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Efficient management of randomised controlled trials: nature or nurture

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A randomised controlled trial sets out to do just one thing—to discover the truth. Pick up any medical journal, and you can read about the need for a good randomised clinical trial to answer a burning clinical question. A trial that will inform, enhance, and, when applicable, change clinical practice. Experienced research committees prioritise the clinical questions that need answering to ensure the health of the nation. They also set guidelines on what constitutes good clinical practice within a research context.[1] Furthermore, the scientific and clinical communities ensure that good scientific modelling is central to trial methodology. How a trial actually happens and how the conclusions that affect clinical practice are arrived at are often less prescribed.

Little is written about the day to day and strategic management of such trials. There are no clearly defined operational models established or any code of practice for managing a randomised controlled trial. The apparent lack of recognition for the role of efficient management in the effective delivery of a trial needs to be addressed. Randomised controlled trials need to be managed like any other organisation. Many clinical trials fail to deliver because of the lack of a practical businesslike approach to getting the job done.

Summary points

- Although the scientific validity of a randomised controlled trial is subject to intense scrutiny, the actual management of the trial often receives little attention
- The knowledge and expertise gained on running earlier trials are not widely disseminated, so new trials are begun from scratch
- Trials need to be marketed properly to ensure that sufficient numbers of participating centres and patients are recruited
- For the day to day running of the trial, robust systems and procedures must be designed that are efficient, effective, and flexible (generic models that can be customised)
- A trial team is needed for the efficient management of a trial and to ease the burden on collaborating groups

Reinventing the wheel

The past 50 years has produced many successful clinical trials, which have changed clinical practice. However, the knowledge and expertise gained on how to run those trials have not been widely disseminated. Again and again, trials are begun from scratch. Often there is nothing but the scientific question along with the enthusiasm and commitment of the principal investigator to make it happen.

A system of "mentoring" and training is being developed by the Medical Research Council and Health Services Research Collaboration to help alleviate needless duplication and provide a network of support for trial teams—in effect, a little "nurturing." In mentoring an experienced trial coordinator works alongside a recently appointed coordinator, giving support and guidance through the setting up phase of a trial on areas unique to clinical trials. The system can also offer ongoing advice and aftercare. Courses on clinical trial management are being developed and will provide training for new and experienced coordinators. The expertise developed in a clinical trial should be valued and not lost as a result of a lack of career structure or a recognised body that could offer direction to individual trialists.

What makes a trial happen?

A randomised controlled trial has a basic scientific methodology. During the long phase of developing a

Tips for marketing a randomised controlled trial

- Budget for costs of marketing when planning the trial
- Striking logo and letterhead
- Editorials or flyers in medical journals
- User friendly, attractive, and stylish trial materials along with tips to ensure their prominence within centres
- Site visits—meet everyone who is involved, directly or indirectly, in the trial
- Targeted poster campaign to encourage recruitment
- Regular newsletters distributed to collaborators and other interested people
- Collaborators' meetings that engender a purpose and esprit de corps—seek opportunities to "piggy-back" small meetings on to other conferences, a cost effective method of getting the message to a wider audience
- Incentives or profile raising products—badges, notepads, pens, certificates of participation
- Partnership with consumer groups—articles in consumer publications

protocol, it will be customised to suit the question being addressed. How the protocol will be put into practice on a day to day basis is rarely considered in any depth until the funding is secured and the clock starts ticking. Trial management involves lateral thinking, good communication, ethical marketing, and common sense. A randomised controlled trial is a huge investment in time, money, and people. For reviewing the literature,[2] developing a protocol, applying for funding, and designing data collection forms there is lengthy consultation and a considered approach, but rarely is this thinking applied to how the trial will actually be managed.

Each trial needs to develop a management blueprint. Setting achievable targets, developing an enthusiastic team, and securing the time and budget to make the whole process efficient and deliverable are part of that blueprint. Assuming that the scientific and clinical questions have been thoroughly reviewed and that the trial has attracted funding on the basis of good science, what are the practical aspects that can lead to the success or failure of a randomised controlled trial?

Marketing

A trial needs to be marketed. A "mentor" working with a trial coordinator on a trial that was failing to recruit subjects asked a simple question, "How do you identify the patients?" The problem turned out to be that general practitioners were unaware that the trial was recruiting patients and needed referrals—an obvious but not uncommon omission. The trial needed to be marketed nationally to achieve its target recruitment.

