Overcoming difficulties with equipoise to enable recruitment to a randomised controlled trial of partial ablation versus radical prostatectomy in intermediate risk, unilateral clinically localised prostate cancer

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Take home message: Recruitment to randomised controlled trials comparing different treatment arms is challenging. Training and support can enable clinicians to feel more comfortable with concept of uncertainty, leading to improved recruitment and informed consent.

Abstract:

Objectives: The PART (Partial prostate Ablation versus Radical prosTatectomy in intermediate risk, unilateral clinically localised prostate cancer; ISRCTN 99760303) study aimed to investigate the feasibility of randomising 80 men to Radical Prostatectomy (RP) or high-intensity focused ultrasound (HIFU). This article investigated how clinicians conceptualised equipoise between the two arms and how this affected recruitment.

Methods: A QuinteT Recruitment Intervention (QRI) was integrated into the study to optimise recruitment. Phase I aimed to understand recruitment, and included scrutinising recruitment log data, conducting interviews with the Trial Management Group and recruiters (n=13), and audio-recording consultations (n=64) where recruitment was discussed with patients. Data were analysed using qualitative content and thematic analysis methods. In Phase II, the QRI team developed and delivered strategies to improve recruitment.

Results: Although they expressed strong support for PART, in the initial stage of recruitment many recruiters found it difficult to maintain a position of equipoise and held preconceptions about which treatment was best for patients. They did not feel comfortable about approaching all eligible patients, and when the study was discussed, biases were often conveyed through the use of particular terminology, poorly balanced information and sometimes direct treatment recommendations. However, after these results were discussed with recruiters during QRI individual and group feedback sessions, they were able to reconsider their sense of equipoise and their presentations to patients became clearer. Recruitment rates increased from 1.4 to 4.5 patients per month and the feasibility study reached its recruitment target.

Conclusion: This study provides insights into the issues affecting recruitment to an RCT comparing very different contemporary treatments for prostate cancer, and showed that training and support, based on the findings of a QRI, can enable recruiters to become more comfortable with conveying equipoise in consultations leading to increased randomisation and informed consent.

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Introduction

Patients with intermediate-risk localised prostate cancer (PCa) are usually offered radical prostatectomy (RP) or external beam radiotherapy (EBRT) with a view to curing the cancer, although these can result in substantial side effects on urinary, bowel and sexual functioning [1, 2]. Partial ablation (PA) techniques have been developed to target the cancer, preserving the rest of the prostate and thus aiming to reduce treatment side effects. These techniques include high-intensity focused ultrasound (HIFU), cryotherapy, photodynamic therapy, brachytherapy and radiofrequency interstitial tissue ablation. A systematic review reported that PA rarely caused significant morbidity and appeared to have a reduced impact on quality of life, although noted that findings were based upon a few experienced centres and there was no level one (randomised) evidence of oncological effectiveness or impact on functional outcomes or quality of life [3].

The PART (Partial prostate Ablation versus Radical prostaTectomy) feasibility study aimed to recruit 80 men with intermediate risk, unilateral clinically localised PCa (defined as Gleason grade score 7 (3+4 or 4+3), > 4mm cancer core length, prostate-specific antigen ≤ 20 ng/ml, clinical ≤ T2b disease) to a Randomised Controlled Trial (RCT) comparing PA or RP. HIFU was identified as the most promising PA technology [4]. However, delivering an RCT of PA against RP was anticipated to be particularly challenging because of the likelihood of strong views among clinicians and patients about two very different treatments [5].

