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How to conduct a randomized trial

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ABSTRACT:

Randomized controlled clinical trials represent the gold standard of research into health-care interventions but conducting a randomized trial requires careful planning, structures and procedures. The conduct of a clinical trial is a collaborative effort between investigators, participants and a range of professionals involved both centrally and locally in the coordination and execution of the study. In this article, the key steps to conducting a randomized controlled trial are summarized.

SUMMARY AT A GLANCE

Clinical trials require extensive management and coordination in order to provide appropriate answers to clinical questions about health-care practices and to comply with the standards of good clinical practice. This article describes the steps required to conduct a randomized controlled trial.

Having completed the steps outlined in the previous paper describing how to design a randomized controlled trial[1] you are now at the stage of conducting a clinical trial. We used the example of evaluating the possible benefits of home-based haemodialysis *versus* in-centre haemodialysis on all-cause mortality in patients with stage 5 chronic kidney disease requiring dialysis. Given that a trial to evaluate the benefits and harms of home *versus* in-centre haemodialysis requires over 2000 participants, such a trial will likely involve a national, and probably an international, collaborative effort to initiate and coordinate study sites to recruit patients. In this article, we summarize the key steps required to conduct successfully a randomized controlled trial (Table 1). Details on additional resources to guide trial conduct are summarized in Table 2.

IDENTIFICATION AND ENGAGEMENT OF INVESTIGATIONAL SITES

Due to the large recruitment targets required and the relatively few eligible patients at each centre, clinical nephrology trials are commonly conducted across multiple investigational sites (multicentre research). A recent such example is the IDEAL trial,[2] an investigator-initiated clinical trial comparing early with late commencement of haemodialysis in 828 patients that included 26 study centres in Australia and eight centres in New Zealand, with four regional coordinating centres. For all such trials, identifying appropriately qualified investigational sites is the key to the trial performance.

Potential investigational sites are first contacted by the trial investigators. Frequently, this first point of contact with

Table 1 Steps involved in the conduct of a clinical trial

1. Identify and engage investigational sites
2. Develop trial governance procedures
   a. Clinical trial research agreements (CTRA)
   b. Clinical trials insurance
   c. Approval from an ethics committee
   d. Access and approval to investigate unapproved therapeutic goods (medicines)
3. Develop trial procedures according to good clinical practice
   a. Guideline documents
   b. Laboratory accreditation
   c. Consenting participants
4. Apply and obtain funding
   a. Government agencies
   b. Charitable organizations
   c. Industry support (running costs and intervention-related expenses)
5. Develop recruitment strategies and methods to identify and overcome recruitment problems
6. Develop data capture methods
7. Engage in oversight of trial progress
   a. Monitoring visits
   b. Regulatory audits
8. Develop procedures for adverse event reporting
   a. Data capture
   b. Reporting to ethics committees
   c. Reporting to regulatory authorities
9. Complete trial termination procedures
   a. Close-out visits
   b. Archiving practices – storage of all trial documents

potential sites involves sending a feasibility survey, which gives information about the trial question, the number and type of patients needed within a given time frame, the study procedures to be completed, and the remuneration to the investigational site to support operational aspects of trial participation. These surveys allow the individual research site(s) to consider if they are able to be, or interested in being, involved in the trial, and conversely, for the trial investigators to assess site resources to determine if the centre is suitable for the trial. In the given example of a clinical trial comparing home-based *versus* in-centre haemodialysis we discussed in the earlier companion article, an investigational site might be selected based on the number of haemodialysis patients at the potential site, the site investigator's acceptance of both home and in-centre haemodialysis modalities (acknowledging the relevance of the research question), and the availability or experience of research staff in the renal unit.

