MALCOLM WILLETT

Are clinical trials units essential for a successful trial?

Today's complex studies need the support and expertise that these units bring, writes **M S Gohel**, but **Ian Chetter** says they are far from essential

M S Gohel consultant vascular surgeon and honorary senior lecturer, Cambridge University Hospitals and Imperial College London, London, UK **m.gohel@imperial.ac.uk**

YES

The first published randomised trial is credited to Austin Bradford Hill in 1948, for a study funded by the Medical Research Council (MRC) to evaluate the role of streptomycin in patients with tuberculosis.[1] The allocation of subjects to treatment arms using sealed envelopes was revolutionary for the era, but clinical trials have come a long way since.

Modern studies are often highly complex, with ever increasing levels of methodological sophistication, near endless regulatory bureaucracy, and stringent quality standards. Clinical trials units (CTUs) are multidisciplinary specialist units that have the specific remit to design, conduct, and report clinical trials. The case for their widespread involvement in all clinical trials is compelling.

The 45 units registered by the United Kingdom Clinical Research Collaboration (UKCRC) have shown that they can deliver complex multicentre clinical trials to the highest standards.[2] The value of CTUs is recognised internationally, with many established units throughout the United States and Europe. They provide not only methodological expertise but also the logistical support and infrastructure that is essential to deliver a challenging clinical trial.

Support at every stage

Experienced CTUs work with investigators to offer support at every stage of a clinical study, from defining the research question to preparing the final report. In particular, staff are likely to have an excellent practical understanding of relevant legal and regulatory issues, knowledge of necessary approvals needed, and extensive experience of data management and randomisation techniques.

Ian Chetter chair of surgery, Hull York Medical School, Hull HU3 2JZ, UK
ian.chetter@hey.nhs.uk

NO

"Essential" means absolutely necessary. To investigate whether CTUs are essential we need to evaluate what constitutes a successful clinical trial, to assess why some trials are unsuccessful, to evaluate what a CTU is and what it can contribute to a trial, and to assess whether CTU involvement affects trial success.

Successful clinical trials are essential to guide clinical practice and are requested repeatedly and persuasively in the literature. A successful trial answers a well formulated and worthy question and measures outcomes that are clinically and socially relevant. The trial must be designed with appropriate methods and conducted so as to minimise bias and maximise statistical power and external validity.

The factors limiting the quality and progress of clinical trials and ultimately their success have been comprehensively classified.[7] Barriers to clinician participation are common—for example, time constraints, concern about the effect on doctor-patient relationships, and insufficient interest in the research question. Barriers to patient participation in clinical trials are also common and include the demands of trial participation, uncertainties regarding intervention, and concerns about patient information and consent. A CTU is unlikely to have much influence on these barriers.

The key factors contributing to the success of clinical trials have also been identified.[8 9] Of paramount importance is efficient and detailed project planning and trial management. This is best provided by an experienced trial manager supported by an efficient, well trained team, the composition of which is dictated by the specific requirements of the individual trial. The UK Trial Managers Network has highlighted the lack of formal, accessible, and appropriate training for trial managers, and embedding an inexperienced trial manager within a CTU may give false reassurance. In

Undoubtedly, many well conducted, high impact clinical studies have been done without CTUs. However, randomised clinical trials in 2015 and beyond are more likely to be large multicentre or multinational studies because these are the only way to achieve the numbers needed to detect moderate treatment effects. In this context, a robust study design, with adequate power and well planned recruitment, reliable intervention delivery, and adherence to follow-up is essential. Moreover, novel aspects of study design, such as interrogation of linked health records (with information governance challenges), registry based recruitment, or randomised trials embedded within a cohort study are increasingly popular strategies.

Health economic analysis, including intricate modelling studies, is a common component of randomised trials. In this rapidly evolving space, is it really feasible to conduct a randomised clinical study without the involvement of a CTU? The major funding bodies do not think so: CTU involvement is either mandated or strongly encouraged by the National Institute for Health Research, MRC, British Heart Foundation, and others.