Given that recruitment was anticipated to be difficult, an embedded QuinteT Recruitment Intervention (QRI) aimed to understand - and subsequently optimise - recruitment [6]. The QRI was developed initially for the Prostate Testing for Cancer

and Treatment trial (ProtecT) study and has been implemented in 25 RCTs [7]. The QRI identified a number of issues that affected recruitment in PART, including organisational barriers and recruiter difficulties with explaining the trial to potential participants (reported in full in Hamdy, Elliott, le Conte, et al, under review). This article focuses specifically on how clinicians conceptualised equipoise in PART, how this changed during the QRI, the impact of this change on recruitment, and also what lessons could be learned for future trials

Methods

Study design

The QRI involved two iterative phases: Phase I sought to identify and understand recruitment difficulties (through analysis of screening logs, interviews with trial staff, and audio-recording consultations where PART was discussed with patients) and Phase II implemented strategies to optimise recruitment and informed consent. The study is reported according to qualitative reporting guidelines (see supplementary file).Ethical approval was provided by the NHS Health Research Authority NRES Committee London – Camden & Kings Cross (14/LO/0640). Written informed consent was provided by all participants.

Data collection

Data were collected in three ways:

Interviews

Semi-structured interviews were conducted with members of the Trial Management Group (TMG) and healthcare professionals who were involved in recruitment. Separate topic guides were developed for the TMG and recruiters (see Additional

File) to ensure coverage of overall study issues (TMG) and recruitment (recruiters), with sufficient flexibility to allow for new issues to emerge. Interviews were transcribed verbatim, checked against the audio-recording for accuracy, and transcripts were imported into NVivo.

Data were analysed by DE using techniques of constant comparison derived from grounded theory methodology, and emerging themes and codes within transcripts and across the dataset were then compared to look for similarities or differences [8]. Emerging themes were discussed with JLD with reference to the raw data. Equipoise was conceptulised as a lack of satisfactory evidence and consensus to suggest that patients would be advantaged or disadvantaged if they were to receive any of the RCT treatments [9-11]. Coding included any instances where clinicians described uncertainty around treatment superiority, as well as any discussion/practices that suggested that one treatment would be better/worse for the patient.

Recorded recruitment consultations

Healthcare professionals recruiting to PART were requested to audio-record appointments where they provided information to eligible patients about the study and treatment options. Recordings were transcribed verbatim, and for this analysis, selected parts related to equipoise issues were extracted. These were analysed as described above for interviews, with the addition of some of the techniques of focused conversation analysis to identify and document aspects of informed consent and information provision that was unclear, disrupted or hindered recruitment [6].

Patient pathway through eligibility and recruitment

Screening logs from all centres were examined regularly for information on the numbers of patients screened, eligible, approached and randomised (Wilson et al, under review) to provide contextual information about recruitment in clinical centres and across the study.

Results

Interviews

The QRI researcher approached 23 participants to take part (including members of the TMG, and representatives from each recruiting site). A total of 13 one-to-one interviews were conducted between July and November 2015. The final sample included twelve recruiters (four of whom were members of the TMG) and one non-recruiting TMG member. Interviews lasted an average of 43 minutes (range=31-53 minutes).

Recorded consultations

Sixty-four recruitment appointments with 54 patients were audio-recorded (five patients had two consultations recorded) between September 2015 and April 2017: 24 as part of QRI phase I and 40 after feedback in phase II. Consultations lasted an average of 27 minutes (range=10-42 minutes). Twelve different recruiters led the consultations. Audio-recordings were obtained from four recruiting sites (see Table 1).

Table 1: Overview of data collected from centres

Site	Number of recruiters	Number with previous training	Number interviewed	Number of recordings pre-feedback	Overview of feedback	Number of recordings post-feedback

Centre 1	5	1	5	9	Group feedback (x3), tips document, individual feedback to one recruiter	3
Centre 2	3	0	2	2	Group feedback, tips document	0
Centre 3	3	0	2	6	Group feedback (x3), tips document, individual feedback to one recruiter	17
Centre 4	3	0	1	7	Group feedback (x2), tips document, individual feedback to one individual (twice)	20
Centre 5	3	3	2	0	Group feedback (x2), tips document	0

Quotations are provided to support the results, and distinctions are made between data from interviews and recorded consultations. Quotes were anonyimised to ensure confidentiality.

