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Clinical Research for Nephrologists

How to design a randomized controlled trial

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ABSTRACT:

Randomized controlled trials are the ideal study design to evaluate the effectiveness of health-care interventions. The conduct of a clinical trial is a collaborative effort between participants, investigators and a range of health-care professionals involved both centrally and locally in the coordination and execution of the trial. In this article, the key steps that are required to design a randomized controlled trial are summarized.

SUMMARY AT A GLANCE

Randomized controlled trials are the ideal study design to answer clinical questions about health-care interventions. This article describes the steps required to design a randomized controlled trial.

You are seeing a 54-year-old patient in your routine dialysis review clinic who has been receiving in-centre haemodialysis for 3 months after presenting acutely with end-stage kidney disease due to severe hypertension. As he has no immediate family members who are suitable kidney donors, he now wishes to consider home haemodialysis as a treatment option particularly so he can dialyze overnight, have more flexibility and achieve his goal of returning to work. Your experience of home treatment is consistent with the published work suggesting potential improvements in clinical outcomes with home haemodialysis, although you are aware the information is limited to cohort studies and unreliable to inform clinical decisions. Given the promising information about the benefits of home haemodialysis, the dialysis team in your department is considering setting up a national collaborative effort to conduct a clinical trial comparing in-centre *versus* home haemodialysis specifically to evaluate the benefits of home-based haemodialysis on clinically-relevant patient outcomes.

Making clinical decisions in nephrology is more difficult when evidence to support a clinical question is unavailable or conflicting. Adequately powered, well-conducted and simple randomized trials that evaluate clinically-relevant outcomes, even when negative, answer important and common questions about health-care interventions in nephrology. For instance, results from randomized trials tell us we can be surer that starting haemodialysis at earlier *versus* later stages of deterioration in the glomerular filtration rate does not affect survival,[1] that correcting anaemia does not improve survival in individuals with chronic kidney disease and diabetes[2] and that aiming for a higher haemodialysis dose does not benefit patients.[3]

Table 1 Steps involved in the design of a clinical trial

1. Getting started
   a. Identify the trial sponsor
   b. Decide the question to be answered by the trial (supported by a systematic review)
   c. Develop a trial proposal and assess its feasibility
   d. Obtain financial support
   e. Set up trial infrastructure
2. Preparation phase
   a. Develop protocol
   b. Obtain ethics committee/institutional review board approval
   c. Generate consent forms
   d. Register clinical trial
   e. Develop case record forms

While large collaborative efforts have answered many relevant clinical questions in nephrology, many more questions still remain open. More and better trials are still needed. The relative paucity of good-quality randomized trials in nephrology[4] highlights the need for additional large and simple randomized trials that provide reliable answers to important clinical questions and that are made possible by strong multicentre collaborations within the nephrology community. In this article, we summarize the key steps involved in designing a randomized controlled clinical trial (Table 1). The key steps in conducting a clinical trial are discussed in a companion review article entitled '*How to conduct a randomized trial*'.[5]

GETTING STARTED

Identifying a trial sponsor

Having entertained the idea of setting up a clinical trial evaluating the benefits of home-based haemodialysis *versus* in-centre haemodialysis on clinically-relevant patient outcomes, the next step is to identify an appropriate sponsor for the trial. The sponsor is the person, organization or company that initiates and assumes responsibility for the clinical trial. The sponsor may be a pharmaceutical, device or biotech company, an individual or group of individuals independent of commercial interests, a governmental body/agency that fosters public health initiatives in specific areas, or a collaborative research group (CRG) that brings together physician investigators and academics to facilitate research. In an investigator-led clinical trial, the investigator who generates the concept of the proposed trial, or a representative CRG, assumes the role of trial sponsor. In a study comparing home with in-centre haemodialysis, the sponsor might be a nephrologist who is a clinical leader in a haemodialysis unit that offers home haemodialysis. Alternatively, the sponsor might be a company releasing a specialized home haemodialysis machine that is interested in evaluating the clinical outcomes associated with the use of the device for home haemodialysis.

The trial sponsor has overall responsibility for trial conduct, including protocol development, obtaining ethical approval, selecting qualified investigators, sites and monitors, ensuring compliance with regulations, informing appropriate bodies of adverse events, monitoring the data for safety and efficacy, providing study supplies, and ensuring the data are analyzed and reported in a timely manner. The sponsor may delegate these responsibilities to a contract research organization (CRO) to conduct the trial on their behalf; however, ultimate legal and regulatory responsibility for the trial remains with the sponsor.

