

Barriers to accrue to clinical trials and possible solutions

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A systematic review of worldwide phase 3 trials over 9 years showed that a third of all trials close early due to poor accrual (Schroen *et al*, 2012). The QUEST (Quality of Life after mastectomy and breast reconstruction) feasibility phase 3 trials (Cancer Research UK feasibility funded; CRUK/08/027) were two parallel randomised studies open across 15 UK centres that aimed to determine the optimal types and timings of latissimus dorsi (LD) back flap breast reconstruction using clinical and patient-reported outcomes (Cancer Research UK, 2011). Systematic reviews had shown no reliable valid evidence addressing this question (Winters *et al*, 2010). Conceivably, the type of breast reconstruction surgery and its morbidities may affect women's health-related quality of life (HRQL) and satisfaction with outcomes. There is some evidence for this in both a prospective cohort study and the first UK National Mastectomy and Breast Reconstruction (NMBR) audit (The NHS Information Centre - Clinical Effectiveness Unit at the Royal College of Surgeons, 2011; Winters *et al*, 2013).

The QUEST feasibility trials were pragmatic in design, with study entry determined by a pre-operative assessment of the requirement for post-mastectomy radiotherapy (PMRT). Women unlikely to require PMRT were randomised to either extended autologous LD (ALD) or implant-assisted LD breast reconstruction (LDI) (QUEST A), while those requiring PMRT were randomised to either immediate ALD or staged-delayed (two-stage skin preserving) ALD procedures (QUEST B) (Cancer Research UK, 2011). Trial development was embraced and informed by national collaborations involving oncoplastic breast surgeons, breast care nurses (BCNs), research nurses and patient advocacy groups. The separately funded (BUPA Foundation) QUEST Perspectives Study (QPS) was a nested qualitative study evaluating the perceptions of patients and HCPs on randomisation to inform trial processes and enhance ongoing recruitment and patient acceptability. QPS

assessed patients' and HCPs' perceptions of equipoise and other aspects of the trial, including patients' perceptions of randomisation (Winters *et al*, 2011). QPS incorporated qualitative methods, and recruited patients both accepting or declining randomisation with the intention of assessing the impact of the decision-making process, so drawing on the lessons learnt from other feasibility studies such as the ProtecT (Prostate Testing for Cancer and Treatment) trial (Donovan *et al*, 2002). The primary objective of the QUEST feasibility phase was to demonstrate that the acceptance rate of randomisation was at least 25%, with a target sample size of 55 patients to each of the QUEST A and B trials within 12 months. After 12 months of recruitment, 17 patients were randomised to QUEST A and 8 to QUEST B with overall randomisation acceptance rates of 19% (17/88) and 22% (8/36), respectively. Patient preference was the predominant reason for declining trial entry, affecting 47 of the 88 (53%) patients approached for QUEST A and 22 of the 36 (61%) approached for QUEST B. Despite extensive efforts by trial teams, both trials were closed to recruitment in December 2012 following recognition of the challenges of achieving satisfactory patient accrual and the limitation of feasibility funding.

An end-of-study survey completed by the centres indicated that only eight centres had sufficient throughput of LDI procedures during 2012 and only two centres were undertaking sufficient numbers of ALD reconstructions. Clearly, these changes in clinical practice would have prevented adequate patient accrual in the main trial regardless of patient preference issues (Millat *et al*, 2005). Technical advances in breast reconstruction using implant-assisted acellular dermal matrices (ADMs) may have diminished the numbers of LD procedures being recommended (Winters and Colwell, 2014). However, it remains true that the main barriers to recruitment in QUEST were patient and clinician perceptions and preferences (Millat *et al*, 2005). Some centres indicated bias on the

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part of some plastic surgeons, with prejudice towards deep inferior epigastric artery perforator (DIEAP) flaps, particularly after PMRT. Furthermore, some plastic surgeons were biased about the concept of randomisation (QPS), possibly reflecting the surgeons' intolerance of 'uncertainty' (McCulloch *et al*, 2005).

The hierarchy of evidence places the meta-analyses of randomised controlled trials (RCTs) at the highest level for evaluating the effects of an intervention, although this rationale has recently been debated (Zuiderent-Jerak *et al*, 2012). Atkins *et al* (2004) emphasise the relevance of study design to the particular clinical question (Atkins *et al*, 2004). In a systematic review evaluating treatment questions, only 40% of hypotheses relating to surgical procedures were amenable to a randomisation design (McCulloch *et al*, 2002). The IDEAL Framework and Recommendations emerged from expert consensus consideration of this challenge (McCulloch *et al*, 2009). The Framework stresses the frequent need for preliminary studies before a surgical RCT can become a realistic prospect, and cites patient and surgeon preferences as one of the key factors that makes this so. Other factors relevant to the QUEST studies are also considered by IDEAL, particularly the effect of surgeon learning curves, the need for preliminary work to achieve real clinician consensus, and the need for measures of operative quality control. None of these factors impact significantly on most drug trials. Their prevalence in surgical trials mandates an approach to developing valid evidence for operations that directly addresses these unique problems.