Phase I: Understanding recruitment challenges

Views on the study design

There was enthusiasm for the PART study, and HIFU was described as an 'exciting' and 'promising' alternative to radical procedures. Although some urologists commented that comparing only one form of PA with RP might exclude patients who expressed preferences for treatment options outside of PART (such as EBRT or cryotherapy), there was agreement that there was most data on HIFU, and until the findings from the ProtecT study – which had not been published at the time – would provide key information about the effectiveness of conventional treatment options, RP was an deemed the most appropriate comparator.

> *Interview, Recruiter 1: "I think this trial is needed because there has been a lot of hype or buzz about HIFU and focal therapy for some years now."*

Previous recruitment experience

Recruitment to RCTs was acknowledged to be challenging, particularly discussing uncertainty and randomisation. Many participants had not received training for their role as recruiters, with the exception of four recruiters who had received training from ProtecT. These appeared more comfortable with the concept of uncertainty and how to convey this to potential patients:

> *Interview, Recruiter 2: "I haven't, personally, been responsible for recruiting to trials […] I have no idea whether HIFU's going to work or not, so it makes it very difficult to know how much of that information to tell patients."*
>
> *Interview, Recruiter 15: "I think we need to be confident on our uncertainty, and you know, I've learned a lot by being involved in ProtecT […] We acknowledge that there are uncertainties in the decision-making, which is why we run clinical trials."*

Discomfort with the eligibility criteria

Recruiters often described how some patient groups, although fulfilling the study's eligibility criteria, were more suitable for a particular procedure. This meant that not all eligible patients were not approached about PART. When patients were approached, this discomfort affected how clinicians communicated with patients. Examples of this are shown in Table 2.

Table 2: Recruiter perceptions of the PART eligibility criteria

Inclusion criterion, according to protocol	Examples of recruiter discomfort
Gleason grade score 7 (3+4 or 4+3)	*Interview, Recruiter 12: "I was just marginally uncomfortable because he had a 4+3 and he was 50 years old and it was quite a significant volume of tumour. I just found myself thinking, "Do you know what? I wonder if you'd be better off having a radical prostatectomy.""* *Interview, Recruiter 9: "3+4's, I think they are maybe the best ones to treat with HIFU, where they've got mainly pattern 3, but a bit of pattern 4. I think you can be pretty confident that you're going to wipe out that pattern 4 when you do the treatment."*

High volume Gleason grade score 6 (> 4mm cancer core length)	*Interview, Recruiter 15: "If somebody had all of the cores from one side, let's say every single core from one side was involved from a mapping biopsy and it was involved with like 80% of four plus three but the other side is completely clear. In theory he is a PART candidate. But actually maybe he is better off with a prostatectomy."*
Life expectancy of ≥10 years	*Interview, Recruiter 9: "I think for some patients let's just say in their 70s, let's say between 70 and 75, I have absolutely no problem saying, "Surgery or radiotherapy, it doesn't matter which one you have. Just choose the one for which the conduct of therapy and the side effects feels best to you". For the people perhaps between 65 and 70 I'm sort of in the same opinion but perhaps slightly leaning towards surgery. For the under 65s I really think that surgery is probably better because of the life expectancy they probably have and the risk of failure going into the long-term and the long-term burden of even fairly mild toxicity from radiotherapy."*

Recruiter bias

Those who had not received support or training for their role as recruiters expressed strong preferences for a particular treatment arm. Advocates of RP expressed concerns that HIFU would not remove all of the cancer, whereas those who favoured HIFU expressed concerns that surgery would be over-treating cancer and compromising quality of life. Consequently, recruiters found it difficult to be in equipoise (see Table 3).

Table 3: Recruiter perceptions of PART treatment options

Recruiter	Examples of recruiter bias
Recruiter 6	*"There's very few patients with whom I still have equipoise with as to whether they should have HIFU or prostatectomy."*
Recruiter 9	*"It's just whether that a prostatectomy is over treating their cancer… and I've got to be honest with them."*
Recruiter 1	*"They are compromising their cancer treatment by taking the risks that we're only treating one part of the prostate. And so there might be another part of the prostate which has some prostate cancer in. So that they understand that, after I've told them."*
Recruiter 12	*"I think of the patients who have been suitable for both surgery and HIFU I have to say I probably steered them towards HIFU whenever they have been suitable."*

The consultations demonstrated that these beliefs were conveyed to patients. There were several consultations where the concept of uncertainty was not introduced. Leading terminology was adopted (i.e. 'gold standard' RP, and 'experimental' HIFU).