RESEARCH GOVERNANCE

Clinical trial research agreements

If the investigational site wishes to take part in the trial, the trial investigators and the individual sites then enter into a clinical trial research agreement. This states that the site will: (i) protect the host institutions and clinical and research staff by procuring the relevant indemnity insurance; (ii) conduct the trial in compliance with good clinical practice (GCP) and under approval by an ethics committee; (iii) comply with the trial procedures developed for data entry and reporting; (iv) permit on-site and remote monitoring and auditing by the investigators (or delegate) or regulatory authorities as required; (v) ensure confidentiality in all trial-related practices; and (vi) retain trial-related documents for the period indicated by the investigators, according to regulatory requirements. Medicines Australia have provided clinical trial research agreement templates that are widely accepted by most Australian hospitals, either unchanged or with minor modifications to suit the policies and practice of the state in which the institution is located. Templates are available on the Medicines Australia website that have been developed specifically for use with: (i) commercially sponsored trials; (ii) contract research organizations; and (iii) collaborative research groups (comprised of physician investigators and/or research academics with no commercial interest in the outcome of the trial). A standardized Medicines Australia Clinical Trial Research Agreement template that is adapted for use in New Zealand is provided by the New Zealand Association of Clinical Research (NZACRes). In the USA, investigators may contract an independent investigator or contract research organization outside of the USA to run a clinical trial, although the US investigators remain responsible for trial conduct under US law.

Clinical trials insurance

Appropriate insurance should be held by the trial investigators. Individual jurisdictions or investigational sites and their host institutions may have specific additional requirements about the level of insurance required before committing to join the trial and, ideally, copies of the investigators' certificate of insurance should be provided to each research site before trial commencement.

Approval from an ethics committee

Central to conducting any research trial involving human subjects is the approval of the trial from a recognised ethics committee. In Australia, applications are made to a human research ethics committee (HREC). This is a requirement of the National Health and Medical Research Council's (NHMRC) National Statement. For multicentre research, a streamlined ethics approval process has been introduced, known as the Harmonization of Multicentre Ethical Review (HoMER), details of which are also on the National Health and Medical Research Council (NHMRC) website. In New Zealand, ethical approval is sought from a Health and Disability Ethics Committee of the Ministry of Health. For multicentre, multi-regional trials, a single application is made to the dedicated Multi-Regional Ethics committee. In Europe,

Table 2 Summary of useful links to websites for more information on specific aspects of trial conduct