Trial fatigue can be a problem. Large sample sizes and long recruitment periods can be overwhelming. The trial should always try to reflect routine clinical practice at a local level. When the international stroke trial had been running for three years it still needed to recruit a further 6000 patients at a rate of 700 a month. These numbers have no practical meaning for a working clinician in a small district general hospital. However, when the recruitment target is translated to "Two patients a month from your centre" it becomes a challenge that even a busy clinician can meet. A poster campaign was mounted putting out this message, and the trial reached its target and delivered on time. In the CLASP (collaborative low-dose aspirin study in pregnancy) trial the strategy used to encourage recruitment was: "We are already the biggest trial ever. CLASP can make a major contribution to the world literature." The trial sample made the biggest single contribution to the meta-analyses, more than doubling the number of women studied worldwide.

A clinical trial is a very odd commodity to manage and "sell." It means, in effect, marketing a club—an esprit de corps.[3] Marketing something as nebulous as this is difficult, exciting, and challenging. Clinical trials need to be packaged in such a way that they offer some sort of kudos or recognition to those willing to participate. These aspects of a trial involve delicate, sometimes controversial, management and marketing skills.

Systems, procedures, and plans

Randomised controlled trials depend on systems, plans, and procedures. Recruitment, randomisation, data entry systems, customised filing, and plans for analysis have to be systematised and systematic. In order to maintain these systems the trial team and collaborators need to understand them. The simplest task has to be taken seriously. Every piece of paper that comes into a coordinating centre must be logged and tracked. There needs to be a logical structure, documentation, and accountability. A large randomised trial brings together a variety of disciplines with one aim, to provide reliable evidence. To do this there has to be clear written procedures that can be followed by everyone involved and that take into account differing practices and working environments.

A trial team must be focused. In the CLASP trial the first version of the follow up form did not ask whether the women had suffered from eclampsia: team members working on the document had become sidetracked by "wouldn't it be interesting" questions. The trial team must never lose sight of the main question

Systems, procedures, and plans needed in a clinical trial

- Computerised systems—customised programs
- Customised trial documentation—protocol, information leaflet, data collection forms
- Recruitment systems—plans for raising awareness, simple entry forms, poster campaign
- Randomisation systems—entry forms, telephone service, randomisation envelopes, fax machines
- Data and patient tracking—Office of National Statistics (Britain), overseas offices of national statistics, in house logging systems, unique patient numbering
- Data entry—computer programs, simple data collection forms, validation systems
- Analysis plans—timelines for data cleaning, validation and close out, programs for analysing sample size
- 24 hour, on call, pager service—human interface with the collaborative group

when tempted to take the opportunity to collect data on anything and everything. The catch phrase for randomised controlled trials of the 1980s and '90s has been "large and simple," but simplifying everything is not always useful. Too few data can actually miss the answer to the problem being addressed.

Good quality data are the result of good trial management. Collecting information on a form and entering it onto a computer is simple. However, ensuring that the data are sensible and reliable is a complicated and detailed process. Validation and quality control are crucial. Technology enables us to do this quickly and efficiently, and trials should be managed whenever possible with the most up to date technology. However, there must be an interface with people, and systems must therefore be flexible and bend, within certain boundaries, according to the needs of the people participating in the trial. If there is no flexibility in the systems used for collecting, checking, and entering data, the data will be less useful and the end product will be unreliable.

Communication

Information technology has enabled countries throughout the world to be included in collaborative research efforts with little extra cost. The telephone has been used for the past 20 years as the most secure form of randomisation and continues to be the most used form of communication. Telephone conferencing has meant much cheaper discussions with collaborators on the other side of the world. The most useful communication tool developed over the past 20 years has been the fax machine. In a randomised controlled trial paper is always a problem, and sending it around the world by "snail mail" is inefficient, especially to destinations where there is no guarantee of its arrival. Email is fast becoming the most efficient means of communication, but its use may be limited in clinical trials, where a paper trail is obligatory. We should take the opportunity to use up to date technology to pass on not only the scientific information but models that have been used to develop and manage successful clinical trials, thereby helping to reduce long and costly learning curves.

The trial team

Developing a multiskilled enthusiastic trial team is a long term investment. The size and composition of the trial team will depend on the size and design of the trial and what institution the trial is affiliated to. The trial team will often be made up of experienced secretaries, administrators, and data managers. Initially, they are unlikely to have any specific knowledge or experience of what constitutes good clinical trial management.

Key members of the trial team

- Principal investigator
- Trial coordinator or manager
- Trial programmer
- Data manager or clerks
- Trial statistician
- Trial secretary

Principal investigator—A clinical trial must have a leader who is able to command the respect of fellow collaborators, other clinicians, and the trial team.[3] The principal investigator should show that he or she values the trial team, be supportive and committed, and be available to take the lead on clinical or scientific issues. However, it is not necessary for this person to be engaged with the day to day running of the trial, although this can bring added value. The principal investigator and the trial coordinator have overall responsibility for delivering the trial.

