PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Martin, Jarad; Keall, Paul; Siva, Shankar; Greer, Peter; Christie, David; Moore, Kevin; Dowling, Jason; Pryor, David; Chong, Peter; McLeod, Nicholas; Raman, Avi; Lynam, James; Smart, Joanne; Oldmeadow, Christopher; Tang, Colin; Murphy, Declan; Millar, Jeremy; Tai, Keen Hun; Holloway, Lois; Reeves, Penny; Hayden, Amy; Lim, Tee; Holt, Tanya; Sidhom, Mark

VERSION 1 - REVIEW

REVIEWER	Sean Collins Georgetown University, USA I am an Accuray Clinical consultant
REVIEW RETURNED	18-May-2019

GENERAL COMMENTS	General This is a well-written manuscript describing a multi-institutional Phase III trial of SBRT plus or minus supplemental IMRT for unfavorable prostate cancer. This series is well suited for publication in BMJ Open because this study is very important. The authors are clearly experts in the field and the paper is for the most part scientifically accurate. Major Compulsory Revisions: The primary endpoint is BDFS. If the HDRB arm has a higher BDFS but is more toxic (> 10% grade 3 toxicity) in the multi-institutional setting would you recommend HDRB as your standard treatment for all future patients? Would it make sense to have two primary endpoints BDFS and Grade 3 toxicity? QOL? Please justify the usage of six months of ADT in favorable high-risk patients. The ASCEND trial does not show differences in arms until after 5 years. It is unlikely that there will be a large difference in BDFS at 5 years between arms in this study. Why not BDFS at 7-10 years? Minor Compulsory Revisions:

	Does the HDRB arm also treat a larger volume of normal tissue? Does the 36 Gy in 12 fractions of the HDRB Arm treat a larger target volume? pelvic nodes? Please clarify this line: Alternatively, the virtual HDRB approach potentials allows for some variation in fraction size sensitivity within and between tumors. Urethral visualization via temporary catheterization or equivalent approaches will be performed. What equivalent approaches? All patients require intra-prostatic markers with intra-fraction motion management strategies to ensure accurate treatment delivery. Are you correcting for translations and rotations or just translations?

REVIEWER	Professor John Staffurth Division of Cancer and Genetics School of Medicine Cardiff University United Kingdom Prof. Staffurth reports non-financial support from Bayer, personal fees from Janssen, outside the submitted work. I have no other conflicts of interest
REVIEW RETURNED	24-May-2019

GENERAL COMMENTS	Thank you for the submission and its a really interesting trial design. I only make these points to assist = there's nothing of real concern. In the eligibility criteria, I wonder if you need to include MRI defined estimate prostate volume >100cc (so that you don't end up with investigators entering patients with borderline volume. Concurrent hormonal therapy - is single agent bicalutamide 150mg od allowed? Aim 1 - I agree with your estimation of 5yr BCC in this patient group. I do have some concerns with the 2-arm nature of the study and that both arms are to some experimental (as your standard protocol appears to 60gy/ 20Fr); comparing the SBRT and HDRB arms you actually have several variations - including overall time, total dose and dose per fraction; whether HDRB is dose escalation compared to SBRT depends on the alpha-beta ratio and whether time is important, which is currently an open debate. I do agree that the HDRB arm needs to be a lot better than the SBRT arm to make it cost effective and acceptable to patients and healthcare commissioners (in the UK anyway)! Aim 2 - I couldn't see any guidance for centres as whether to adopt the central KBP planning or to stay with their local plan. This could lead to centre-by-centre variation and introduce unintended bias. Finally did you consider delivering a subvolume boost to MRI-defined lesions? Good luck

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

This is a well-written manuscript describing a multi-institutional Phase III trial of SBRT plus or minus supplemental IMRT for unfavorable prostate cancer. This series is well suited for publication in BMJ Open because this study is very important. The authors are clearly experts in the field and the paper is for the most part scientifically accurate.

Thank you for this kind overall assessment.

Major Compulsory Revisions:

The primary endpoint is BDFS. If the HDRB arm has a higher BDFS but is more toxic

(> 10% grade 3 toxicity) in the multi-institutional setting would you recommend HDRB as your standard treatment for all future patients? Would it make sense to have two primary endpoints BDFS and Grade 3 toxicity? QOL?

Amongst all possible endpoints, disease control is generally considered the most important, and as such we have powered the trial for biochemical-clinical control. Late toxicity in particular is also of relevance, and this is an important secondary endpoint. We have now added the reference for our phase 2 'Virtual HDRB' experience (Pryor et al 2019), which shows ~3% transient G3 toxicity, which makes this unlikely to be a common event in the current study. The vast majority of recent and current randomized trials in prostate cancer radiotherapy treatment intensification follow this similar approach. Rather than trying to add the complexity of co-primary endpoints, we aim to report efficacy as the primary endpoint with toxicity (and other factors including patient reported quality of life) in a secondary manner, and then allow clinicians to make their own conclusions regarding any trade-offs.

