

Solving the Challenges of Large Multicenter Trials in Anesthesia

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ABSTRACT

This paper describes many of the challenges encountered when establishing a large multicentre trial in cardiac anaesthesia. We address funding, authorship, multisite ethics review, patient recruitment, data quality management, communication with individual sites, and strategies to enhance cooperation and patient recruitment.

Keywords: *cardiac anaesthesia, anaesthesia, multicenter trials, methodology.*

INTRODUCTION

Large randomized controlled trials, testing new treatments in routine clinical practice, can optimize generalizability and so are clinically relevant and reliable (1). They thus provide the best evidence of effectiveness (2, 3). Most large trials are multicenter studies, and often conducted in many countries. Despite being labelled as “simple” or “pragmatic” trials (1, 3, 4), reflecting their focus on easy-to-administer treatments in routine settings, they create a number of difficult challenges for those involved. However the rewards are great and include the opportunity to answer important clinical questions reliably, to publish in top-ranked journals, and to be recognized by your peers. We would like to share our experience of establishing a large multicenter trial testing two interventions

in coronary artery surgery (5). The aspirin and tranexamic acid for coronary artery surgery (ATACAS) trial is a factorial designed trial in 4600 patients, designed to detect thrombotic (principally myocardial infarction (MI), stroke, and death) and bleeding complications – see www.atacas.org.au. We reasoned that although aspirin may increase bleeding, there is some evidence that it could reduce thrombotic complications after coronary artery surgery. The opposite can be said for antifibrinolytic therapy. In both cases there are insufficient randomized trials to address these questions unequivocally. A large multicenter trial is required (5). Pharmaceutical companies are unlikely to fund such research, and so specialty or government research bodies must provide financial support.

PROTOCOL DEVELOPMENT AND PLANNED SUB-STUDIES

The effort and commitment to undertake or contribute to a large multicenter trial

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is substantial. Before embarking on such a project, the aims and study hypothesis should be clearly outlined, hopefully addressing a clinically important question. A supportive literature review will provide a background and justification for conducting such a trial. There are often opportunities to design small sub-studies at selected centres, requiring additional data collection, increasing opportunities for authorship and additional publications. The explanatory data can be used to link the effects of an intervention to selected intermediate outcomes that may correlate with the main study aims. For the ATACAS trial we are conducting substudies to investigate aspirin non-responsiveness in a subset of our study population, perioperative genomics with the iPEGASUS group, and the effects of tranexamic acid on seizure risk.

The study protocol describes the science of the research project, and the study procedures manual the structure and processes that allow it to be properly conducted.

STUDY MANAGEMENT

Experienced trial management and leadership are vital for successful large scale clinical trials. Numerous individual centers, sometimes with their own research interests and studies, must arrive at a consensus regarding study procedures and data collection, inclusion of other clinicians (not just anaesthesiologists) and language and cultural differences, all of which test goodwill and cooperation on a multinational scale. Trials should have a core group of co-investigators responsible for the overall management and running of the trial, headed by a Principal Investigator (PI). The PI, co-investigators, and perhaps other experts, constitute the trial steering group. Some bodies recommend that the chairman of the trial steering committee should not otherwise be involved

in the trial (6). The trial steering committee should meet at regular intervals throughout the life of the trial to discuss overall management, progress and policy decisions. Trial management includes data management, data security and back-up, quality checks, review of patient safety and including consideration of reports from the trials' data and safety monitoring board. Each individual site reports via the study chief investigators to the steering committee. Ideally each site should have a lead investigator who takes responsibility for overseeing the study at their site, for which they should be acknowledged in the final publication. Financial management should be continually assessed throughout the trial (7).

FUNDING

Large trials require substantial funding. The ATACAS trial is primarily funded by the Australian National Health and Medical Research Council (NHMRC). Being government provided, such funding is usually limited, and when considering the costs and demands on clinicians and research staff, it is usually insufficient to properly fund all aspects of the trial. Most centers have other cardiothoracic research projects which may compete for patients, research staff availability, and interest from local clinicians. There may be competition with pharmaceutical company-funded projects which typically provide much higher rates of remuneration (8, 9). The ATACAS trial is an investigator-initiated trial, funding individual sites Australian Dollars (AUD) 700 (about Euro 390) per patient enrolled; we have been involved in some pharmaceutical company-funded studies providing funds at 5-10 times that rate.