Successful randomisation in surgical trials is straightforward where the stakes are low and the clinical community is either in genuine equipoise or largely favourable to the new treatment. Therefore simple trial designs predicated on basic surgical interventions like the ROSSINI trial (Pinkney *et al*, 2013), wound edge protection devices to prevent surgical site infection after laparotomy, and other simple yet beneficial surgical interventions such as skin flap fixation sutures (quilting) or tissue glue to reduce donor site seromas after breast reconstruction presented no challenges to patient recruitment and randomisation (Daltrey *et al*, 2006; Llewellyn-Bennett *et al*, 2012). However, where there is significant investment of 'professional capital' in learning and promoting a new technique, things are more difficult. New surgical techniques like acellular dermal matrix (ADM)-assisted implant breast reconstruction, however, pose challenges related to surgical learning curves, with doubling of surgical complications in the first 12 months of the surgeons' experiences compared to standard submuscular implant reconstructions (McCarthy *et al*, 2012). This is an issue that frequently frustrates efforts to perform an RCT, whereby the clinical community and patients often 'move on' accepting inferior evidence from observational studies to the extent that it can quickly become 'too late' to do an RCT, as appears to have happened with ADMs (McCarthy *et al*, 2012). Clearly, this phenomenon is very different from drug-related clinical trials where patients are often 'blinded' to their randomisation allocation (Barkun *et al*, 2009).

The QUEST feasibility trials showed that the major challenge to recruitment was patient preference (McCarthy *et al*, 2012). However, this begs the question about how these preferences arose. The provision of appropriate information based on patient values is a key element in achieving adequate recruitment in surgical trials (McCulloch *et al*, 2002). In QUEST, a trial process checklist was introduced to assist centres with informing patients of the treatment options and aid discussions about the trial. There were challenges in integrating these new communication processes within established patterns of clinical working at participating sites. However, centres where teams were strongly motivated by the trial aims adapted well to standardising information provision. QPS results highlighted the importance of identifying 'early' patient preferences, and of pro-active initiatives to ensure that patients are informed about the trial information (Winters *et al*, 2011). At

3 months into the trial, the introduction of the 'open access' policy to all women regardless of initially expressed preferences resulted in an increase in patient numbers approached and recruited. Furthermore, the principle that patients may 'shift their views' from expressing a strong preference to one of equipoise reduced the numbers of patients declining trial entry based on initial preference. The quarterly screening logs of randomisation acceptance rates increased from 14% (1/7) (May to July 2011) to 33% (7/21) women (May to July 2012) in QUEST A. Likewise, QUEST B showed a similar rise in randomisation acceptance rates of 0% (0/2) (July to September 2011) to 38% (3/8) (July to September 2012).

Much has been learned from the landmark ProtecT trial, which aimed to compare three treatment arms (surgery, radiotherapy, and active monitoring) in men invited for prostate cancer screening within primary care (Donovan *et al*, 2002). Despite equivalent survival outcomes between treatments, randomisation had previously failed. ProtecT therefore used a nested trial of recruitment strategies, including nurse-led information on the rationale for the trial, to remove investigator bias from the information and consent process. Two randomisation pathways were permitted (three or two arm trials, respectively), and a patient preference arm was also agreed upon. ProtecT's qualitative research used audio recording of recruitment interviews and in-depth interviews to explore and balance communication on equivalence, including changing the order of presenting treatments. Exploratory studies on Corbett's seven descriptions of randomisation showed that the majority of clinicians 'dislike the emphasis given to chance' at such a stressful time (Jenkins *et al*, 2002). In ProtecT, recruiters needed to confidently express that men were eligible for all three treatments, of which the most effective was unknown, and that a trial was needed, with randomisation providing a plausible way of reaching a decision (Donovan *et al*, 2002). Removing the participating clinician from the information and consent process resulted in more patients being willing to be randomised.

The underlying message about the importance of both quantitative and qualitative research funded and timed to inform and change trial processes early on remains highly relevant to feasibility trials, as was shown in the Quartet (Qualitative research to improve recruitment to trials) study (de Salis *et al*, 2008). Perhaps the QUEST experience might have been different if the studies of patient and HCP perceptions had preceded the randomised feasibility studies, to identify potential barriers to recruitment and address them prior to recruitment commencing. As the ProtecT trial demonstrated, it is essential to develop tailored information to fully inform participants and address any concerns (Donovan *et al*, 2002). To overcome the preference problem in future, we need to consider alternative trial designs such as parallel preference arms and the 'cohort multiple randomised controlled trial' design (Relton *et al*, 2010). But we will also need to consider developing shared decision-making tools linked to analyses of large cohort and registry data helping patients to understand their treatment choices. In future, it is crucial to understand how to communicate the rationale for the trial so that potential participants understand the equipoise for treatment options and can appreciate how their participation may help others. Furthermore, the QPS shows the urgent need to address the public misunderstanding of randomisation.

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