 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%

Table 1: Schedule of Assessments as per SPIRIT Guidelines.

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

[1] To be done within 60 days of registration.

[2] To be done no more than 2 weeks post registration and within 4 weeks of starting treatment.

[3] To be performed between 6 weeks post SBRT treatment completion.

[4] From commencement of ADT.

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

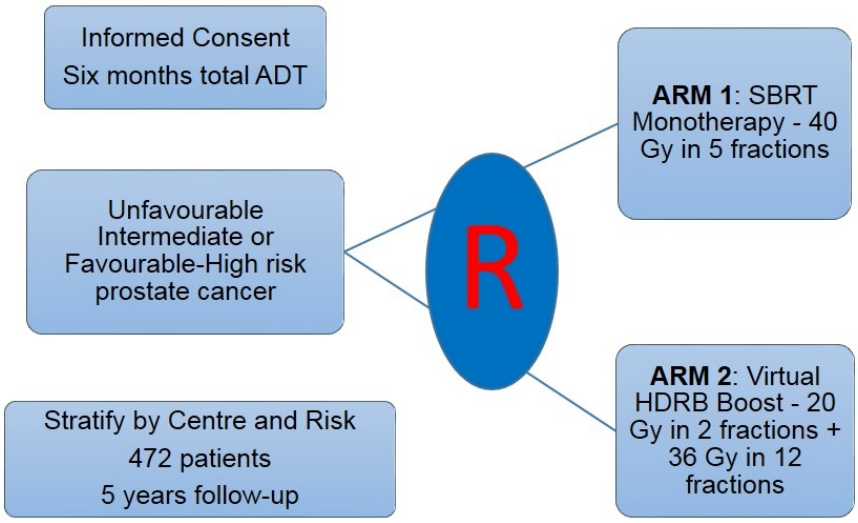

Figure 1: NINJA Trial Schema

161x84mm (150 x 150 DPI)

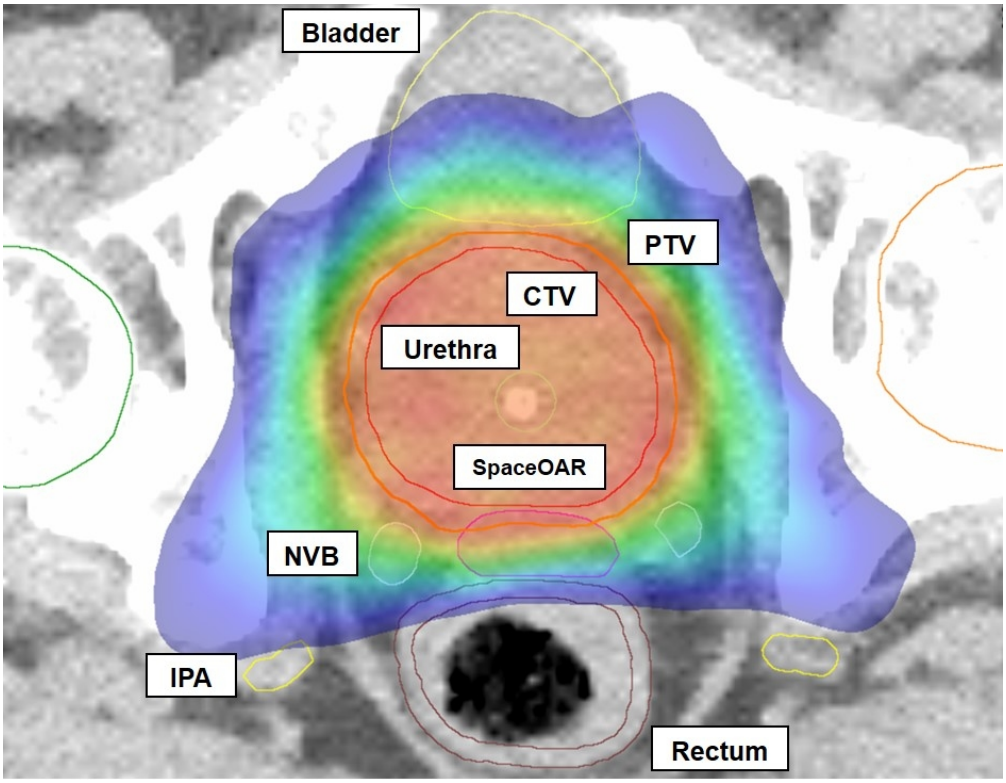

Figure 2 – NINJA Dosimetry example showing very conformal nature of high dose treatment to the Planning Target Volume (PTV). [CTV=Clinical Target Volume, NVB=Neurovascular Bundle, IPA=Internal Pudendal Artery]