	Region		
	Australia and New Zealand	European Union	USA
Clinical trial research agreement	In Australia, templates available on the Medicines Australia website: www.medicinesaustralia.com.au/pages/page39.asp In New Zealand, information available at the New Zealand Association of Clinical Research (NZACRes) website: www.nzacres.org.nz/		
Ethics committees	In Australia, information is available at the National Health and Medical Research Council website: www.nhmrc.gov.au/health_ethics/hrecs/hreclist.htm. Also, refer to the National Health and Medical Research Council National Statement on Ethical Conduct in Research Involving Humans (2007). Available from the Australian Government National Health and Medical Research Council website. www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/e72-jul09.pdf. In New Zealand, information available at the Ministry of Health website: www.ethicscommittees.health.govt.nz/	In the UK, refer to the National Health Service National Patient Safety Agency National Research Ethics Service website at www.nres.npsa.nhs.uk/ In Europe, governed by the European Union Directives 2001/20/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:EN:PDF) and 2005/28/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:EN:PDF)	Further information on US Food and Drug Administration (FDA) regulations relating to good clinical practice and clinical trials is available at the FDA and the Department of Health and Human Services (DHHS) website: www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm
Therapeutic goods approval	In Australia, refer to the Therapeutic Goods Act of 1989 available at the Australian Government Department of Health Office of Legislative Drafting and Publishing (OLDP) website: www.comlaw.gov.au/ComLaw/Legislation/ActCompilation1.nsf/0/840CB0162B421D54CA256FBF00121547/$file/TherapeuticGoods1989_WD02.pdf In New Zealand, refer to the requirements under the Medicines Act available in the New Zealand Medicines and Medical Devices Safety Authority Guideline on the Regulation of Therapeutic Products in New Zealand: www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/Part%2011.doc		Refer to the US Department of Health and Human Services website. FDA regulations relating to GCP and clinical trials: www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm
Good clinical practice	In Australia, see the Therapeutic Goods Administration's note for guidance on good clinical practice (GCP) document: www.tga.gov.au/docs/html/ich13595.htm In New Zealand, see the New Zealand Regulatory Guidelines for Medicines: www.medsafe.govt.nz/hot/Consultation/DraftNZRGMVol3.doc	Governed by the European Union Directives 2001/20/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:EN:PDF) and 2005/28/EC (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2005:091:0013:0019:EN:PDF)	Governed by the FDA regulation on Protection of Human Subjects (21 C.F.R. Part 56): www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm
Informed consent	Refer to the National Health and Medical Research Council website National Statement (www.nhmrc.gov.au/_files_nhmrc/file/publications/synopses/e72-jul09.pdf) and the Therapeutic Goods Administration's note for guidance on GCP (www.tga.gov.au/docs/pdf/euguide/ich/ich13595.pdf)		Informed consent requirements are detailed in the FDA regulation on Protection of Human Subjects (21 C.F.R. Part 56): www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm
Data capture	Best practice recommendations in the Clinical Data Acquisition Standards Harmonization (CDISC CDASH) document (http://xml.coverpages.org/CDISC-CDASH-v10-2008-10-01.pdf)		
Adverse event reporting	In Australia, refer to the NHMRC position statement for adverse event reporting on their website: (www.nhmrc.gov.au/_files_nhmrc/file/health_ethics/hrecs/reference/090609_nhmrc_position_statement.pdf) In New Zealand, information can be found at the New Zealand Medicines and Medical Devices Safety Authority (Medsafe) website: www.medsafe.govt.nz/	New Zealand Medicines and Medical Devices Safety Authority (Medsafe) website: www.medsafe.govt.nz/	Refer to the FDA regulation on Protection of Human Subjects (21 C.D.R. Part 312) available at www.fda.gov/ScienceResearch/SpecialTopics/RunningClinicalTrials/ucm155713.htm

multicentre trials must obtain approval from the ethics committee of the clinical coordinating centre within each European state in which the trial is to be conducted before the trial commences. Before a trial can commence within the European Union, the investigators must also submit a request for authorization to the competent authority of the member state where they propose to conduct the trial. In the USA, ethics approval is sought from institutional review boards as set out in the Code of Federal Regulations Title 21 Part 56 (21 C.F.R. Part 56) of the Food and Drug Administration (FDA) and the Department of Health and Human Services (DHHS).

Access to unapproved therapeutic goods

Clinical trials using a therapeutic product not registered with the Therapeutic Goods Administration of Australia, or using a registered product for an indication other than its registered purpose, must be registered with the Therapeutic Goods Administration under one of two schemes. The Clinical Trial Notification scheme requires the Therapeutic Goods Administration to be notified of the investigational product(s) used in the trial, the institutions at which the trial will be conducted, the investigators of the trial, and the NHMRC-registered HREC that approved the trial conduct at each site. This is a notification scheme where no data is reviewed by the Therapeutic Goods Administration, but responsibility for reviewing safety data from the trial is imposed on the approving ethics committee, and the trial may not commence until the clinical trial notification documents have been lodged. The Clinical Trial Exemption scheme involves submission of an application to conduct the clinical trial, and requires the Therapeutic Goods Administration to review, comment on and approve the application prior to commencement of the trial. These schemes are legislated under Australia's Therapeutic Goods Act of 1989. In New Zealand, the investigators must seek approval for the use of a medicine in a trial when it is a new chemical entity or a new or different form, delivery system or formulation of an established medicine, which does not have consent to market in New Zealand. The Director-General of Health may grant such an approval under Section 30 of the Medicines Act after receiving a favourable recommendation from the Health Research Council's Standing Committee on Therapeutic Trials (SCOTT) about the safety of the medication and the appropriateness of the trial protocol together with approval from an ethics committee. In the USA, the investigators must comply with regulations under the federal Food, Drug and Cosmetic Act and complete an Investigational New Drug application (IND) before a clinical trial can be initiated. For the haemodialysis trial we are considering, neither the Therapeutic Goods Administration nor New Zealand regulations would require notification under either scheme, unless an unregistered (unapproved) investigational product, or a product registered for a different indication, was administered in conjunction with the dialysis intervention.