Recruiters also provided unbalanced accounts of the procedures (i.e. discussing the advantages of HIFU and only the disadvantages of the RP), and sometimes provided treatment recommendations. Following this, patients often expressed clear preferences for a specific treatment and declined PART.

> *Consultation, Recruiter 2: "If you have surgery, with the kind of disease you have, you'd almost certainly not die of prostate cancer." (Patient declines PART, opts for RP)*

> *Consultation, Recruiter 9: "You've then the option of partially destroying the part of the prostate where the cancer is, and in your case, it's on the left-hand side. That's called 'focal destruction'. […] It's all done very cleverly […] It is a potentially attractive option […] It's quite favourable." (Patient declines PART, opts for HIFU)*

Between January and November 2015 (during the first Phase of the QRI), only 15 men had been recruited and the average number of patients agreeing to be randomised was 1.4 per month, with a conversion rate (the numbers of eligible men invited to join PART who then went on to be randomised) of 20%. The lead site had recruited the majority of these, whilst some sites had not recruited any patients at all (see Table 4).

Table 4: Recruitment by each centre

	2015				**2016**				**2017**
Centre	**Jan-Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	**Jan-Mar**	**Apr-Jun**	**Jul-Sep**	**Oct-Dec**	**Jan-Mar**
Site 1	4	5	2	4	4	2	5	2	9
Site 2	*Activated 05/15*								
Site 3	*Activated 06/15*			1	2	5	1		1
Site 4	*Activated 10/15*			1		2		3	4
Site 5	*Activated 11/15*			2		7	4	2	10
Total	**4**	**5**	**2**	**8**	**6**	**16**	**10**	**7**	**24**

Optimising recruitment

Summary of training

In November 2015, the QRI team presented the findings of phase I to the CI and TMG, and strategies to improve recruitment and informed consent were agreed. This included group feedback sessions, individual feedback and tips documents (see Table 5). Sessions were interactive, with open discussions encouraged (Mills et al, in press). Training focused on:

- Ways in which recruiting to RCTs differs to standard practice
- The lack of randomised evidence comparing RP with HIFU
- The extent to which there was community equipoise (i.e. by demonstrating the conflicting biases for the treatment arms)
- Examples of how recruiter beliefs could influence patient preferences
- The importance of exploring preferences to ensure men were making a fully informed decision

Table 4: Summary of PART recruitment interventions

Date	PART recruitment interventions
November 2015	Preliminary QRI findings discussed with CI
December 2015	Full descriptive report on recruitment issues sent to CI
December 2015	Two-part recruitment session at Collaborator's Meeting
December 2015	Group feedback session at centre 3
December 2015	Recruitment email sent to all recruiters
December 2015	Recruitment newsletter sent to all recruiters
February 2016	Tips document sent to each recruiter
February 2016	Recruitment newsletter sent to all recruiters
February 2016	Individual feedback meeting with recruiter from centre 1
March 2016	Group meeting at centre 2 to discuss recruitment
March 2016	Group feedback session at centre 3
March 2016	Website updated to include patient information about PART
April 2016	Recruitment newsletter sent to all recruiters

April 2016	Group feedback session at centre 1
April 2016	Group feedback session at centre 5
May 2016	Recruitment newsletter sent to all recruiters
May 2016	Individual feedback meeting with recruiter from centre 4
May 2016	Individual feedback meeting with recruiter from centre 3
Funding variation request – July 2016 – September 2016	
September 2016	Recruitment newsletter sent to all recruiters
October 2016	Recruitment email sent to all recruiters
October 2016	Group feedback to centre 3
January 2017	Recruitment email to all recruiters
January 2017	Individual feedback with recruiter from centre 3
January 2017	Group feedback session at centre 1
February 2017	Recruitment email sent to all recruiters
March 2017	Individual feedback with recruiter from centre 4

Changes to recruitment and informed consent

Phase II of the QRI began in November 2015, and continued for the duration of recruitment. During this time, an average of 4.5 patients a month were randomised and the conversion rate increased from 20% to to 37%. Furthermore, after the initial intervention in December, several centres (rather than predominately Site 1) began recruiting more consistently (See Table 3). Analysis of the recordings available post-feedback highlighted changes to the way that recruiters discussed the study and treatment options (See Table 6).