159x123mm (150 x 150 DPI)

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym p1 Title page Heading
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry p5 Trial Registration
	2b	All items from the World Health Organization Trial Registration Data Set p5 Trial Registration
Protocol version	3	Date and version identifier p13 Methods, Study Design
Funding	4	Sources and types of financial, material, and other support p25 Declarations, Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors p1-2 Title page
	5b	Name and contact information for the trial sponsor p3 Trial Sponsor
	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 p26 Funding and Acknowledgement sections
	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) p26 Acknowledgements
Introduction		
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 p6-11 Background
	6b	Explanation for choice of comparators p6-11 Background and p16-19 Statistical Considerations

Objectives	7	Specific objectives or hypotheses p11 Final paragraphs of Background
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) p11-12 Background, Summary
Methods: Participants, interventions, and outcomes		
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 p13 Methods/Design, Study Design
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) p13-14 Key Trial Eligibility Criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 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.
	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) p25 Declarations, Ethics Approval and Consent to Participate
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not Applicable – it is exceedingly rare for a patient on a Radiation Oncology Clinical trial to not adhere with their cancer treatment
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Not Applicable
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 p17-19 Endpoints NINJA Aim 1-3 and Other Sub-studies
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) p40 Table 3

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 p16-19 Statistical Considerations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size p13-14 Key Trial Eligibility Criteria
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
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 p16-17 Statistical Considerations, 2nd paragraph
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 p16-17 Statistical Considerations, 2nd paragraph
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions p16-17 Statistical Considerations, 2nd paragraph
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how p16-17 Statistical Considerations, 2nd paragraph
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not Applicable
Methods: Data collection, management, and analysis		
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 p15-16 Outcome Reporting
	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 p15-16 Outcome Reporting

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol p15-16 Outcome Reporting
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol p16-19 Statistical Considerations
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses) p16-19 Statistical Considerations
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation) p16-19 Statistical Considerations
Methods: Monitoring		
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed p15-16 Outcome Reporting
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial p15-16 Outcome Reporting
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct p15-16 Outcome Reporting
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor Not Applicable
Ethics and dissemination		
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval p25 Declarations, Ethics Approval and Consent to Participate
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) p15-16 Outcome Reporting

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) p25 Declarations, Ethics Approval and Consent to Participate
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
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 p15-16 Outcome Reporting
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site p25 Competing Interests
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 p17 Statistical Considerations, paragraph 2
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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 p25 Consent for Publication
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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 Not applicable

*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" license.

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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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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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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-

RT-PC study completed accrual in 2015, and presented early toxicity data in 2016 showing no significant differences between the control and SBRT arms.(13, 14) Initial efficacy results from this study were presented in 2018, showing no differences between the two arms. Recent guidelines from ASTRO, AUA and ASCO have incorporated prostate SBRT monotherapy as a treatment option for centres experienced in this technique.(15) Bringing this together, although SBRT monotherapy can currently be considered investigational, it is likely to gain wider acceptance as a standard treatment option in the near future. Hence our plan is to commence NINJA as a randomized phase 2 study, but to convert to a fully powered phase 3 study with SBRT monotherapy as the control arm as the evidence base continues to mature.

Strong evidence exists for superior disease control through the use of a brachytherapy boost compared with conventional radiotherapy.(16, 17) Despite this, the use of brachytherapy continues to decline, partly due to concerns regarding higher risks of significant late GU toxicity.(18) Also, the lack of evidence for improved disease control translating to improved survival has limited uptake, although the poor sensitivity of conventional staging investigations may contribute to superior local control being overwhelmed by undiagnosed micro-metastatic disease. The emergence of PSMA-PET as a more sensitive and specific staging modality makes revisiting the radiotherapy dose-escalation question highly relevant.(19, 20) An alternative approach to brachytherapy is a 'virtual HDR boost' where 2-3 large doses designed to mimic HDRB are delivered via stereotactic techniques with an additional fractionated External Beam Radiation Therapy (EBRT) component. Relatively small virtual HDRB series with nearly 4 years follow up have shown this approach to be feasible, although often using specialised equipment such as the Cyberknife platform.(21, 22) Virtual HDRB has also been proven feasible in the setting of multicentre phase 2 trial in Australia, with 135 men enrolled on the PROMETHEUS trial (ACTRN12615000223538) where 2 fractions of 9.5-10Gy are followed by an EBRT component of either 46Gy in 23 or 36Gy in 12 fractions. Early data from PROMETHEUS shows no grade 2-3 late GI toxicity after 24 months and grade 2 late GU toxicity prevalence rates of <7% out to 3 years. Promising efficacy signals are also becoming evident, with almost ablative PSA levels being observed consistent with excellent disease response.(23)

