Manuscript

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For UK oncology trials, recruitment and retention of participants are ongoing issues [1, 2]. Barriers include clinician views regarding treatments [3-5], challenges of multi-disciplinary team work [5, 6], clinician time constraints [7] and restrictive eligibility criteria [7]. Additional barriers for patients include travel distance to trial sites, typically large cancer-specific hospitals [3, 7] and the fact that cancer often affects older people and participation may depend on carer support. Various socioeconomic, cultural and language barriers have been found to exclude certain groups from trial recruitment generally [8, 9]. This editorial describes an intervention which supports recruitment within trials and explores how this intervention has been applied in an oncology setting.

What is the QuinteT Recruitment Intervention?

The QuinteT[1] (Qualitative Research Integrated within Trials) Recruitment Intervention (QRI) [10] is a flexible intervention designed for adaptation to the individual trial. It aims to uncover and understand reasons for recruitment difficulties, then identify and implement actions to address these. The QRI is best integrated during study design: the QRI team (usually a co-applicant and QRI researcher and both from the QuinteT Research Group) supports the central trial team's development of study processes, with QRI input beginning in earnest as sites open and recruitment begins. The aim is to avoid known pitfalls identified in other trials during set-up, then address barriers as they arise [6, 10]. The QRI has been implemented in some form in over 80 trials in the UK and internationally, including feasibility/pilot and main phase RCTs [11]. Barriers and actions identified in feasibility/pilot studies can inform recommendations for main phase randomised controlled trials (RCTs).

The QRI is a mixed methods intervention with two phases [10, 12] although in practice phases I and II run iteratively and in tandem. Phase I involves collection and analysis of data to identify and understand recruitment obstacles by triangulating insights from quantitative and qualitative data analyses as follows:

Mapping a patient's recruitment pathway using the Screened, Eligible, Approached, Randomised framework (SEAR) [13]

QRI researchers support the central trial team in designing the trial screening log. Once recruitment begins, the QRI team regularly analyse screening data and share insights with the Trial Management Group (TMG) regarding the point on the pathway where patients are 'lost' to recruitment for the trial as a whole, or at individual sites. These data also enable monitoring for how inclusive the randomised population is as compared to the eligible population.

Audio-recording discussions between patients and clinicians recruiting to the trial

QRI researchers provide recruiting sites with audio-recorders and training resources, including examples based on evidence from other trials of how to structure discussions about trial participation and optimise understanding for informed consent (see SCC-AFTER:Panopto [14]).

QRI researchers then analyse recordings of actual trial discussions with the aim of identifying best practice for discussion of this particular trial with potential participants.

Interviews with trial staff and/or patients

QRI researchers interview TMG and recruiting site team members to identify barriers encountered and ideas for overcoming these. Interviews may also be undertaken with patients who decline trial participation, to uncover reasons for this, and with those who accept, to understand their experiences of being recruited and taking part. Patients who decline trial participation consent separately to the QRI. They can choose to consent to recording the discussion about trial participation or an interview or both; many do so willingly, to contribute to understanding of how decisions about participation are made.

Analysis of study documents

QRI researchers contribute to the design and development of the trial protocol. In collaboration with the trial team and patient advisory group, the QRI researchers support development of the Participant Information Sheet (PIS) to ensure trial interventions are presented in a balanced way (with equipoise).

Observations of study meetings

QRI researchers attend trial meetings, for example TMG and Trial Steering Committee meetings, to identify additional barriers and facilitators to recruitment, e.g. the publication of new evidence or guidelines from relevant professional bodies, which may impact on clinical equipoise.

Data collected during Phase I is analysed, triangulated and findings fed back to the Chief Investigator/s (CI) and TMG to identify actions which can be implemented rapidly to benefit recruitment. Phase II involves implementation of actions. Actions may be trial wide or site/recruiter specific. Most can be incorporated within existing trial protocols and processes, whilst some may require amendments to processes:

Personalised feedback for clinicians engaging in audio-recording of trial discussions and group feedback or training sessions

Optional one-to-one sessions are offered to individual clinicians for feedback of findings from analysis of audio-recorded trial discussions. The QRI researchers may run trial-wide or site-specific workshops to disseminate information on key barriers identified and potential solutions. For example, solutions to optimise numbers of eligible patients approached and optimum ways of presenting trial information can be shared with site teams. Where analysis of screening log data shows substantial variation in how eligibility criteria are applied between recruiters or across recruiting sites, case vignettes may be used to promote peer discussion of equipoise issues and encourage consistency in application of eligibility criteria.