Trial coordinator or manager is a key person, responsible for the day to day management of the trial,[3] although the title for this role is arbitrary. "Administrator" is often used, but it does not reflect the uniqueness of the knowledge required. The trial coordinator manages all aspects of the trial—marketing, finance, staff issues, data collection, centre enrolment, and strategic development of the trial. How do you get a patient "flagged" in Britain? How do you export a drug to Thailand? Who will provide a 24 hour randomisation service? These are the sort of questions that face a trial coordinator on the first day of a new trial. Often trial coordinators work in isolation, going through the painful process of developing complicated systems that have probably been used elsewhere but never written down. There is no manual to use as a reference point.

Trial programmer—A trial needs customised computer programs. The trial programmer should be involved early on in the planning stages, because intricate programs take months to develop. Lack of early input from the programmer can make it necessary to extend the life of a trial, and this has all sorts of knock-on effects for budgets and contracts.

Data managers and data clerks work closely with the trial coordinator in developing systems and getting to know the participating centres and the data on individual patients intimately.

Trial statistician—A randomised controlled trial must have statistical input, but a statistician does not need to be employed full time. In most cases statistical input is required during the planning phase, interim analyses, and final analysis. Therefore, it is possible to employ a statistician on a consultancy basis. When possible, it is preferable to use the services of a statistician in the institution to which the trial is affiliated who could be available at short notice.

Trial secretary—The value of the trial secretary is often underestimated. A randomised controlled trial

will generate an inordinate number of telephone calls and mountains of correspondence, mailshots, newsletters, faxes, and emails. It is crucial that the secretary is pleasant and efficient on the telephone and is able to prioritise his or her work.

Large trials must not produce huge amounts of work for the body of clinicians willing to participate. Consequently, this means a great deal of work for the team of the coordinating centre. Efficiency is paramount. The systems and procedures within the coordinating centre must be simple and focused on the task. Even simply date stamping every piece of paper that comes into the trial office has a purpose, and its value cannot be overemphasised. A data manager working on the long term follow up of a trial should be focused on that particular task and not be distracted by other needs of the trial office. Members of the trial team need to be familiar with all aspects of the trial but should have an in depth knowledge of their own area of work, not only for the trial but for their job satisfaction and career development.

A group of clinicians come together because they want to contribute to the science that forms the basis of their everyday practice. The trial team needs to nurture the collaborative group by helping with the boring mundane aspects of a trial. Nothing should be too much trouble for the trial team: the team should not wait for collaborators to ask for help but should be proactive and make life easier for them. Most importantly, the team should motivate and instil a sense of ownership among the collaborators. This should lead to swift recruitment and good quality data.

A trial cannot be managed by a committee. Although a large randomised trial needs a steering committee to give direction on policy, oversee the professional conduct of the group, and give an independent opinion on management matters, it is not a substitute for trial management. As trial coordinators or managers, we should seek to increase the knowledge base from which trials operate. In order to do this we must value our trial management skills, pass on experience, and develop clinical trial management in a meaningful and professional way.

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Experimentation and social interventions: a forgotten but important history

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The research design of the randomised controlled trial is primarily associated today with medicine. It tends either to be ignored or regarded with suspicion by many in such disciplines as health promotion, public policy, social welfare, criminal justice, and education. However, all professional interventions in people's lives are subject to essentially the same questions about acceptability and effectiveness. As the social reformers Sidney and Beatrice Webb pointed out in 1932, there is far more experimentation going on in "the world sociological laboratory in which we all live" than in any other kind of laboratory, but most of this social experimentation is "wrapped in secrecy" and thus yields "nothing to science."[1]

The Webbs argued for a more "scientific" social policy, with social scientists being trained in experimental methods and evaluations of social interventions being carried out by independent investigators. They were apparently unaware that a strong tradition in experimental sociology had already been established, mainly in the United States. This was a precursor to a period between the early 1960s and the late 1980s when randomised controlled trials became the ideal for American evaluators assessing a wide range of public policy interventions. This history is conveniently overlooked by those who contend that randomised controlled trials have no place in evaluating social interventions. It shows clearly that prospective experimental studies with random allocation to generate one or more control groups is perfectly possible in social settings. Notably, too, the history of

Summary points

Many social scientists argue that randomised controlled trials are inappropriate for evaluating social interventions, but they ignore a considerable history, mainly in the United States, of the use of randomised controlled trials to assess different approaches to public policy and health promotion

A tradition of experimental sociology was well established by the 1930s, built on the early use of controlled experiments in psychology and education

From the early 1960s to early 1980s randomised experiments were considered the optimal design for evaluating public policy interventions in the United States, and major evaluations using this design were carried out

This approach became less popular as policy makers reacted negatively to evidence of "near zero" effects

Lessons to be learnt about implementing randomised controlled trials in real life settings include the difficulty of assessing complex multi-level interventions and the challenge of integrating qualitative data

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