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Zhong, J., Slevin, F., Brown, S. et al. (2026) Challenges and Solutions in Conducting Randomized Controlled Trials Evaluating Prostate SBRT: Lessons Learned From the RO-PIP Trial. International Journal of Radiation Oncology - Biology - Physics, 125 (1). pp. 188-192. ISSN: 0360-3016

https://doi.org/10.1016/j.ijrobp.2025.11.033

Editorial

Challenges and Solutions in Conducting Prostate SBRT Trials – Lessons Learnt from the RO-PIP Trial

Randomised controlled trials (RCTs) remain the gold standard for evaluating the efficacy and safety of medical interventions. The Reirradiation Options for Previously Irradiated Prostate cancer (RO-PIP) trial aimed to determine feasibility of recruitment to a randomised study of high dose rate brachytherapy (HDR BT) or stereotactic body radiotherapy (SBRT) reirradiation for locally recurrent prostate cancer [1]. This is an area lacking randomised evidence to guide treatment decisions which results in uncertainty regarding the optimal management of patients with locally recurrent prostate cancer after previous radiation therapy. As a result, patients may be recommended for different salvage treatment options including surgery, high-intensity focused ultrasound, cryotherapy or reirradiation based on local clinician expertise and preference. The RO-PIP trial ultimately found that adequate recruitment within a two-time period to a randomised study of BT or SBRT for treatment of locally recurrent prostate cancer did not appear feasible and highlighted several challenges of designing and conducting RCTs comparing new treatments and technologies with varying degrees of invasiveness, such as SBRT, a non-invasive treatment, vs brachytherapy, a minimally invasive treatment requiring a general anaesthetic. These trials pose unique ethical, methodological, and practical challenges and lessons learnt are transferrable to other prostate SBRT studies, across de novo, salvage and oligometastatic settings These barriers often lead to poor recruitment, patient and clinician preference bias, and, ultimately, trial failure or inconclusive results. In this editorial we will discuss these challenges and propose potential solutions (See Table 1 for a summary of challenges and solutions).

Lack of Equipoise

Patient and clinician preference strongly influences randomised radiotherapy studies. Due to imbalanced equipoise, both clinicians and patients may struggle to accept the uncertainty between options when one treatment appears more or less intensive or in the case when there is a historically accepted and practised therapy due to local expertise even without a comparative evidence base. Clinicians may pre-select treatment pathways for patients based on their own biases, never offering the trial as an option. Treatments like SBRT are perceived as less invasive, with fewer side effects and shorter recovery times compared to more invasive treatments such as surgery and brachytherapy. Although the latter is minimally invasive it does require a general anaesthetic. These perceptions could influence patient preferences, resulting in low willingness to be randomised and higher crossover rates. In RO-PIP, older patients or those with comorbidities may have preferred SBRT over BT given its convenience (only five outpatient treatments) and non-invasive nature. Similar

issues have been reported in other trials. The SPARE trial (radiotherapy vs surgery for muscle invasive bladder cancer) failed to recruit adequately as some patients were not suitable for both treatments while others randomised to surgery withdrew and opted for RT instead [2]. Likewise, the SABRtooth trial (SBRT vs surgery for early stage lung cancer) also failed to recruit sufficiently with older patients and/or those with comorbidities often favouring SBRT [3].

Clinician biases may also steer patients towards specific arms, either overtly or subtly, undermining equipoise, highlighting the need for clear and transparent information and communication at all stages [4, 5]. The consultation and discussion with the patient could result in the clinician inadvertently influencing their decision for example through the use of terminology such as “experimental” or “little evidence” which may deter the patient from newer therapies towards one which is the “gold standard” or “accepted” treatment. Patients may not fully understand the experimental nature of the trial and may assume that the treatment recommended by their doctor is superior. This is particularly problematic when one arm is seen as “newer” or more technologically advanced [6]. Finally there may be additional ethical concerns. When one treatment is significantly more invasive, concerns about patient harm or acceptability can arise, especially if equipoise is not well established or if there is limited data on long-term outcomes [7]. Using scripted equipoise language for recruiters can help maintain a level of fairness and creating balanced decision aids with patient and public input ensures a neutral approach to the presentation of treatment options.