Refining the question to be answered by the trial

In this step, the sponsor, funding body and ethics committee must all be sure the proposed trial is a responsible use of health research resources: that it asks a question that needs answering. First, it is important to know whether the trial will address a question that is important to patients and clinicians. Structured consultation of patients and clinicians in the field of kidney disease is warranted. Such consultation recently indicated that patients' key priorities for health research are not necessarily new pharmaceutical agents but include prevention of kidney disease, improving access to transplantation, increasing caregiver support, reducing symptoms and complications of treatment, and improving understanding of psychosocial aspects of chronic kidney disease.[6] Second, the sponsor should know whether the question that the trial will ask is not already appropriately addressed by existing data. This is important ethically: the principles of good clinical practice dictate that before a trial is started, the foreseeable risks and inconveniences should be weighed up against the anticipated benefits. Accordingly, if a clinical question has been addressed by adequately-conducted previous research, then there is no mandate to conduct the trial as every trial participant is potentially exposed to some level of increased risk. If, however, a clinical question about a health-care intervention has not been adequately evaluated before, then the clinical equipoise required to conduct a trial ethically exists; that is, there is genuine uncertainty about whether or not an intervention will be beneficial. Evaluating the existing published work also ensures that the limited funding available for independent clinical research is not wasted on studies that duplicate existing data.

To know whether existing trials address the clinical question, or if the existing trials are suboptimal, investigators should perform a formal systematic review of the intervention question before designing the trial.[7,8] Notably, fewer than 50% of investigators may be aware of an existing systematic review when designing their trials.[9] Publishing and funding bodies have now implemented several innovations to improve the relevance of clinical research through incorporation of existing trial information. The *Lancet* requires that a systematic review or at least a structured qualitative

summary of existing data is incorporated into any trial report published in their journal.[10] The Consolidated Standards of Reporting Trials (CONSORT) statement, designed to improve transparency in trial reporting, strongly recommends placing the results of a trial in the context of existing evidence.[11] The CONSORT guidelines recommend that the sponsor conduct a systematic review of the research question before embarking on a new study or identify a relevant review done by someone else, and then design the study to take account of the relevant successes and failures of the prior studies, and of the evidence within them. In other words, the trial should be planned to fill the relevant knowledge gaps in the existing evidence. In addition, the National Institute of Health Research (NIHR) Health Technology Assessment (HTA) programme in the UK commissions systematic reviews of key clinical questions for policy-makers and funding bodies including the National Institute for Health and Clinical Excellence (NICE), stating that 'individual trials are rarely sufficient to justify new treatments'.[12] Practical information on how to conduct a systematic review and how to appraise the findings of a systematic review are available in other articles in this series.[8,13]

A search of the published work on the question of home *versus* in-centre haemodialysis identifies no relevant systematic reviews or randomized trials answering the clinical question posed, suggesting that a randomized trial comparing home *versus* in-centre haemodialysis is needed.

Developing a trial proposal and evaluating its feasibility

In this step, the sponsor or investigator formulates the exact question that the trial will aim to answer. The clinical question determines the requirements for the trial, including the number of participants, primary outcomes, details of the intervention and comparator, and duration of the trial. A template for a formulated research question is 'In patients with X condition (population), does (intervention) improve (outcome), compared with (comparator)?' For the case scenario being considered here, the research question might be, 'In patients with stage 5 chronic kidney disease requiring maintenance haemodialysis therapy, does home haemodialysis improve all-cause mortality compared with in-centre haemodialysis?'

Assessing the feasibility of such a trial proposal requires a careful, detailed estimate of the number of patients in a defined time period that would likely be able to be enrolled in the study when potential barriers to trial recruitment are considered (Table 2). Typically, such recruitment approximations tend to be overly optimistic (often more than double actual recruitment) and it is therefore often advisable to conduct a site feasibility survey to try to further refine estimates. These estimates should be compared against prospective sample size calculations.[16] Many study proposals fall over at this stage because mortality studies require thousands of patients and most surrogate outcome studies require hundreds of patients to achieve adequate statistical power. For the proposed home haemodialysis study, a sample size of 1075 patients per group (2150 overall) would be required in order to have 80% power to demonstrate a 30% reduction in mortality in the home haemodialysis group compared with the in-centre haemodialysis group, assuming a type 1 error probability of 0.05, median survival of 5 years in the control arm, a recruitment period of 4 years, an additional follow-up time after end of recruitment of 2 years, a 1:1 randomization ratio, a dropout rate of 20% and a drop-in rate of 5% in the intervention arm. This would require involvement of many centres from multiple countries, such that it may be advisable to initially conduct a pilot, or vanguard, study of 50–100 patients to assess recruitment feasibility, and safety and efficacy with respect to surrogate outcome measures (e.g. blood pressure, left ventricular hypertrophy). Simplifying the trial design will also improve the recruitment and progress of a large trial.