Large clinical trials aim to address clinically important questions, often testing simple inexpensive interventions. There is a compelling

argument that such trials ought to be funded by the health (not medical research) budget because of the opportunities to immediately improve outcomes of healthcare (1, 10).

PROCUREMENT OF STUDY DRUG

Initial management hurdles can include sourcing of study drug and matched placebo, and these issues can vary across countries because of differences in the status of the study drug licensing. For ATACAS, we approached the pharmaceutical companies that produce aspirin and tranexamic acid to assist with free supply of study drug and matched placebo.

For aspirin, this proved to be relatively straight-forward and positive, but for tranexamic acid it resulted in a two year delay and eventual disappointment. We subsequently arranged our own purchase of tranexamic acid from the UK, leaving us with the cost-burden for supply of this drug to most ATACAS sites around the world. This of course also delayed the commencement of the trial.

Following public announcement of the results of the BART trial (11), and the market withdrawal of aprotinin around the world (12), the initial purchase price of tranexamic acid went from AUD30 (about € 17) per box to AUD100 overnight.

This added a new and unexpected cost burden to the study.

Fortunately this did not interrupt recruitment although it highlights how trial budgets can suddenly be tested.

GOVERNANCE

Before enrolling participants in a clinical trial individual sites must gain approval by their hospital's institutional review board or ethics committee (13).

Another mandatory step is informed consent (14), for which local expectations and requirements can vary, as well as sometimes introducing a need for translation of such documents.

The time line for this process from beginning (initial contact with site) to end (management receiving the approval letter) averages six months. This is a major barrier for many sites who may otherwise be interested in collaboration (15).

AUTHORSHIP AGREEMENT

Researchers are rated according to the quality and quantity of their publication record. Large trials involve many individuals, but only some deserve authorship on the main publication(s). Others may share in authorship of subsidiary publications. In any case, all of those involved in the conduct of a large trial should be acknowledged, and this is typically published as an appendix to the main publications.

For this reason acknowledged site leaders ought to be given credit for their leading role within their own institutions.

Authorship is a vexed topic, and it cannot be overstated: who and under what circumstances each collaborator is included in the authorship or acknowledgement lists must be outlined at the *beginning* of the trial, and ideally a signed authorship agreement be completed in order to avoid disappointment and conflict.

INDEMNITY

Multicenter trials should have a clinical trial agreement (CTA) signed with each individual site. This pertains to both pharmaceutical-sponsored and investigator-initiated trials.

The CTA document requires legal review

and comment from each site. This adds cost and poses another potential for delaying start up of the trial.

Pharmaceutical-sponsored trials have the resources to provide their own indemnity insurance, but investigator-initiated trials rarely can because such funding is not included in most research funding bodies' budgets.

In such cases it is usual to ask that individual sites cover their own indemnity costs, because the study procedures usually only involve currently established therapies.

As we, and others (10), argue, investigator-initiated large pragmatic trials ought to be considered "public good" research and so individual institutions should support such trials.

SITE SELECTION

Site selection is vital to a successful trial. It relies on some research infrastructure and staffing, to identify eligible patients for recruitment, study interventions and follow-up (16).

Initial site investigators invited to join the ATACAS trial were those previously involved in other multicenter trials (17-20), and have proven track records. All sites were asked to discuss the feasibility of undertaking the trial with their respective cardiothoracic surgical colleagues. Support from the surgeons at each institution was an essential component for the trial. New sites were also sought.

Publicity for the trial occurred via presentation at scientific meetings, establishment of a trial website (www.atacas.org.au), and journal publication (5).