Virtual HDRB may represent a significant biological dose escalation compared with SBRT monotherapy. Assuming prostate cancer has an alpha beta ratio of 1.5 Gy, 40 Gy in 5 fractions and virtual HDRB would be equivalent to 110 and 120 Gy in 2 Gy equivalent fractions respectively. Modelling of RCT data suggests that each extra Gray in dose translates to ~2% improvement in disease control.(24) The virtual HDRB approach also acknowledges the possibility of heterogeneity in the alpha-beta ratio, and therefore potentially allows for some variation in fraction size sensitivity within and between tumours. A reasonable question would be whether the excellent results seen with HDR brachytherapy boost could be safely translated into the stereotactic setting on the basis of this increase in biological dose delivery. This is the fundamental question which drives NINJA.

Knowledge Based Planning

Knowledge-Based Planning (KBP) has the potential to simultaneously improve and automate the radiotherapy planning process. KBP uses previous cases to build a model of an optimal treatment plan which can then be applied to the current patient. Previous work suggests that KBP can provide faster and frequently better plans,(25) but this has not been prospectively assessed in a multicentre fashion. NINJA provides an ideal opportunity for this.

Radiotherapy plan quality is critically important in achieving optimal treatment outcomes. The Australia-led TROG 02-02 study for patients with locally advanced head and neck cancer showed that non-protocol compliant plans had a locoregional control and overall survival decrement of 24% and 20% respectively.(26) Via TROG, Australia has become leaders in the use of approaches such as stringent credentialing and real time review (RTR) of RT contours and plans, with work in prostate cancer subsequently showing very low rates of protocol deviations both in the definitive prostate and post-prostatectomy irradiation scenarios.(27, 28)

An issue with the current RTR process is that although a plan can be deemed satisfactory, it is difficult to determine whether it could be improved. As treatment techniques evolve, satisfying the dose constraints in clinical trial protocols can

become progressively easier. Knowledge-Based Planning (KBP) has emerged as a promising approach to assess and improve plan quality. In KBP, a model is developed using a range of patient anatomies and target volumes. This can then be rapidly applied to a new case to either generate a plan de novo, or to compare with a conventional plan. The Radiation Therapy Oncology Group (RTOG) 0126 prostate cohort was selected to study treatment plan quality variations. This work examined the high-dose Intensity Modulated Radiation Therapy (IMRT) patients using a KBP model to identify the plans that best met the dosimetric aims of the protocol.(29) Focusing on Grade 2+ late rectal toxicities with an outcomes-validated normal tissue complication probability (NTCP) model, the high-dose arm of RTOG 0126 patients treated with IMRT patients had a 15.1% cumulative incidence of Grade 2+ rectal complications.(30) KBP plans were predicted to lead to a 4.7% risk reduction in this rate, which therefore may have cut this incidence by a third. The observed quality variations in RTOG 0126 give the strongest evidence yet that suboptimal planning is a critical problem in multi-institutional radiotherapy clinical trials and in the wider practice of radiotherapy. KBP has yet to be robustly assessed in a multicentre fashion, where the heterogeneity of planning systems and personnel would be expected to be greatest.

MRI Radiotherapy Planning

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

Many centres now acquire both a CT and a MRI scan for each patient, but co-registration of these datasets introduces significant error mostly under the influence of bladder filling and varying rectal distension. An attractive alternative would be to create a substitute CT (sCT) from the MRI dataset to allow RT dose calculation. Our team has developed a hybrid atlas-voxel based technique of sCT generation which

showed high agreement in both mean monitor units (0.3%+/- sd 0.8%) and dose delivery (3-dimensional gamma pass rate at 2 mm/2% level of 100% +/- sd 0%.(31) A group of Swedish centres have shown similar findings in a retrospective, multicentre study,(33) and our group is prospectively evaluating this approach in 2 centres (HIPSTER study - ACTRN12616001653459). Given the advantages of MRI for prostate cancer, and the improving access to MRI in Australia (including radiotherapy departments with dedicated planning MRI facilities), this is another area ripe for wider assessment, implementation and eventual broader application.