As the design and implementation of multicentre clinical trials (such as this one) is challenging to new and established investigators alike, several organizations offer specialized assistance for the coordination and conduct of trials, including assessing feasibility. In nephrology, the Australasian Kidney Trials Network (www.aktn.org.au) is specifically established to help potential investigators: (i) develop a well-formulated research question; (ii) identify and obtain adequate funding; (iii) assess the feasibility of the proposed clinical trial; (iv) identify participating centres; and (v) provide necessary infrastructure support.[17] In the UK, the Renal Association together with Kidney Research UK oversee the UK Kidney Research Consortium which can advise on the development of new clinical research (www.renal.org) in partnership with the National Institute of Health Research which oversees Clinical Research Networks, including the Renal Specialty Group (www.crncc.nihr.ac.uk/). In the USA, specialized trial networks assist with clinical research although the areas of expertise tend to focus on specific conditions, for example, rare diseases (The National Institutes of Health Rare Clinical Diseases Research Network) and acute kidney injury (Acute Kidney Injury Network (AKIN)).

Financial support

Randomized clinical trials are expensive and need funding support from governmental and/or non-governmental agencies. A number of reasons are behind the extremely high cost of modern trials (in the USA, the cost to enrol a trial subject is approximately $US 15 000).[18,19] Clinical trials represent potential income for pharmaceutical companies reaching hundreds of millions of dollars. Such a potentially lucrative financial investment can be reflected in high levels of compensation to research groups and the contract research organizations who run the trials. Such reimbursement may be

Table 2 Potential barriers to trial recruitment and feasibility

Category	Barrier
Protocol-related	Restrictive inclusion or extensive exclusion criteria
	Excessive scheduled visits
	Excessive or invasive tests
	Excessive or incomprehensible patient information sheet and consent forms
	Protocol complexity and stringency
	Excessive length of follow up (leading to investigator fatigue)
Infrastructure	Lack of staff (e.g. research nurse, data managers)
	Information technology constraints (internet access, IT support, computing facilities)
	Insufficient research office space
	Excessive ethics committee requirements/costs
	Contract negotiations (inadequate and/or excessive delays)
	Inadequate pharmacy/radiology/pathology facilities
	Inadequate facilities for storage/archiving
	Lack of adequate equipment (e.g. –80°C or –20°C freezers, centrifuges, 12-lead electrocardiogram machines)
	Excessive overhead charges
Research staff-related	Inadequate time
	Preconceived biases about study interventions
	Inadequate trial reimbursement
	Excessive paperwork
	Fear of regulatory authority audit
	Inadequate research experience
	Involvement in competing trials
	Unhappiness with publication authorship status
	Trial fatigue
	Lack of awareness of overall trial recruitment
Clinician/treating physician-related[14]	Inadequate time
	Excessive paper work
	Research protocol too complex; difficulty following trial procedures
	Fear of losing control over patient care
	Interference with doctor–patient relationship
	Perceived conflict between roles of physician and scientist
	Lack of staff to support referred patient
	Lack of knowledge about clinical trials; inadequate research experience
	'Inviting patients to enter a trial is embarrassing'[15]
	Feelings of personal responsibility if one treatment clearly better
	Difficulty with informed consent
	Lack of support from trial staff
Patient-related	Fear of getting a placebo in place of actual treatment
	Belief that study treatment will be inferior to standard treatment
	Fear of side-effects
	Fear of being a 'guinea pig'
	Worry about uncertainty of treatment offered in trials
	Fear that trial involvement would have a negative effect on the relationship with their physician
	Mistrust of medical profession
	Unfavourable social circumstances for trial participants (e.g. young children, transportation difficulties)
	Costs incurred through participation (e.g. childcare, travel)
	Comprehension/literacy/language difficulties
	Cultural barriers
	Religious beliefs
	Non-compliance
	Psychological issues

well above a reasonable and realistic cost that covers trial expenses and may include monetary incentives for patient recruitment. Income from trial research may also be used by institutions to fund other non-trial-related research and drive up per-patient costs in the trial. Making a trial simpler and investigator-led may reduce costs and still ensure that the trial is large enough to answer the trial question.[20] A large and simple trial of in-centre *versus* home haemodialysis would have few inclusion and exclusion criteria (all patients on chronic haemodialysis treatment through permanent

access), collect minimal data at entry and follow up, and not include extensive and careful follow up of complicated outcomes (e.g. quality of life and echocardiography). Investigator-initiated trials currently coordinated by the Australasian Kidney Trials Network have recruitment targets varying between 110 and 1200 patients and cost between $A2000 and $A6000 per patient to run.