Please justify the usage of six months of ADT in favorable high-risk patients.

The recent TROG RADAR study showed a 3% improvement in prostate cancer specific survival for a largely very high risk population for 18 months of ADT compared with 6 months. In our more favourable high risk population where we both mandate baseline PSMA-PET staging and exclude men with risk factors suggestive of a >15% risk of metastatic failure, the absolute benefits of a longer course of ADT would be smaller. This is now referenced and expanded in the methods as follows:

All patients will receive a total of six months of Androgen Deprivation Therapy (ADT).(33, 34) 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.

The ASCEND trial does not show differences in arms until after 5 years. It is unlikely that there will be a large difference in BDFS at 5 years between arms in this study. Why not BDFS at 7-10 years?

Even for ASCEND, despite improved biochemical control with >10yr follow-up, the use of brachytherapy continues to fall. In the strengths and limitations section, we acknowledge that the use of a medium term surrogate endpoint of Biochemical Clinical Control at 5 years is less robust than a longer term survival endpoint.

Minor Compulsory Revisions:

Does the HDRB arm also treat a larger volume of normal tissue? Does the 36 Gy in 12 fractions of the HDRB Arm treat a larger target volume? pelvic nodes?

The relevant section of the methods has been expanded to elaborate on this aspect:

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.

Please clarify this line: Alternatively, the virtual HDRB approach potentials allows for some variation in fraction size sensitivity within and between tumors.

The relevant sentence has been reworded and expanded to address this:

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.

Urethral visualization via temporary catheterization or equivalent approaches will be performed. What equivalent approaches?

The wording of this line has been amended to improve clarity:

Urethral positional estimation via temporary catheterization or equivalent approaches such as high-resolution sagittal MRI can be performed.

All patients require intra-prostatic markers with intra-fraction motion management strategies to ensure accurate treatment delivery. Are you correcting for translations and rotations or just translations?

Translations only. Our rationale for not correcting for rotational motion is expanded and referenced now:

Rotational corrections do not need to be applied due to minimal dosimetric impact from such motion.(Wolf et al, 2019)

Reviewer: 2

Thank you for the submission and its a really interesting trial design.

I only make these points to assist = there's nothing of real concern.

In the eligibility criteria, I wonder if you need to include MRI defined estimate prostate volume >100cc (so that you don't end up with investigators entering patients with borderline volume.

Further eligibility criteria have been added as below:

Prostate volume <100cc, and patients can only be randomized after a plan has been generated showing that protocol compliant treatment can be performed.

Concurrent hormonal therapy - is single agent bicalutamide 150mg od allowed?

Due to the vast majority of randomized date for hormonal therapy with radiotherapy using ADT or maximal androgen blockade, we have not allowed single agent antiandrogen treatment.

Aim 1 - I agree with your estimation of 5yr BCC in this patient group. I do have some concerns with the 2-arm nature of the study and that both arms are to some experimental (as your standard protocol appears to 60gy/ 20Fr); comparing the SBRT and HDRB arms you actually have several variations - including overall time, total dose and dose per fraction; whether HDRB is dose escalation compared to SBRT depends on the alpha-beta ratio and whether time is important, which is currently an open debate. I do agree that the HDRB arm needs to be a lot better than the SBRT arm to make it cost effective and acceptable to patients and healthcare commissioners (in the UK anyway)!

Thank you for these comments. We agree that both arms are currently

experimental, but discuss in the introduction that the momentum is moving towards SBRT monotherapy becoming a standard treatment approach. As with any emerging treatment, the Virtual HDRB outcomes will need to be clearly superior to justify an eventual adoption of this approach in the future, giving good justification to perform this clinical trial.

Aim 2 - I couldn't see any guidance for centres as whether to adopt the central KBP planning or to stay with their local plan. This could lead to centre-by-centre variation and introduce unintended bias.

Centres who produce a protocol compliant plan will not be mandated to switch to a KBP generated plan, as the differences can often be of minimal potential impact with some trade-offs such as increased Monitor Units or dose to other structures. We outline that the incidence of switching to the KBP plan is one of our endpoints, but the collection of both original and KBP plan data will allow further analysis of what dosimetric differences are observed across the entire cohort.

Finally did you consider delivering a subvolume boost to MRI-defined lesions?

We considered this, but given the very high disease control reported for both SBRT monotherapy and Virtual HDRB Boost series, as well as the lack of randomized data showing a benefit for subvolume boosting, we have not included this as part of the protocol.

VERSION 2 – REVIEW

REVIEWER	Sean Collins Georgetown, USA Accuray clinical consultant
REVIEW RETURNED	25-Jun-2019

GENERAL COMMENTS	The authors have addressed my concerns.

REVIEWER	Prof John Staffurth Division of Cancer and Genetics School of Medicine Cardiff University UK Non-financial support from Bayer, personal fees from Janssen and Astellas, outside the submitted work. I have no other conflicts of interest
REVIEW RETURNED	17-Jul-2019

GENERAL COMMENTS	I am happy with the responses to the original reviewers comments