Important safety net

Many clinical trials fail to deliver, often because of inadequate recruitment, poor delivery of the intervention, or losses to follow-up. In an evaluation of 114 multicentre studies performed up to 2003 (before modern CTUs), less than a third recruited the target population within the specified period.[3] Although there may be genuine unforeseen explanations for why a clinical trial does not thrive, contingency planning and early recognition of problems are important to salvage the situation. Trial managers, statisticians, and other CTU staff with extensive experience of multiple clinical trials are best placed to anticipate difficulties and propose remedies.

In much the same way that high volume clinical centres are more likely to "rescue" a patient with complications, a high volume trials unit may be more likely to rescue a failing study. Unfortunately, poor research governance or even research misconduct may taint clinical trials.

In an review of 2047 retracted articles, 1379 (67.4%) were withdrawn because of research misconduct.[5] CTUs are not a panacea for all suboptimal research practices or trial failures, but the expertise of the team and inherent quality assurance processes may help minimise breaches from good clinical practice.

Ethical case

Perhaps the most compelling justification is ethical. All clinical trials involve patients and are often funded by government or charitable grants. Modern clinical trials are enormously expensive (about £8000 per recruited patient in the UK[6]) and are therefore a precious resource, with a direct effect on the participants and, potentially, the wider patient population. It is an ethical imperative that researchers do everything to optimise study design, ensure appropriate sample size calculation, perform robust analysis, and report findings to published standards. The best way to achieve these goals is with the early involvement of an experienced CTU.

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Rather than questioning the importance of CTUs, the time has come for researchers to recognise their value in all clinical trials.

an attempt to improve efficiency and make savings, CTUs have created the role of "portfolio trial managers." These managers often have to deal with several tasks across a diverse range of trials with varied challenges. This approach promotes generic over trial specific skills, may dilute detailed involvement with individual trials.[10]

We need internationally accepted, evidence based standards for high quality management of trials and a guideline for those running clinical trials, much the same as produced for writing trial reports and protocols.[11 12] Without specific training and guidelines, successful trial management can be fraught with difficulties. These are not necessarily resolved by engaging a CTU.

The UKCRC defines a CTU as a specialist unit set up to design, conduct, analyse, and publish clinical trials.[13] A CTU can provide expert statistical, epidemiological, regulatory, and methodological advice and coordination. It seems logical that centralisation of these different experts within one unit, a CTU, improves convenience and facilitates the effective undertaking of trials, especially those that are multicentre, large, or complex. However, no systematic review has assessed whether trials supported by a CTU are better designed and conducted, and have more impact than those without CTU support. So although a successful trial requires dedicated staff with the appropriate knowledge and skills, this need not be provided by a CTU. Indeed, a report analysing factors that limit trial success recommends further research into "the optimum structure, staffing and organization for the conduct of large and small trials."[7]

No guarantee of success

What is also clear is that the involvement of a CTU does not guarantee success. An analysis of 114 multicentre trials with CTU support funded by the NIHR and MRC showed that 45% failed to recruit 80% of the prespecified sample size. Less than one third of the trials recruited their original target number of participants within the time originally specified, and about a third required extended time and resources.[3] Indeed, there are examples of trials with CTU support failing in clinical areas where trials without CTU involvement have succeeded.[14 15 16] This may be because CTUs, especially with recent subspecialisation, become divorced from the patient and clinical communities.

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The overwhelming majority of successful clinical trials do not have CTU involvement. CTUs are generally used only in phase III and IV trials. Far more phase I and II trials are performed than higher phase trials, so many successful trials do not involve a CTU.

The UK has only 45 CTUs, so it is currently impossible for a CTU to be involved with every clinical trial in the UK. Demand hugely outstrips supply. If all trials had to be managed by a CTU many important research questions would remain unanswered unless there was a large and rapid expansion of CTU numbers.

Adds considerably to cost

Finally, the expense associated with CTU involvement means that trials become too costly to go ahead and is a key reason why commercial research usually doesn't use CTUs.

Many factors contribute to the success or failure of a clinical trial, and the involvement of a CTU is by no means a panacea. Indeed, if researchers were to adopt the mantra that clinical trials units are essential for a successful trial, a huge volume of valuable research would not be conducted, with considerable detrimental consequences to patients and at a huge loss to society.

Cite this as: *BMJ* 2015;350:h2823