Loss of Autonomy

Patients may perceive randomisation as a loss of control or fear of being allocated to a less desirable arm, particularly when comparing treatments with different modes of delivery (e.g., two weeks of outpatient radiotherapy vs. an invasive procedure requiring general anaesthetic on one or more occasions). Using a staged consent process allowing sufficient reflection time and follow-up by neutral recruiters would help alleviate some of these concerns. Using multimedia in the form of videos and testimonials may also help to normalise the randomisation process and depict each arm in more equal light.

Information Complexity and Burden

Radiotherapy treatments are technically complex, and the information provided to participants is often written at a level above the average reading age of the general population. Overly long, difficult to read trial documentation and patient information sheets deter participation and limited understanding. A recent UK multidisciplinary-panel national consensus on best practice in patient-centred radiotherapy clinical trials recommended that

patient information sheets should be cocreated with patient advocates, simplified and individualised wherever possible, including for people from under-served groups, such as patients with an educational disadvantage, auditory/ visual/ learning difficulties and patients with limited English-speaking proficiency [8]. In addition, use of decisions aids and videos can further improve understanding.

Site-to-Site Variability

Variability in recruitment across centres is common as observed in RO-PIP due to differences in local infrastructure, service set-up and local preferences. Some sites failed to randomise any patients despite apparent eligibility, due to limited oncology research capacity, workflow gaps and inability to effectively identify potentially eligible participants, lack of buy-in from key staff, or unclear communication strategies [9]. Patients may also be referred for other therapies before research teams can engage leading to referral leakage. To address this, screening logs can be mandated to ensure all suitable patients are approached and specific screening tools for multi-disciplinary team meetings could be used to prompt teams to flag suitable patients. Monthly benchmarking across sites may help keep recruitment momentum going at each site.

Restrictive Eligibility Criteria

Having stringent inclusion/exclusion criteria may also reduce the number of eligible participants, compounding recruitment difficulties. Trials which have multiple compulsory requirements such as imaging or translational substudies may also deter patients from taking part due to the impact and disruption on their life. Making some of these translational elements modular or optional can help improve patient engagement while aligning biosampling with routine blood collection or standard of care hospital visits reduces the number of disruptive hospital visits.

Logistical and Access Barriers

Even short SBRT regimens entail travel, time-off work and potentially parking or accommodation issues. This can lead patients in choosing the least disruptive treatment option e.g. brachytherapy which can be completed in one hospital visit as opposed to several visits for SBRT. Facilitating remote telephone or virtual appointments and follow-ups may help to reduce these burdens. Visits can also be compressed e.g. coordinating pre-treatment scans with appointments, pre-assessment reviews and consent. Travel and accommodation support/ reimbursement and parking passes should also be provided and highlighted in the PIS. In order to reduce follow-up fatigue and patient drop-out from frequent, lengthy questionnaires, core patient reported outcome measures (PROMs) and

health-related quality of life (HRQoL) assessments can be simplified and also collected remotely.

The Role of Qualitative Methodologies

In response to these issues, incorporating qualitative methods into trial design has shown promise. One well-established framework is the QuinteT Recruitment Intervention (QRI), which systematically investigates and addresses recruitment difficulties in real time during a trial.

Key features of the QRI include:

- Mapping the Recruitment Pathway: Understanding each stage where potential participants may drop out or be filtered out.
- Audio-recording Consultations: Capturing how clinicians explain the trial and assess whether true equipoise and randomisation are communicated clearly.
- Interviews with Patients and Clinicians: Exploring attitudes, preferences, and barriers to participation or randomisation.
- Feedback and Training: Providing recruiters with real-time feedback to improve their communication and trial engagement strategies.