A 'Tips and Guidance' document or video resources for clinicians for trial-wide dissemination

The QRI researchers create 'Tips and Guidance' documents based on analysis of data collected in Phase I. For example, patient preferences may be identified as a barrier to recruitment: a 'Tips and Guidance document' can provide guidance for clinicians recruiting to the trial on how to explore these preferences, establish the rationale that underpins them and address any possible misconceptions [15, 16]. In one trial, the CIs created videos which shared insights on how to

structure recruitment discussions: CARE Chat - Latest top tips for recruitment conversations [17].

Changes to trial documentation or processes if indicated

The QRI researchers, through analysis of data collected in Phase I, particularly the audio-recordings of recruitment discussions, may uncover misinterpretation of trial information. This may indicate that amendments to study documentation, particularly the PIS, could be helpful.

The effectiveness of the QRI

The QRI was first developed in the ProtecT trial [18], which randomised participants to radical prostatectomy, radical radiotherapy or active monitoring for localized prostate cancer. Initial recruitment barriers identified included the name of the non-intervention arm and how the trial was described to potential participants. Following implementation of changes to content and delivery of study information (see Table 1), recruitment rates rose from 40-70% [19]. The QRI has since been implemented across numerous clinical specialties, including oncology RCTs, and is particularly helpful when comparing immediate intervention (e.g. surgery or radiotherapy) with an active monitoring approach.

The effectiveness of the QRI has been examined systematically in five surgery and oncology RCTs [20]. All five trials successfully recruited to target. Three showed an improvement in randomisation rates following QRI Phase II actions. The remaining two trials recruited above target, having incorporated QRI specific training prior to, then throughout recruitment. Clinicians interviewed in four of these five trials attributed improvements in recruitment to the QRI intervention. The QRI was also viewed as a factor in contributing to the success of the CARE trial [21]. High levels of commitment from the CIs and TMG towards the QRI have been identified as key facilitators in enabling its implementation and its impact on recruitment [6, 22].

Why are oncology RCTs difficult to recruit to and what have we learnt?

QRIs integrated within a number of oncology RCTs have identified various challenges [4, 5, 18, 23]. The multi-disciplinary nature of oncology trials, which often compare treatments including surgery, radiotherapy, and chemotherapy, requires involvement of surgeons, oncologists, pathologists, radiologists, specialist nurses, therapeutic radiographers, medical physicists, pharmacists and research staff. This can be logistically challenging, time consuming and involves potential participants interacting with multiple clinicians along their care pathway who may influence perceptions of equipoise between interventions [4, 5, 24]. Cancer, and its severity, can be an emotive condition which may influence how patients perceive interventions [19]. We outline how the QRI has been implemented in three oncology RCTs, key challenges found and examples of how the QRI helped overcome these (Table 1).

[Table 1: How the QRI has been implemented in three oncology RCTs and actions to overcome challenges]

Future work

The QRI evolves with integration into new trials, with oncology trials being particularly important for the QuinteT research group. The SCC-AFTER trial, with integrated QRI, will compare the efficacy of adjuvant radiotherapy and close clinical follow-up with close clinical follow-up alone in reducing loco-regional recurrence following complete excision of high-risk primary cutaneous squamous cell carcinoma (ISRCTN: ISRCTN54806122) [25]. The SCC-AFTER QRI was set up in collaboration with the SCC-AFTER CIs, Centre for Trials Research at Cardiff University and TMG. The importance of greater inclusivity in cancer RCTs is recognised [1] with funders such as the National Institute for Health and Care Research (NIHR) now requiring inclusivity as a condition of funding. The QRI within SCC-AFTER has been modified to include a Study within a Project (SWAP) to closely monitor how inclusive trial recruitment is, with a particular focus on people with multiple long-term conditions (MLTCs) as part of the NIHR SWAP programme.

SCC-AFTER opened to recruitment in December 2024. QRI actions during SCC-AFTER study set-up included input into the wording of the PIS and the creation of a 'Tips and Guidance' document for recruiters, based on knowledge accumulated across previous trials, which will be updated with content specific to SCC-AFTER as new findings emerge. During recruitment the QRI/INCLUSION SWAP team will: compare the screened, eligible, approached and recruited populations for key sociodemographic variables relevant for optimising inclusivity; conduct qualitative interviews to explore site team members' perceptions of barriers to recruitment, particularly those that may impact on patients with MLTCs; help facilitate audio-recordings of recruitment discussions and conduct interviews with patients to provide insights into how well information about the trial is understood.