Summary

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

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

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

Aim 3: ***MRI only Planning***: MRI will give dosimetry similar to standard CT planning.

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-

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

Time-dose-fractionation planning details

Clinical Target Volume (CTV): Entire prostate and proximal 10mm of seminal vesicles. No elective nodal irradiation permitted.
Planning Target Volume (PTV): For SBRT treatments, 3mm uniform expansion from CTV. For Virtual HDRB 36 Gy in 12 fraction component, 7mm uniform expansion from CTV.
SBRT Monotherapy arm: 40 Gy in five fractions delivered 2-3 times per week, prescribed to CTV D95%.
Virtual HDRB Boost Arm: 20 Gy in two fractions prescribed to CTV D95% delivered once a week followed by a two week break and then 36 Gy in 12 fractions delivered 5 times per week prescribed to PTV D95%. See tables 2a-c for dose constraints, and Figure 2 for an example of the SBRT dosimetry.

Quality Assurance

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

Treatment Delivery

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

Outcome Reporting

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

Statistical Considerations

The statistical justification required to achieve the primary efficacy endpoint (Aim 1) is as follows. BCC is a hybrid of biochemical failure via the nadir plus two definition, deployment of salvage treatments, or the detection of local, regional or metastatic relapse via imaging. Using a similar endpoint as well as a short course of ADT, the CHHiP study 60 Gy arm had 90.2% and 84.2% BCC for intermediate and high risk patients respectively.(41) The ASCENDE-RT study also included intermediate and high risk men, managed with 12 months of ADT, and the experimental arm delivered 46 Gy in 23 fractions of EBRT alongside a LDR Brachytherapy boost.(17) At 5 years, the BCC was 89% in the brachytherapy boost cohort, although with a higher risk patient mix than we are going to accrue on this protocol. Allowing for differences in inter-trial comparisons, we estimate BCC ~86% in the standard SBRT arm. Similar data has been reported for single arm SBRT monotherapy series.(12) For a superiority RCT design, we will aim for a hazard ratio of 0.5 in 5-yr BCC for the virtual HDR arm ie 93%. An HR of 0.5 is chosen because this translates to an absolute improvement of 7%, and any improvements less than this are unlikely to be

clinically significant. With alpha 0.05, power of 80%, and drop out of 2% the required phase 3 sample size is 472 men.

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

Endpoints NINJA Aim 1 – Radiobiological Dose Escalation

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

Endpoint NINJA Aim 2 – KBP Advantage

KBP models will initially be developed for the SBRT monotherapy and virtual HDRB arms. The training sample for the NINJA KBP model will come from the SPARK and PROMETHEUS cohorts, and will be continuously improved during the NINJA trial. As new cases are accepted to the trial they will be incorporated into the knowledge-based dose prediction models to broaden the geometric experience and improve future prediction accuracy. The NINJA KBP automated planning routines' performance will be validated on an independent validation sample of cases (holding

back 20% of SPARK/PROMETHEUS cases) to ensure that the final KBP plans are effecting plans that match the dosimetric goals of the NINJA protocol.

All NINJA patients will have a plan generated as per local standard of care by the treating centre. If sites are capable of utilizing KBP locally, they will be provided with the NINJA KBP routine. All plans will then be uploaded to TROG to be compared with a KBP generated plan. If the site was submitting a manually generated plan, an automated report will be returned to the treating centre within 24 hours, at which time they can decide whether to proceed with their original manual plan or to replan based on the KBP recommendations. If the site utilizes the NINJA KBP routine, a central quality check will be performed to ensure proper use of the model, but no further recommendation will be made to the submitting site. The utility of KBP will be assessed by recording the rate of replanning following receipt of the KBP plan.

Endpoint NINJA Aim 3 – MRI Planning Validation

This sub-study will be for centres with access to MRI scanning with appropriate accessories such as a flat top couch. Patients will have a CT and a MRI performed in the planning position. Clinicians will contour all target volumes and organs at risk on the MRI. Sites who have not been validated for MRI based planning will go through a credentialing phase, where the first 5 patients will have the planning processes assessed.(31) Following credentialing (or evidence of previously fulfilling this requirement), the MRI will be exported for remote generation of a sCT. A plan will then be created on the sCT, and copied onto the planning CT. The dosimetry of these will be compared at points within both the target volume and critical structures. If the isocentre dose is within 2% and 3D Gamma comparison at 2%/2mm criteria > 90% pass-rate for the entire scanned volume, then the sCT plan will be deemed accurate and used for patient treatment. After ten such patients, centres will have the option of no longer performing a routine planning scan, but instead using in vivo dosimetry to confirm accurate dose delivery with the same criteria as for the sCT and planning CT comparison. The utility of MRI planning will be assessed via:

- Accuracy – The proportion of plans where both the isocentre dose and Gamma comparison are within the stated constraints. Deemed accurate if >95%.