Rahbari et al (21) challenge the surgical community to optimize study power using properly conducted, pragmatic (multi-center) trials with large sample sizes. Variation in surgical practice, surgical skill and

surgeon preference have proven to be obstacles to large multicenter trials in surgery (8), but Devereaux et al. (22) have suggested solutions.

RESEARCH NURSES/COORDINATORS AND PATIENT RECRUITMENT

It is very important that the infrastructure and staff to conduct research at each site are actively sought, available and most importantly supported (23-26). Sites that have limited infrastructure in place to conduct research must commence with recruitment of a research nurse or coordinator, and this takes time (recruitment, training). The coordinating center for the trial can assist in this regard.

Constant communication and availability of assistance has proved to be important in facilitating this role. The research nurse is responsible for the screening, recruitment, consent, data collection, data storage, subject logs, data entry, and protection of human subjects in clinical trials (*Figure 1*) (27).

It is vital that the research nurse be supported by the site investigator, and participating units (28), as this will be the main contributing factor to the success or failure of patient recruitment (25). It has been previously reported that the individual undertaking the recruitment can influence recruiting patients to the trial (29). No difference was found when doctors or research nurses were examined, but there was a statistically significant difference when recruitment was undertaken by the operating surgeon (29).

This therefore highlights the importance of having the support from all disciplines involved in the research.

A recent survey of trials published in the *Lancet* or *BMJ* found that nearly 60% of

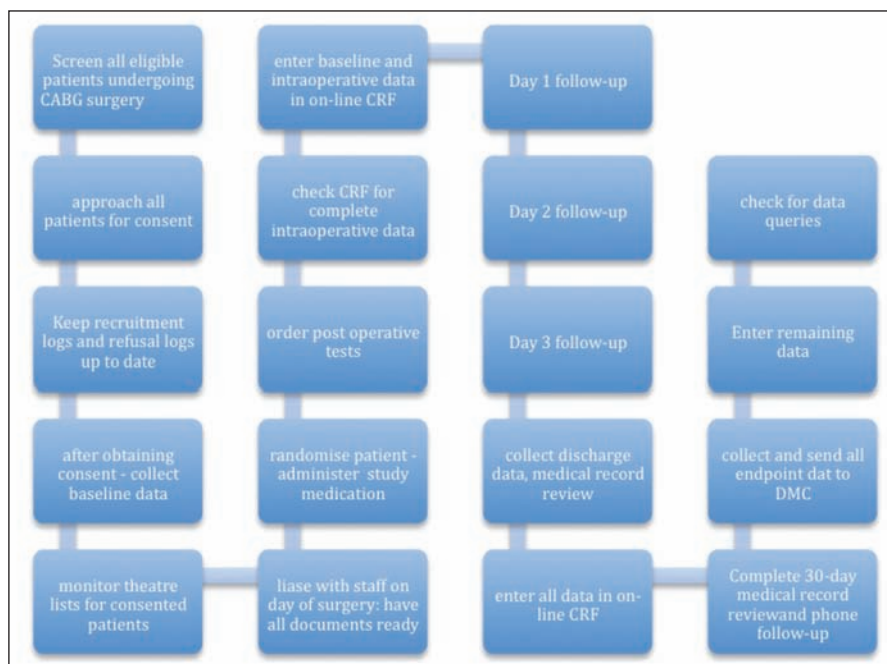


Figure 1
Day-to-day role of the research nurse.

trials had either failed their recruitment target or required an extension of their planned recruitment period (29). Recruitment of participants to trials is one of the most important aspects to a successful trial (23, 24, 30).

It has long been recognized that recruitment is a much greater problem than is perceived by the investigator when instigating and designing of the trial (8, 24). During the course of the trial it is important to implement and identify strategies to overcome barriers to recruitment (31).

Delays in recruitment lead to important scientific answers being left unanswered, increased unidentified costs, early closure of trial (8, 23-25, 30, 31), statistical power may be reduced (29, 31), poor morale (16), and delayed uptake into clinical practice.

Studies have shown that individual site training and regular feedback and communication to staff improve recruitment rates (15, 32). Start-up meetings, personalised education and training visits assist in im-

proving recruitment (29). The management team provide the following process to assist with site recruitment (*Figure 2*).