Table 6: Before and after feedback

Pre-feedback	Post-feedback

	Consultation: *Recruiter: "I think you are most suitable for focal treatment with HIFU […] I think the research study that I was going to be talking about is probably not relevant for you."*	*Consultation:* *Patient: "What do you think?"* *Recruiter: "I've been a consultant for years and I sit here telling men what's going on, telling them they've got cancer, they ask me what treatment we go for, and I try and help them and steer them in the direction, but, at the end of the day, I have to sometimes stop and say, "Actually, there isn't really any evidence that this treatment is better than that one because there have never been any proper trials comparing properly treatment A with treatment B. To get proper results, you have to actually do it in a randomised way." There is a study called PART, that we're very much involved with…"*
Recruiter 9	*Consultation:* *Patient: "What would be your advice? Which treatment, in this particular case?"* *Recruiter: "I think that surgery or radiotherapy, for someone who is young and fit like you, with slightly more bulky disease, would be more appropriate. So, I don't think the trial is right for you."*	*Consultation:* *Recruiter: "I don't think that there's an obvious, "You must go one way or the other." The reality is, there's such a lack of evidence, we just don't know. I'm a fan of both treatments, if that makes sense, and regularly I'm referring people for both sorts of treatments […] The more I have these discussions and the more I reflect on it all, it does make me think, "You know what [name] a lot of what you say is based on very little evidence." We don't really know whether treatment A and is better than treatment B."*
Recruiter 12	*Consultation:* *Recruiter: "I think of the patients who have been suitable for both surgery and HIFU I have to say I probably steered them towards HIFU whenever they have been suitable. Partly I am trying to build my experience and partly it is a less toxic treatment. It fits in with the first idea of do no harm. You also have the ability to save the situation."*	*Consultation:* *Recruiter: "I have to say it's very difficult. I feel that both treatments would be very good for you. I could sit here and sing the praises of each modality of treatment actually and it's difficult to say which would be best in your situation. And partly, if you're looking for something in the short-term that was good, then you might say, "Well, HIFU has less side effects up front." But in the longer term there's uncertainty about whether you need repeat treatment, on-going monitoring, all of that uncertainty. We don't know what the long-term results are – 10, 15, 20 years – we don't know the results of focal treatment. Whereas with surgery we know those true outcomes, but we know also that it carries a greater burden of side effects. I can't tell you which of those packages is best overall, only this kind of study will tell us that."*
	Consultation: *Patient: "I think my concern, I mean I was interested in HIFU because it carries the least possible side effects. I know it's in its infancy but I think-"* *Recruiter: "A bit beyond infancy I would say but yes."* *Patient: "About 15 years?"* *Recruiter: "I think HIFU has been probably around for that sort of time. Focal therapy treatment has probably been going from around 2007/8, something like that. We've got quite a lot of outcome which is going to*	*Consultation:* *Patient: "HIFU sounds like an attractive idea."* *Recruiter: "I think the important thing to realise is that we also think it's an attractive idea…but it's very important in what we do to establish evidence to really know that attractive ideas turn out to be good ideas […] The only problem is that we don't have long term follow up. We certainly don't have this randomised evidence. There is a body of opinion which says that in your case, intermediate risk prostate cancer, we don't really know which is better; surgery with whole gland therapy or focal therapy."*

