Predicting Success or Failure of Recruitment to Clinical Trials

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Background

A significant proportion of clinical trials fail to recruit to time or target. Such failure represents a waste of time, effort and money, causes reputational damage and has major ethical implications. The issue has assumed even greater importance in the light of the NIHR CRN High Level Objectives that ain to increase the proportion of studies in the NIHR NCRN portfolio delivering to recruitment target and time with the imminent introduction of strict metrics and time lines.

The Portfolio Balance and Delivery Group recognizes this as an important problem and are, therefore, putting considerable effort into determining the underlying reasons.

Within the trials community there is no lack of opinions as to the difficulties faced and their potential solutions but these opinions differ widely and there is neither consensus nor any sound evidence-base for opinions expressed.

Aims:

To develop guidance that can predict likelihood of recruitment failure so that we can avoid such trials in the first place, improve trial design to enhance practicality or offer increased support to trials that are deemed likely to be difficult to run, before they 'get into trouble'.

Methods

Data was garnered from three sources,

a) Results of an NCRN questionnaire to Trials Units and Research Network Managers previously circulated to collect opinions.

b) Documents provided by Ms Kate Law and Ms Julie Hearn at Cancer Research UK that listed all trials that had CTAAC funding withdrawn before completion, over the last 5 years, for whatever reason.

c) Detailed interviews with senior trial coordinators and research nurses.

The senior trial coordinators and research nurses were asked to…. 'think of …..trials that were recruited to easily. What were the reasons? Similarly what were the reasons behind trials that were difficult? How were problems resolved and what have you learned?

It was evident that researchers were very enthusiastic about the project and keen and to talk. All showed considerable insight and expressed interest in working towards solutions sharing best practice. All information gathered was considered Confidential are Individual trials/centres /sites/ PIs/coordinators etc. are not identified in this document.

Certain limitations of the whole project and others relating to the above methodology were readily apparent. For example, many adverse factors can only be seen in retrospect e.g. overoptimistic recruitment projections and the degree of support from the clinical community. As such, they are

not good prognosticators. Furthermore, 'difficult' trials can still be run effectively with enough enthusiasm and support.

Results – Predictors of poor recruitment

Trials which involved randomizing across different treatment modalities, e.g. radiotherapy vs. surgery or chemotherapy vs. arterial embolisation were always seen as challenging. Patients and investigators tended to have strong opinions on which arm offered optimal chance of benefit so that discussion regarding randomisation proved difficult. Unblinded randomization against-placebo/observation was also challenging. Patients and investigators were uncomfortable with any study that involved an arm with no active therapy. Any significant disturbance of patient pathway was perceived to present difficulties to investigators as was hidden 'complexity' with a study.

Certain clinical disciplines with an underdeveloped record in trials such as surgery and hepatology were identified as problem areas. Respondents perceived that such investigators, as noted above, tended to have strong opinions as to the most appropriate treatment (despite lack of objective evidence). Thus they often did not feel to be in equipoise and this was compounded by a lack of familiarity with processes involved in clinical trials and appropriate training in Good Clinical Practice. Where 'eligibility' or a decision about which trial to become involved with required agreement across several specialties recruitment appeared severely hampered. Potential investigators were also inhibited by a lack of research time in their job-plan and access to research nurse support. Despite these adverse factors several examples of dramatic 'turnarounds' consequent upon enthusiastic support from a trial team were evident.

Competing treatments or trials were an obvious (but often unrecognized at the outset) cause of poor recruitment. Commercial trials where there was 'payment per patient ' could be perceived as more attractive than academic trials as were trials that offered a simple treatment suitable for large numbers of patients – as a way of enhancing recruitment figures. New treatments (of proven efficacy) sometimes became available during recruitment period. Insomuch as these factors only became apparent during the course of a trial, they were poor predictors.

"Geography" could also be a negative factor. Small number of treatment sites and patients reluctance to travel unless benefit was perceived to be large often limited recruitment. Setting up acceptable systems for treatment and follow-up to be carried out locally, obtaining accreditation for blood tests etc all require additional set up or further travel for trial co-coordinator and not surprisingly any international component widely seen as presenting a major hurdle.

Factors Predicting Recruitment - 'equivocal'

An experienced PI was usually seen as a 'positive' for a trial but not always. The experienced investigator might be too busy with too many trials on his/her plate. Conversely, an Inexperienced PI was usually considered in a negative light but in some cases it was remarked that he or she may have more time and be very keen to be successful and build reputation.

Trials involving rare tumours or small subgroups of common tumours were usually difficult to recruit to particularly when usually negative, especially when cases were spread across several disciplines. There were however several examples of where these problems were overcome by highly focused enthusiastic centres of expertise.

Factors Predicating Good Recruitment

Cancers where there was no established treatment available and enthusiastic patients and investigators believed in the new drug were the best recruiting trials and in this setting most adverse factors could be overcome. This was particularly the case when an network of sites or a series of trials (such as ESPAC 1,2,3,4….ABC 01/02/03/04 etc) or, in the case of hematology, purpose-built networks had been established. In this setting relevant patients could be readily informed of trial options.

The key 'on the ground' driver of a good recruiting trial was a dedicated team that feels ownership of the trial and take responsibility for results. PIs, co-ordinators, research nurses and clinical research fellows were especially negative about being moved from trial to trial and, interestingly strongly felt 'it was their job' to challenge negativity toward trials by other NHS staff.

A trial of simple design, wide eligibility, and one that sits comfortably within the current patient pathway (with no extra visits) was the one most likely to succeed.

Conclusions

Predictors of negative outcomes, include randomizing across different modalities, unblinded randomization against-placebo/observation and any significant disturbance of patient pathway as well as clinical disciplines with undeveloped record in trials, and adverse 'geography'.

Predictors of positive outcomes include 'No established treatment available', established networks of sites/series, simple design, wide eligibility, within current pathway trials.

Ways of overcoming negative outcomes are available. Trial coordinators and research nurses often felt their expertise is underutilized.