QRI has been successfully used in trials comparing surgery vs. non-surgical alternatives (e.g., radiotherapy) and in contexts where patients may find randomisation especially challenging due to treatment modality differences [10, 11]. Having such methodology in place also ensures the study is more reproducible and allows future trials to be better informed.

Additional solutions include involving patient and public involvement and engagement (PPIE) representatives throughout trial development to minimise trial complexity and participant burden, and co-design of patient-facing materials to ensure clarity and accessibility. Alternative formats, such as videos and multimedia tools, may help improve accessibility and engagement, particularly for under-served groups. The UK National Institute of Health Research (NIHR) commissioned the INCLUDE Project (Innovations in Clinical Trial Design and Delivery for the Under-served) in 2017 which provides a roadmap to give a strategic level overview of potential points for intervention to improve inclusion of under-served groups across the life of a research study [12].

Solutions for Improving Trial Design

To enhance the success of trials involving therapies of differing invasiveness, a number of measures can be instigated. Utilising screening logs in the feasibility step is a necessary and compulsory step to identifying common reasons for nonparticipation or barriers to involvement such as inability or preference to not travel far to a treatment centre. Review of participant recruitment at trial management groups (TMGs), including consideration of potential barriers and solutions in consultation with PPIE TMG members may also help to optimise recruitment. As discussed, embedding qualitative research methodologies early will help to inform trial feasibility and recruitment strategies. Using a more pragmatic trial design such as incorporating patient preference arms or staged consent processes to allow more flexibility while still gathering comparative data may encourage more patients to be involved and improve representation and inclusivity [13].

The communication of equipoise, a challenging and complex issue in its own right, must be improved and the development of training materials for recruiters to convey the genuine uncertainty around treatment options will help.

Using adaptive trial designs by incorporating elements such as early stopping for futility, response-adaptive randomisation, or integrated cohort designs could improve the uptake of future RCTs evaluating new therapies. Pragmatic trials aim to offer an approach to evaluating therapies in real-world settings, in a complementary way to explanatory RCTs [14]. Intentionally incorporating broader eligibility criteria, flexibility in intervention delivery, and simplified patient processes, a recently published policy review outlines their role in oncology [15] Where inclusion of conventional randomisation is prohibitive to evidence generation, alternative approaches to trial design may be necessary, including trials within cohorts [16] or externally controlled trials [17]. Each come with their own limitations, which should be evaluated in the specific disease, intervention and population setting. Careful consideration of the feasibility of evidence generation is critical to determining the most appropriate trial design.

Given the strong influence of patient preference for specific treatments in RO-PIP, it is crucially important that patients and/ or advocacy groups are fully involved in the design of these studies from the outset, to ensure that their perspectives can shape the eligibility criteria, randomisation and interventions and the endpoints which are used. It will also work to ensure trial design is thoughtful, acceptable and understandable. Working with PPIE groups, particularly patients treated with reirradiation for locally recurrent prostate cancer, to further understand the potential

benefits and harms of different treatment options will be invaluable when considering future studies in this area. Patient-centred outcomes, including HRQoL, should be prioritised, with data collection streamlined to minimise additional burden beyond standard care. Such measures will improve acceptability, inclusivity, and, ultimately, the likelihood of recruitment success in radiotherapy trials.

Conclusion

Prostate SBRT trials face significant challenges due to strong patient and clinician preferences, treatment invasiveness, and therapeutic misconceptions, all of which undermine equipoise and hinder recruitment. Randomisation is particularly difficult when comparing novel, less invasive options like SBRT to more established minimally invasive therapies such as brachytherapy. To overcome these barriers, early patient stakeholder involvement and embedding qualitative methodologies could help understand relevant patient perspectives, identify and address communication issues or barriers, and optimise future trial design and recruitment to ultimately generate robust comparative evidence to guide treatment for recurrent prostate cancer. The lessons learned from RO-PIP regarding such aspects trial design, recruitment and delivery could equally be applied when considering how to optimise the successful conduct of radiotherapy trials in general.

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