Good clinical practice

Guideline documents

In order to maintain high standards of clinical research, achieve consistency in the interpretation of guidelines and requirements for new products registration, and reduce delays in drug development, the pharmaceutical regulatory authorities of Europe, Japan and the USA united to form the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The ICH develops and publishes GCP guidelines that describe the responsibilities and expectations of all collaborative partners involved in a clinical trial. Although compliance with ICH GCP is not legislated in Australia, the Therapeutic Goods Administration has adopted the guideline as an accepted standard for the design, conduct and reporting of a clinical trial, and has published a document based on the ICH GCP guideline (CPMP/ICH/135/95), annotated with comments by the Therapeutic Goods Administration. In order to be recognized as a well-conducted trial nationally and overseas, and to maximize patient safety, all Australian-led clinical trials must comply with the Therapeutic Goods Administration's note for guidance on the GCP document. Compliance with the NHMRC's National Statement is legislated under the National Health and Medical Research Council Act of 1992. The ICH GCP guideline also applies to clinical trials conducted in New Zealand; additional requirements may apply when the GCP guideline conflicts with New Zealand legislation. Details are provided in the New Zealand Regulatory Guidelines for Medicines. Guidelines for trials conducted in the European Union are governed by the European Union Directives 2001/20/EC and 2005/28/EC, which operate in addition to ICH GCP requirements. The ICH GCP guideline reflects US regulations for trial conduct, which are governed by the DHHS FDA Code of Federal Regulations.

Laboratory accreditation

Investigators may require that laboratories responsible for performing laboratory testing for the trial have appropriate accreditation. In Australia, the authority responsible for accrediting laboratories is the National Association of Testing Authorities (NATA). The equivalent authority in New Zealand is the International Accreditation New Zealand (IANZ). Usually, the triallists will request a copy of each site investigator's NATA or IANZ certificate before initiating the site to commence recruitment.

Consenting participants

Informed, voluntary consent is a concept fundamental to modern clinical research trials, since the Nuremburg Code of

1949.[3] Although consent to medical treatment in a clinical setting is ruled by the judicial system, usually through case law by suing for trespass or negligence,[4] consent to research is largely regulated by administrative bodies.[5] This means ethical codes of conduct are the most important documents for regulating this practice, in lieu of extensive legislation in Australia. The NHMRC's National Statement and the Therapeutic Goods Administration's note for guidance on GCP provide extensive guidance on the practice of obtaining informed consent from research participants. Investigators can refer to these guidelines when consenting patients to research, particularly with respect to the National Statement's section on consenting participants in an existing, unequal relationship (e.g. that of doctor and patient). In the USA, informed consent requirements are detailed in the FDA regulation on Protection of Human Subjects (21 C.F.R. Part 56).

Funding

Investigators have a long-held belief that the conduct of independent randomized clinical trials is an expensive exercise requiring, in most cases, an interaction with the pharmaceutical or device industry as a sponsor. Funding for investigator-led clinical trials is, on the contrary, available from many governmental sources including the National Institutes of Health and the Department of Veterans Affairs in the USA, the National Health and Medical Research Council (NHMRC) in Australia, and the Health Research Council of New Zealand (HRC). In the UK, funding is available from the Medical Research Council (MRC), the National Health Service, and the Health Technology Assessment Programme (HTA); and in the European Union, funding can be obtained from the Community Research and Development Information Service for Science (CORDIS).