- 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 ≥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 resonanted 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)

to ensure broad consumer awareness of NINJA. The Trial Management Committee will continue to include our consumer advisors in ongoing discussions regarding accrual and toxicities to gain their perspective on any changes to the conduct of the trial which might be advisable.

NINJA is designed with numerous potentially practice changing outcomes; consumers will remain critical throughout the trial to maximise integration of these into wider clinical practice. Several of our team are very active on social media, which can make direct connections with consumers about our findings. Many of our clinician CIs and AIs are regular speakers for local prostate cancer support groups.

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 Uropathology
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

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

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

manuscript. 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 will remain involved in the conduct and reporting of the study, and have read and approved the final manuscript.

Acknowledgements

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Figure Captions:

Figure 1: NINJA Trial Schema

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]

Table 1: Selected current and pending randomized trials investigating SBRT for prostate cancer

Trial	***Control Arm(s)***	***Experimental Arm***	***n***	***Progress***
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%

Table 1: Schedule of Assessments as per SPIRIT Guidelines.

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

[1] To be done within 60 days of registration.

[2] To be done no more than 2 weeks post registration and within 4 weeks of starting treatment.

[3] To be performed between 6 weeks post SBRT treatment completion.

[4] From commencement of ADT.

[5] Note that PSMA-PET is mandated for high risk patients. Whole Body Bone Scan with CT or MRI of the pelvis +/- abdomen are acceptable for unfavourable intermediate risk patients.

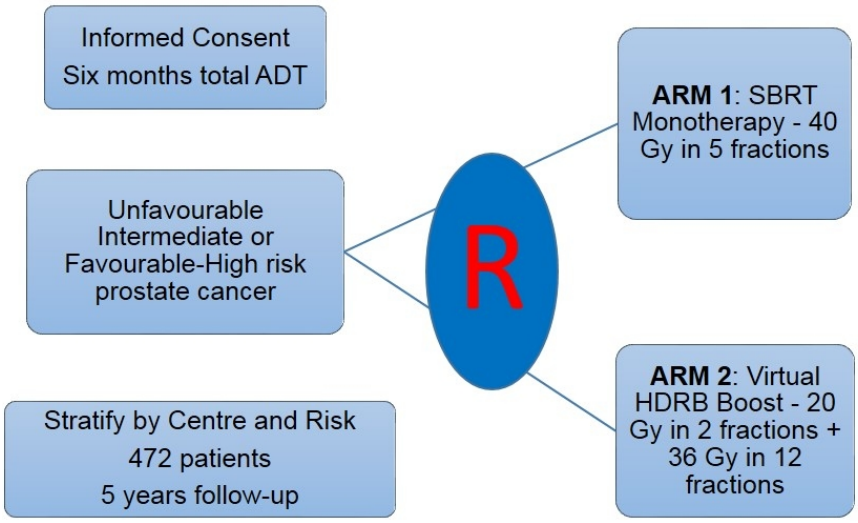

Figure 1: NINJA Trial Schema

161x84mm (150 x 150 DPI)