Implementation of the QRI within oncology RCTs has already provided insights into how to improve recruitment. Integrating the QRI into more RCTs, across medical, surgical and radiation oncology, will help build the evidence base to optimise recruitment to these trials in future.

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Table 1: How the QRI has been implemented in three oncology RCTs and actions to overcome challenges

RCT	Aim and trial context	Why was recruitment predicted to be challenging?	QRI Phase I: data collection methods	Examples of challenges identified	QRI Phase II: Examples of actions to overcome challenges	QRI impact
ProtecT [19]	Randomised patients to radical prostatectomy, radical radiotherapy and active monitoring for localised prostate cancer [26].	For surgeons to recruit effectively there was a need for them to convey equipoise. Widely held expectations that patients would prefer radical prostatectomy over radical radiotherapy or active monitoring.	• Audio-recordings of recruitment discussions • Interviews with patients • Interviews with urologists and nurses	A lack of equipoise in how clinicians presented the trial approaches. Patient interpretation that 'watchful waiting' amounted to 'watch and wait while I die' [19].	When discussing the RCT with patients, it was recommended that active monitoring was presented first, followed by surgery and radiotherapy [19]. The name 'watchful waiting' for the non-intervention arm was replaced with 'active monitoring'.	Both the recruitment rate and the proportion of those accepting the randomly allocated intervention increased following QRI actions (26).
MARS 2 [5]	Randomised patients with resectable mesothelioma to receive either chemotherapy (up to six courses), or chemotherapy and (extended) pleurectomy decortication (two courses of chemotherapy, followed by surgery and up to four further courses of chemotherapy) [27].	Owing to the two interventions being very different [5].	• SEAR data collection • Audio-recordings of recruitment discussions • Interviews with patients • Interviews with oncologists, research nurses /practitioners/ co-ordinators, surgeons, respiratory/chest physicians, TMG members	Established regional multidisciplinary team (MDT) meetings were crucial for identifying patients and determining eligibility. Referrals from sites not operating within this structure were more ad hoc leading to missed patients or delayed referrals making patients ineligible in some cases. Some patients arrived at the recruiting site with expectation of a treatment, with this often aligning with the referring specialist's views on whether the condition should be treated with chemotherapy or surgery [5].	Sharing solutions identified by site teams to minimise missed referrals, such as highlighting eligible patients on MDT lists in advance and regular contact with specialist lung nurses to support effective identification of eligible patients. Promoting sharing of information about the trial amongst colleagues at referring sites to support more balanced presentation of the trial approaches in initial discussions [5]. Supporting clinicians recruiting to the trial to comfortably engage with patient treatment preferences and convey equipoise.	Personalised feedback from analysis of the audio-recordings recruitment discussions was viewed positively by recruiters and impacted their practice in the trial [5]. Clinicians from 12 sites provided a total of 55 audio-recordings of recruitment discussions– highlighting the acceptability of this part of the QRI.
OPTIMA PRELIM [4]	Randomised patients with hormone sensitive early breast cancer to adjuvant chemotherapy (current care) vs 'test-directed' (using a multi-parameter assay) treatment decision, resulting in adjuvant chemotherapy or no chemotherapy [28].	Patients usually offered adjuvant chemotherapy could be allocated to 'no chemotherapy' [4].	• SEAR data collection • Audio-recordings of recruitment discussions • Interviews with oncologists, research nurses and TMG members	Oncologists' routine practices affected recruitment, for example, not all clinicians felt comfortable offering the trial to all eligible patients. This was observed through selective application of the trial eligibility criteria. Before presenting the RCT to patients, often clinicians introduced chemotherapy provision as a beneficial treatment before moving on to introduce the trial and its rationale. This approach could be challenging for recruiters trying to convey equipoise and confusing for patients.	Clinicians from different sites meeting in peer-to-peer feedback sessions to discuss concerns about the eligibility criteria, with discussion prompted by clinical vignettes developed by the Chief Investigator. A 'Tips and Guidance' document disseminated across sites providing recommendations on how to structure recruitment discussions and convey equipoise [4]. There were revisions to the PIS to convey a more balanced portrayal of the trial including specific advantages and disadvantages. In particular, a line in the PIS was revisited that stated that the multi-parameter assay might not work and that patients might find that they should have had chemotherapy. Clinician descriptions of uncertainty about the assay derived from the audio-recordings were used to inform the revised PIS wording [28].	The number of patients who were approached about the trial showed a significant improvement following QRI interventions [20]. OPTIMA Prelim proceeded to OPTIMA main study with a target recruitment of 4,500 patients.