In Italy, the Italian Agency for Drugs (Agenzia Italiana del Farmaco (AIFA)) started a novel funding program for independent research on drugs in 2005, primarily sponsoring randomized trials of interventions which are unlikely to be funded by other bodies (e.g. head to head trials of different therapeutic interventions which are used in standard clinical practice).[6] Charitable organizations and philanthropic agents also offer funding independent of and in partnership with government funding. Industry support may also be available to assist with the running costs and intervention-related expenses in investigator-led trials. Such funding may be available from both pharmaceutical and device companies, although the investigators and the funding source should remain independent, particularly with regard to trial design, analysis and the decision to publish.

Participant Recruitment

Recruitment strategies

Recruitment of patients is frequently *the* rate-limiting step in the successful conduct of a randomized trial: only approximately 10% of patients approached for a clinical trial are eligible and actually enrolled in the study.[7] Recruitment is critical: without participants, a trial will fail. Barriers to recruitment come from both potential participants (too sick; time poor; travel difficulties; fear of research; lack of interest or understanding) and from investigators (losing control over patient care; uncertain clinical equipoise; competing interests for, or lack of engagement with, investigators). A clear overall management strategy to monitor recruitment and respond to recruitment difficulties is essential. Specific strategies to improve recruitment might include:

1 Group seminars with potential participants to explain the study. This has been shown to increase the likelihood of attending a screening enrolment visit.[8]

2 Computer-based querying of potential study participants may reduce the number of pre-screening phone calls and reduce the costs of screening.[9]

3 Defined infrastructure so that trials are integrated into routine practice. This involves improving the network of collaborating clinical trial centres, such as offered by the Australasian Kidney Trials Network.

4 Targeted recruitment teams. Trained recruiters who have enthusiasm and detailed understanding of the trial aims, who employ user-friendly terminology and who appeal to altruism may improve recruitment rates.[10]

Other barriers to trial progress

Other barriers to the success of clinical trials include resource-related barriers (limited funding opportunities and difficulties in sourcing investigational products, especially for clinical research groups trials) and process-related barriers (lengthy legal or contractual negotiations; timelines for ethical review; inconsistencies in regulatory requirements between sites). In order to appropriately manage these potential barriers, these processes need to be realistically timetabled and budgeted for, before trial commencement.

Data capture

All data collection instruments (including paper case record forms, and all forms of electronic case record forms such as database forms and online forms) should be designed according to the Best Practice Recommendations in the Clinical Data Acquisition Standards Harmonization (CDISC CDASH) document. Recommendations in this document include observing the principles of necessity and sufficiency (collecting only the data required to answer the trial questions and to provide appropriate safety information), ensuring adequate review of case record forms by all members of the study team (statisticians, clinicians, programmers, data entry personnel, scientific and regulatory experts and pharmacovigilance personnel), maintaining clarity, and containing clear guidelines for completing data entry. Data collection at

trial sites are monitored at routine monitoring visits carried out on behalf of the investigators.

Study monitoring

Routine monitoring visits

The investigators/institutions are required to conduct the trial in compliance with the protocol agreed to by the investigators and regulatory authorities. The endorsing ethics committees approving a clinical trial have the overall responsibility for the monitoring of that clinical trial. Accordingly, the trial should be monitored by appropriately qualified personnel according to established procedures specified by the trial investigators. The monitor should represent the investigators or be an appropriately qualified delegate. The trial monitor, on a pre-specified schedule, should verify that the site investigators continue to have adequate qualifications and resources; the investigational product or other intervention is being appropriately administered; the approved protocol is being followed; written, voluntary and informed consent is correctly obtained for each subject; the site investigators and the trial staff are adequately informed about the trial; the investigators are enrolling eligible participants; all trial records are accurate, complete and maintained; and the case record form entries can be verified against trial-related source documentation.

