

Evaluating the cost-effectiveness of remote versus on-site initiation visits: a randomised controlled trial

Background

Randomised controlled trials (RCTs) can be problematic and complicated to set up, and often suffer from problems with slow recruitment; limiting the potential for meaningful conclusions to be drawn from studies. A key problem that has been identified in the setting up phase of RCTs relates to the delays that can occur prior to submission for R&D approval. It is possible that greater contact with recruiting centres in a trial may reduce delays, although this does not appear to improve recruitment rates (Lienard, Quinaux et al. 2006, Treweek, Mitchell et al. 2010).

Preliminary contact with sites recruiting into multi-centre RCTs generally takes two forms: initial contact prior to R&D application, and site set-up visits that take place once approval has been granted. In the first instance, healthcare professionals at local sites are contacted to discuss the trial rationale and design, and obtain agreement from sites for their participation in the study. This initial contact also provides the opportunity to finalise local arrangements and obtain any additional information that may be necessary prior to submission for R&D approval.

While it is usually necessary to undertake on-site *set-up* visits to provide training on trial processes and materials and ensure the study will be conducted according to standards of Good Clinical Practice, earlier site *initiation* can take two forms: face to face on-site initiation visits or remote initiation via email and telephone correspondence. Both methods have been adopted in surgical trials to date, although the effect of on-site versus remote initiation visits on time to R&D submission and subsequent patient recruitment, is unclear as similarly long time delays have been reported across studies despite variations in approach (Brealey et al, unpublished work).

Research objectives

To investigate the costs and effectiveness of providing on-site initiation visits at trial sites (prior to application for research governance approval) on subsequent set up times, recruitment measures, data collection and the costs associated with each approach. This study will inform the feasibility of undertaking such a comparison across other trials.

Design

A randomised controlled trial of on-site initiation visits versus remote site initiation (via email and telephone correspondence).

Recruitment and randomisation

Sites that are contacted to discuss the set-up of a surgical trial will be included in this sub-study and blinded to their involvement in order to prevent any change in attitudes towards site set up and recruitment. The hospital site of the Chief Investigator and trial sponsor will be excluded from this study as this site is not only involved in recruitment but is substantially involved in setting up the trial in general.

At first point of contact, sites will be randomised to receive either face to face on-site initiation visits or remote initiation via email and telephone correspondence. The randomisation sequence will be generated by computer at York Trials Unit and sites will be allocated on a 1:1 ratio.

Minimisation will be used to ensure the groups are balanced in terms of important characteristics that may impact on a site's ability to get set up and recruit: 1) whether the Principal Investigator (PI) has previous experience of working on a multi-centre surgical

RCT, 2) whether the site has a research nurse in place, 3) the size of the hospital catchment area.

Interventions

On-site initiation

Meetings will be arranged to meet the PI, research nurse and, ideally, the radiology contact person at the site to discuss the trial processes and requirements of the hospital site. A site initiation checklist will be used to ensure all important topics are discussed and in an attempt to standardise discussions across sites. A record of costs associated with on-site visits will be kept using the main trial database, including researchers' time when contacting sites (e.g. telephone, email), visiting sites and travel costs.

Remote site initiation

Email and telephone correspondence will be used to discuss the trial processes and requirements of the hospital site. This will be undertaken primarily with the PI, but also with the research nurse and radiology contact person where appropriate. As for the on-site group, a site initiation checklist will be used to ensure all important topics are discussed and to standardise discussions across sites. The costs associated with remote site initiation will be estimated by keeping a record of the telephone and email correspondence at each site to estimate researchers' time use.

Outcome measures

Set-up:

- a) Time from first contact to R&D submission
- b) Time from first contact to R&D approval
- c) Time from first contact to set-up meeting prior to recruitment commencing

Recruitment:

- d) Number of eligibility forms returned (estimate of screening activity)
- e) Proportion of consenting patients out of eligible patients screened
- f) Number of patients recruited: Total
- g) Number of patients recruited: For the number of months the last site set up has to recruit
- h) Time from first contact to time of first recruited patient per site
- i) Time from first contact to average time to recruitment per site
- j) Time from first contact to time of recruitment of each patient

Data collection:

- k) Hospital forms: Proportion returned (after first request and in total)
- l) Hospital forms: Time to return
- m) Patient questionnaires: Proportion returned
- n) Patient questionnaires: Time to return (after first request and in total)

The costs associated with each approach will also be examined using information about the researcher's time use and travel costs of each trial arm.

Research nurse's and local PI's opinions and satisfaction with set up processes, recruitment and data collection will also be explored using a follow-up survey that will be administered at the end of the trial. This will include asking sites whether they would prefer to have on-site or remote set up initiation.

Statistical considerations

Statistical analysis plan

All analyses will be conducted on an intention to treat basis by including all sites based on the groups they were assigned to at randomisation. Analyses will be conducted using SAS version 9.1 or later or STATA version 11 or later. All outcomes will be summarised descriptively overall and by trial arm. Group differences and 95% confidence intervals will be reported. Owing to the small number of anticipated trial centres (around 8 centres per arm), no formal statistical tests will be undertaken on site-level outcomes. Any patient-level outcomes will be compared between trial arms using appropriate tests for the type of outcome data. Group differences will be summarised descriptively and reported using 95% confidence intervals. The statistician will remain blind to the intervention group until all data summaries and results are finalised.

Cost and consequences in terms of patient recruitment will be compared. If it is deemed appropriate, an incremental cost per patient will be calculated. Primarily, estimates will be made using the researchers' records of time and costs associated with site initiation in each group. However, time associated with site liaison once sites are set up to start recruitment will also be considered.

Ethical considerations

Within this nested sub-study, sites will not be informed that they are to be randomised to receive either on-site or remote initiation visits. Both approaches are commonly used to set up sites in RCTs and we do not anticipate any negative implications for patients as all sites will receive the same amount of training in trial procedures when setting up the site after R&D approval.

Should sites be randomised to the 'remote initiation group' and subsequently the local site Principal Investigator feel that they would benefit from face to face contact to discuss the trial, this will take place and the site will remain in the study and be analysed under the assumptions of intention to treat.

Recruitment at sites will be monitored on an on-going basis by the trial co-ordinators and at regular Trial Management Group meetings. If the trial is not meeting recruitment targets and monitoring indicates substantial differences in recruitment rates at sites in either trial arm, a decision may be taken to end the study so as not to jeopardise patient recruitment in the main trial.

References

Lienard, J. L., E. Quinaux, E. Fabre-Guillevin, P. Piedbois, A. Jouhaud, G. Decoster, M. Buyse and O. European Association for Research in (2006). "Impact of on-site initiation visits on patient recruitment and data quality in a randomized trial of adjuvant chemotherapy for breast cancer." *Clin Trials* **3**(5): 486-492.

Treweek, S., E. Mitchell, M. Pitkethly, J. Cook, M. Kjeldstrom, T. Taskila, M. Johansen, F. Sullivan, S. Wilson, C. Jackson and R. Jones (2010). "Strategies to improve recruitment to randomised controlled trials." *Cochrane Database of Systematic Reviews*(1).