Newsletters are used to disseminate information to all sites and focus on recruitment techniques, addressing frequently asked questions, current and new sites, future meetings, changes to the database and recently published literature relevant to the study.

DATA MANAGEMENT AND MONITORING

Data collection from multiple sites, in various time zones, needs to be streamlined and secure.

For the ATACAS trial we use paper-based case report forms (CRF) at each centre, and the data are later transferred onto a web-based form. The online data entry is accessed through a password-protected link on the trial website.

The site also offers a trial summary, recruit-

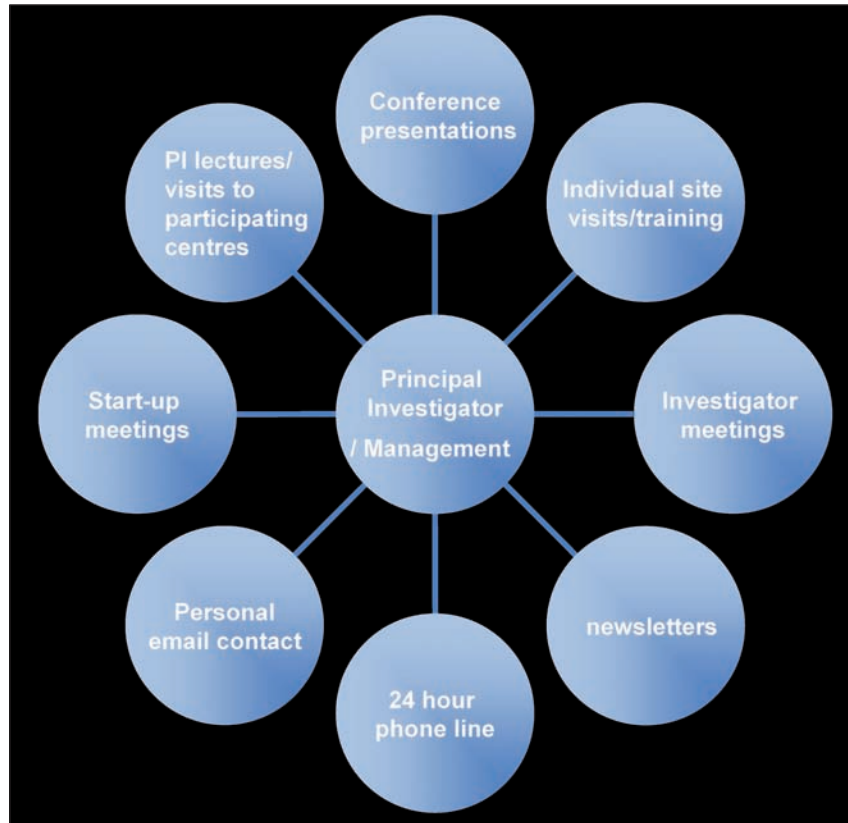


Figure 2
Personalising the trial.

ing centres, current randomisation and also a trial register interest section for any sites wishing to participate or contact the management team.

The web-based database therefore allows for the original study CRF to be retained at each site for audit and privacy purposes, as well as reducing the time spent in identifying and resolving data queries, and minimising data entry errors.

This has been identified as one factor that may assist in increasing efficiency (29). We believe simple study procedures encourage participation in multicentre trials.

Careful monitoring of the recruitment process throughout studies is vital, and enables the management center to identify problem areas at individual sites (25).

These logs can be sent to the data management center on a monthly basis and

tabulated for review by the steering committee. If a site has a lag in recruitment, the research manager or project officer can initiate communication with the site to assist in identifying areas requiring assistance.

Correct and complete study procedures can be checked, including consent, secure data storage, and verification of trial events.

CONCLUSIONS

Large multicenter clinical trials are demanding but ultimately rewarding in that they provide reliable answers to everyday clinical problems.

Clear guidelines on all aspects of the trial procedures assist in a teamwork approach to overcoming the many barriers to successful completion of such trial.

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