The Challenges of Clinical Trial Set-Up: Expectation Vs Reality

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BACKGROUND

Evidence-based healthcare demands doctors, nurses and allied health professionals utilise a diverse range of 'evidence' to inform and justify clinical decision making[1]. Much of this evidence comes from clinical research, however, the relative authorities of research study designs creates a hierarchy of evidence which places randomised controlled trials (RCTs) at the top due to their ability to control for bias[2].

RCTs also play a crucial part in the regulatory process whereby new therapeutics can gain access to the drugs market, or an existing drug can be licensed for a new purpose[3]. Pharmaceutical companies develop and finance such studies, and, within the UK, commonly seek to locate them within suitable and appropriate NHS sites. Part of the success of these RCTs is in their initial set-up, which aims to minimise the potentially negative impact of poor recruitment and retention of participants[4].

The process of RCT set-up within the NHS varies depending on the clinical area, the size and experience of the research team, and the nature of the study. Whilst a wealth of literature exists concerning the ethical considerations of RCT initiation[3,5], a similar body of work on the practical aspects of trial set-up, such as how expected and unexpected challenges can be successfully negotiated remains absent. The lack of value placed on this aspect of the clinical trial process is underscored by the National Institute for Health Research (NIHR) national costing template, which does not currently provide funding for the tasks associated with trial set-up.

AIM

The aim of this study is to explore the anticipated and unexpected challenges encountered during the set-up of a large, complex RCT, and to examine the role of the research nurse in the response to and resolution of those challenges.

METHODS

Prior to the initiation of a large RCT within the field of HIV and sexual health, data were collected from the research nurse team exploring expectations surrounding the trial set-up. A qualitative approach generated data which was organised into four categories:

1. Insights into the anticipated challenges
2. Predicted strategies for managing those challenges
3. Solutions to challenges
4. Timescale and outcome

Throughout the subsequent set-up process the research nurse team engaged in a reflective process structured around these categories, and met weekly to critically discuss and share experience. Following the successful initiation of the trial, expectations were then examined in relation to the actual challenges encountered.

Results

Thirteen areas were identified as potentially posing challenges to trial set-up. These are detailed in table 1. Within these areas, unexpected as well as predicted challenges were encountered. Whilst some of these challenges were minor concerns, other presented significant problems that required the research team to develop new ways of working to ensure the safe, effective and timely initiation of the RCT.

The biggest challenges encountered were in the areas of laboratory capacity, well population, policy change and training as discussed in the table 2.

Table 1 : Anticipated challenges to trial set-up

Geographical location/logistics	• Study based at a different site to research team. Consideration had to be given to unfamiliar working systems, different patient pathways, different shift patterns and staffing.
Recruitment target	• Target of 50 participants: challenge of recruitment and retention. • Manpower: medical, nursing and pharmacy staff. Supplies and storage.
Trial experience	• Study site had not been a centre for many RCTs: staff training. • No previous experience working in partnership with the research team.
Couriers	• Unsuitable courier/previous experience. • Development of SOP for sample collection.
Storage/Workspace	• Suitable storage for lab kits/site files/patient case report form. • Suitable clinic rooms, and space for monitors to work.
Laboratory capacity	• Manpower for processing and timing of samples.
Experience in sexual health	• Research nursing team have no experience in sexual health, which is essential for this RCT. • Training in DBS testing and STI screening swabs
Result management	• Establish a timely system for reviewing lab results. • Management of participants who have toxicity grading 3 or 4. • Management of participants diagnosed HIV positive during the trial
Electronic records	• Site is paper-light, research staff will require training in local database. • How to manage monitoring visits: access to paper only or electronic?
Un-blinding phase	• Happens once the last participant reaches week 96 of the study. • Participants will need to be seen within 6 weeks of this happening. Need to consider staffing , physical space , lab capacity
Policy change	• The potential introduction of Pre-Exposure Prophylaxis (PrEP) for HIV in Scotland may affect recruitment. Timeframe uncertain.
Well population	• RCT targets a well population: late afternoon/early evening clinics to suit population and help maximise recruitment.
Training	• Multiple trial-specific systems to set up and access.

Table 2: Major challenges encountered during set-up

Laboratory capacity

- The lab was off-site: it was identified 3 months into set up that PK sampling must be processed within 30 minutes, which was unachievable with the established system.
- Ambient samples must be shipped on the day of collection, and as participants would attend evening clinics this posed issues with sample processing.
- **Solution:** Research nurses needed to process the samples. Equipment was loaned from the sponsor, training undertaken and a lab set up on site. This took approximately 3 months to resolve and required an amendment to the site's contract.

Well population

- The predicted challenge had been recruitment occurring during evening clinics at the site.
- An unexpected issue occurred in relation to pharmacy: drug dispensing could only occur on specific dates and times within the week due to staffing, and shipment of drug had to be received at the main pharmacy then transported to site.
- **Solution:** Permission was sought from the sponsor to request the study drug prior to a participants' study visit. In addition, increased funding for pharmacy staff was obtained. These amendments required the development of an SOP for drug shipment which needed to be reviewed by the sponsor. This took approximately 3 months to resolve.

Policy change

- The research team anticipated that PrEP may become available in Scotland, but not in the near future. However, in November 2016 it was announced that PrEP would be introduced in 2017, potentially impacting recruitment.
- In this situation there was no solution. It was highlighted by the research team in their recruitment strategy as a potential barrier to recruitment, and its impact is yet to be determined.

Training

- Anticipated training needs included unfamiliar IT systems, the study protocol and the development of knowledge and practice in sexual health. A newly-appointed research nurse would also have multiple training requirements.
- The training of the newly-appointed research nurse was unexpectedly delayed, however, due to staffing issues. This meant they would not be in post and fully trained on the study until after the RCT had been initiated. Despite the initiation visit for protocol training being cancelled twice, this proved to be the case.
- Again, there was no solution to this issue. Research sits within routine NHS clinical practice, and as such is vulnerable to unrelated staffing and management issues.

References
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Conclusion

Overall, the RCT took approximately six months from site identification to the site initiation visit, and presented many challenges for the research team. Some of the anticipated problems were dealt with promptly due to the experience of the research team, and the utilisation of established protocols and SOPs. However, the unexpected challenges that arose required an investment of time and resources from the research nursing team to identify practical solutions to these problems, which necessitated the development of new ways of working, and enhanced personal skills.

The experience managing these unforeseen challenges highlighted the lack of guidance available relating to the practical aspects of trial set-up for less experienced research staff. As this is an exploratory study, further research is required to gain a more in-depth account of the vital role research teams play in the set-up of RCTs, and other clinical trials. Without this knowledge, this aspect of the research remains undervalued, reflected by the lack of reimbursement for trial set-up currently provided within the National template.