	be published. […] We have some confidence that the results will be okay otherwise we wouldn't be doing it."	
Recruiter 2	*Consultation:* *Recruiter: "I can tell you why I think surgery is good and what's great about surgery, but I'm not here to tell you what is great or not great about radiotherapy or HIFU."*	*Consultation:* *Recruiter: "I don't know [if HIFU is as good as surgery] because we haven't done the study yet. But the data would support that it appears to be as good, yes. But I can't answer that question in terms of cancer control. What I can say for sure is that if you had the HIFU, you're likely to have a quicker recovery. You'll be out of hospital quickly. Generally people are less tired afterwards, less fatigued and they tend to have a quicker recovery from the HIFU treatment. And it probably has less impact on erections. It certainly has less impact on incontinence."*
	Consultation: *Recruiter: "I think surgery would be a good treatment choice for you".*	*Consultation:* *Recruiter: "In terms of advice […] it's not for me to tell you what treatment to have. You have to pick your treatment based on what you want but on the side-effects. And I'm here to tell you what are the pros and cons of different treatments."*

Discussion

The PART study aimed to evaluate the feasibility of recruiting men with intermediate risk PCa to HIFU or RP. A QRI was integrated to identify and address barriers to recruitment. Early in the feasibility study, in phase I of the QRI, recruiters without previous experience found the concept of equipoise difficult and often disclosed their instincts about the most suitable treatment for patients. A number of strategies were implemented to enable recruiters to discuss their views about the treatments and the trial, and then support them to more clearly convey uncertainty and equipoise to patients. During the second phase of the QRI, there was an increase in recruitment from 1.4 patients per month to 4.5 patients per month. After the first QRI intervention in December, centres began recruiting more consistently. There was also evidence to suggest that the QRI had influenced clinicians' practices and led to clearer presentations of equipoise to patients. Whilst it is not possible to determine the precise impact that the QRI had on recruitment, this suggests it had a positive

impact. The PART study randomised a total of 82 men, demonstrating that it is possible to recruit to an RCT of RP versus HIFU.

Previous research has shown that recruiters can find the dual roles of clinician and researcher conflicting [12]. Their experience can lead them to favour one treatment arm in general or for patients with particular disease characteristics or health states. A recent study in six trials showed that even when recruiters intended to convey equipoise to patients, they often failed to do so or provided unbalanced information, and some undermined equipoise with recommendations [13]. A systematic review indicated that didactic based learning may not necessarily be most effective for recruitment training [16] and so, in PART, training and support was delivered in a way that encouraged discussion and collaborative decision-making about equipoise and uncertainty so that recruiters could find their own position of equipoise and then understand how they could communicate this more clearly. This study indicates that it is possible to change how recruiters present information to patients. Moreover, the confidence of recruiters who received training from ProtecT [14, 15] suggests that the effect of training is sustained.

The main strength of this research is the use of qualitative methods to provide important insights into clinician equipoise. The QRI adopted a range of qualitative data collection methods to gain an in-depth understanding of recruitment processes, how the trial was presented and how patients were responding to the trial. We were able to compare and contrast data – for instance, interviews showed participants' intention to recruit, but the consultations demonstrated ways in which they unintentionally steered patients towards particular treatments. Recording consultations also enabled us to compare how recruiters with little previous

experience presented equipoise before and then after training. The opportunity to feedback findings quickly to change practices was a key strength, highlighting the applied nature of the QRI [17].

This study has several limitations. It was conducted in one trial with an observational design, and so findings need to be interpreted with caution. Not all consultations were recorded and there was considerable variability in how many recordings each site provided, meaning that initial feedback was based on only a small number of recorded consultations, although interviews provided an opportunity for a larger number of recruiters to describe how they discussed PART with patients. Although recruitment rates increased after Phase II interventions and there were notable changes in how the recruiters conveyed equipoise in the consultations, there may have been other factors that increased recruitment, making it difficult to determine the precise impact of the QRI [6].

Conclusion

Recruiters can find it difficult to recruit to a trial comparing different treatment arms such as PA and RP. However, this research suggests that training and support can enable them to feel more comfortable with concept of uncertainty, so that a larger pool of participants can be approached and equipoise presented more clearly to facilitate informed decision making.

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None declared.

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