Audits

Audits of all aspects of a trial can occur in addition to the investigator-led monitoring of a trial site. Audits are conducted on behalf of investigators to investigate the quality of the research being conducted at an investigator site, including ensuring investigator standard operating procedures (SOP) are being adhered to, that ICH GCP or other appropriate regulatory guidelines are being complied with, and that the trial monitor is providing adequate quality control. Audits from a regulatory authority can also be conducted, as per local legislation and regulations, and include audits of the investigators' systems or processes, the investigator site(s), and external vendors or facilities. All trial audits are required to be performed by an independent person, namely, one that is not directly involved in the system or process that is being audited. Audits of a clinical trial can be routine, or 'for cause', which means triggered by an event or occurrence.

Adverse event reporting

Researchers involved in clinical trials have specific reporting requirements for adverse events (any untoward medical or laboratory occurrence to a trial participant while involved in the trial). Adverse events should be reported to the triallists by the individual site investigators in accordance with the protocol. An adverse event is considered 'serious' (an SAE) if it results in death, hospitalization or extension of hospital stay, permanent disability, congenital defect or any other event classified as 'important' in the opinion of the treating physician. SAE, including suspected unexpected serious adverse reactions (SUSAR, events that are serious, according to the criteria outlined above; unexpected, i.e. not included in the list of known side-effects; and a reaction, i.e. at least possibly attributable to the product), require reporting to the approving ethics committee (Australia) and the investigators, who in turn may have reporting requirements to regulatory authorities (e.g. the Therapeutic Goods Administration), a data and safety monitoring board (DSMB), the trial management committee (TMC) and the supplier of the investigational product. For further details, the reader is referred to the NHMRC position statement for adverse event reporting on their website. In New Zealand, suspected unexpected SAE that occur in a patient within New Zealand and involve breaking of the randomization code must be reported to the responsible ethics committee and the New Zealand Medicines and Medical Devices Safety Authority (Medsafe). Additional information about reporting timelines and forms can be found in the regulatory information at the Medsafe website. In the USA, under Investigational New Drug Application (IND) regulations, the investigators must notify the FDA and all participating investigators in writing of any adverse experience association with the use of the drug that is both serious and unexpected (21 C.D.R. Part 312).

Trial close-out

Close-out visit

The study close-out visit is a specialized monitoring visit that deals with the conclusion of a trial at the site. It involves ensuring all participants' follow-up visits are completed, that site records are all completed and any outstanding queries answered, that all adverse events are followed to resolution, and that arrangements for records archiving have been made.

Archiving

In order to comply with the Therapeutic Goods Administration's requirements, all essential documents from a clinical trial conducted in Australia have to be retained for a period of at least 15 years after the trial has ended. In practice, however, the primary reason for record retention is for product liability, and the potential requirement for investigators to produce records at any time during the life of a product in response to an adverse outcome associated with the product. Essential documents that need to be retained by the investigators include the complete research dataset, safety reports and copies of all relevant ethical approvals. The documents to be retained on-site include the site trial master file, signed patient information sheet and consent forms, and

medical records. At the end of the retention period, it is the investigators' responsibility to inform the site that records can be destroyed.

Reporting trial results

The investigators have a responsibility to disseminate the results of a trial in a timely manner to fulfil obligations to trial participants, ethics committees and funding agencies. Reporting of clinical trial results should conform to the CONSORT guidelines when submitted for publication.[11] A publication requirement of many clinical journals is that the clinical trial must be registered with an appropriate clinical trials registry at the commencement of the trial.

CONCLUSION

When planned and conducted according to the regulatory and ethical principles outlined in this article, a randomized clinical trial has an increased chance of being successfully completed and answering an important clinical question. A trial must protect the welfare and safety of its participants above all else and provide rigorously obtained data to inform clinical decision making. Standard and legislated procedures and guidelines need to be followed throughout a trial to ensure a successful and ethical trial is conducted.

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