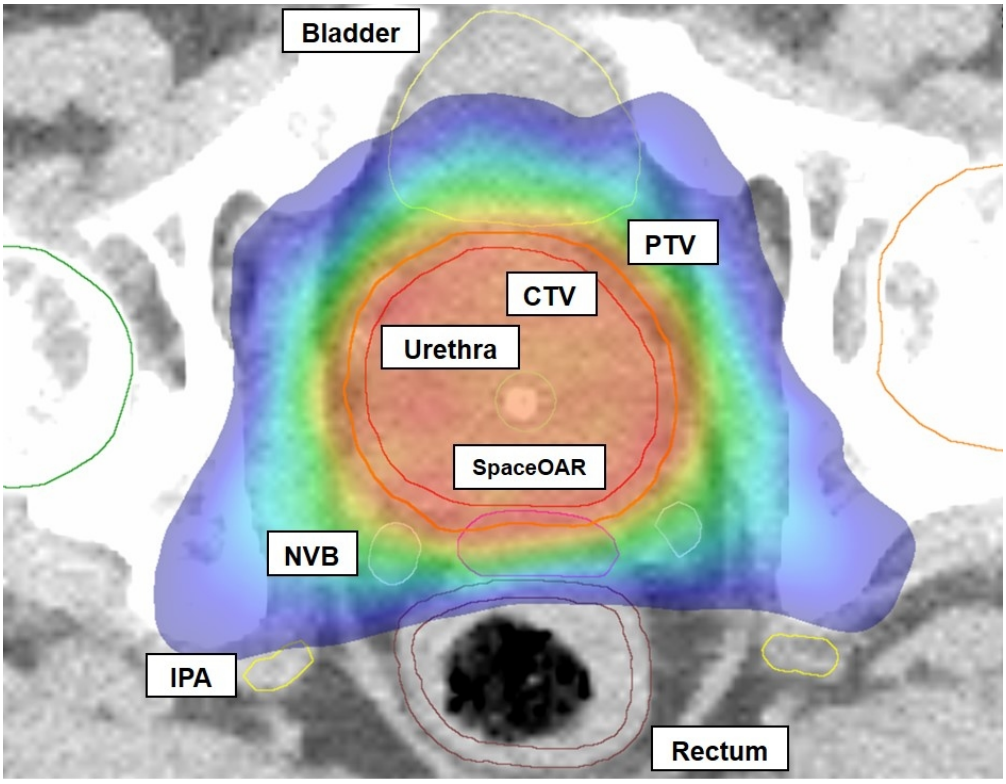

Figure 2 – NINJA Dosimetry example showing very conformal nature of high dose treatment to the Planning Target Volume (PTV). [CTV=Clinical Target Volume, NVB=Neurovascular Bundle, IPA=Internal Pudendal Artery]

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SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description
Administrative information		
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym p1 Title page Heading
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry p5 Trial Registration
	2b	All items from the World Health Organization Trial Registration Data Set p5 Trial Registration
Protocol version	3	Date and version identifier p13 Methods, Study Design
Funding	4	Sources and types of financial, material, and other support p25 Declarations, Funding
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors p1-2 Title page
	5b	Name and contact information for the trial sponsor p3 Trial Sponsor
	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 p26 Funding and Acknowledgement sections
	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) p26 Acknowledgements
Introduction		
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 p6-11 Background
	6b	Explanation for choice of comparators p6-11 Background and p16-19 Statistical Considerations

Objectives	7	Specific objectives or hypotheses p11 Final paragraphs of Background
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) p11-12 Background, Summary
Methods: Participants, interventions, and outcomes		
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 p13 Methods/Design, Study Design
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) p13-14 Key Trial Eligibility Criteria
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered 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.
	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) p25 Declarations, Ethics Approval and Consent to Participate
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) Not Applicable – it is exceedingly rare for a patient on a Radiation Oncology Clinical trial to not adhere with their cancer treatment
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial Not Applicable
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 p17-19 Endpoints NINJA Aim 1-3 and Other Sub-studies
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) p40 Table 3

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 p16-19 Statistical Considerations
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size p13-14 Key Trial Eligibility Criteria
Methods: Assignment of interventions (for controlled trials)		
Allocation:		
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 p16-17 Statistical Considerations, 2nd paragraph
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 p16-17 Statistical Considerations, 2nd paragraph
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions p16-17 Statistical Considerations, 2nd paragraph
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how p16-17 Statistical Considerations, 2nd paragraph
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial Not Applicable
Methods: Data collection, management, and analysis		
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 p15-16 Outcome Reporting
	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 p15-16 Outcome Reporting

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	p15-16 Outcome Reporting
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	p16-19 Statistical Considerations
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	p16-19 Statistical Considerations
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	p16-19 Statistical Considerations
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	p15-16 Outcome Reporting
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	p15-16 Outcome Reporting
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	p15-16 Outcome Reporting
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Not Applicable
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	p25 Declarations, Ethics Approval and Consent to Participate
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	p15-16 Outcome Reporting

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) p25 Declarations, Ethics Approval and Consent to Participate
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable Not applicable
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 p15-16 Outcome Reporting
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site p25 Competing Interests
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 p17 Statistical Considerations, paragraph 2
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 Not applicable
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 p25 Consent for Publication
	31b	Authorship eligibility guidelines and any intended use of professional writers p26 Authors Contributions
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code Not Applicable
Appendices		
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates Provided as supplementary material
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 Not applicable

*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" license.