In the USA, the National Institutes of Health supports both investigator-initiated studies and requests for applications for newer trials that they consider would be of importance to kidney disease patients.[21] The National Health and Medical Research Council (NHMRC)[22] and the Health Research Council of New Zealand (HRC),[23] in addition to charitable groups and trusts, offer competitive funding grants for clinical research in Australia and New Zealand, respectively. Pharmaceutical, device and biotech companies frequently sponsor large clinical trials and serve as a significant source for funding of newer interventional products. However, pharmaceutical companies will usually assess the investment in terms of financial return, so if the potential trial question or intervention is not marketable or does not otherwise represent a commercial benefit to the company, significant funding from this source may be difficult to procure. This is often the case for large trials of long established, 'off-patent' interventions or process of care strategies, such as early intervention or screening, that are unlikely to reap substantial commercial gain for a pharmaceutical company.

Setting up the trial infrastructure

In this step, the sponsor of the trial identifies the personnel necessary for the conduct of the trial. Although there is no standardized structure for a clinical trial, the most common organizational structure is to have three primary teams (or committees) (Fig. 1). The first of these is the trial management committee. This group of individuals, led by the chief principal investigator (PI), is responsible for the day-to-day management of the trial, and may include other clinicians, a statistician, trial manager, research nurse and data manager. This group reports to the trial steering committee which provides overall supervision of the trial and ensures that it is being conducted in accordance with good clinical practice. The trial steering committee may be headed by an individual who is independent of the investigators who designed and implemented the study, and may include statistical expertise, lay individuals, site PI and site or regional study coordinators. The data monitoring committee (also known as the data safety monitoring board (DSMB)) is the third major body overseeing the trial. The data monitoring committee is a group of independent advisors who review the trial protocol before it is implemented, review study implementation and progress, evaluate the accruing unblinded data to detect evidence of early, significant benefit or harm for participants while the trial is in progress, and make recommendations to the clinical research group concerning the trial's continuation, modification and/or publication. No standardized structure for the data monitoring committee is required, although it has been recommended that the committee is established before the trial begins and is typically made up of 5–7 members (an uneven number may help decisions made by voting) headed by an experienced chair together with clinicians with expertise in the specific disease and/or treatment under study, biostatisticians, epidemiologists and ethicists/patient advocates. The trial's statistician or an independent statistician is responsible for preparing updated reports to the data monitoring committee, which communicates its findings to the trial steering committee, sponsor or PI in an advisory capacity.[24] In New Zealand, a Data Monitoring Core Committee, established by the Health Research Council, provides independent monitoring of clinical trials conducted in New Zealand. Guidelines are available at the Health Research Council Data Monitoring Core Committee website (www.hrc.govt.nz/root/pages_regulatory/Data_Monitoring_Core_Committee.html). An outcomes or end-points committee may also be formed for the trial which consists of independent experts in the field who adjudicate trial end-points and who are blinded to treatment allocation.

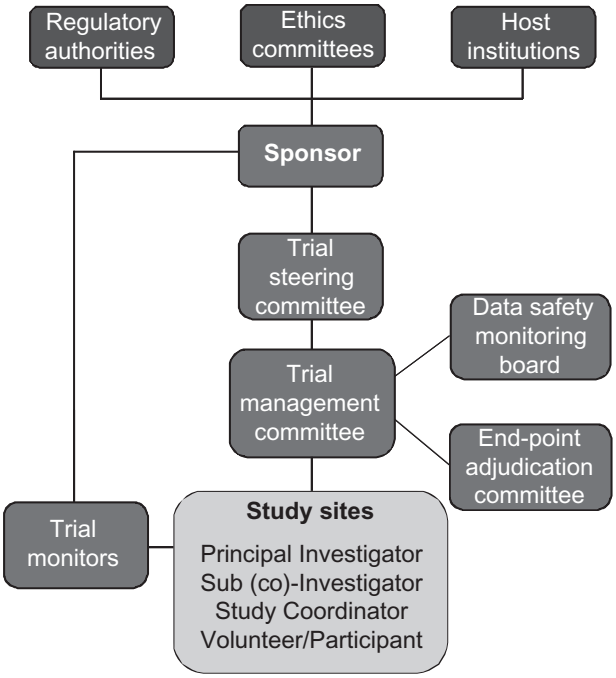

Fig. 1 Infrastructure of clinical trial.

PREPARATION PHASE OF THE TRIAL

Protocol

At this step, the trial protocol is developed. This is a detailed document that sets out the conduct of the study, ensures

consistency in the running of the study across all participating staff and institutions, helps the study team develop case report forms and trial databases, and is used to seek approval from ethics committees and financial support from funding organizations. The protocol describes the trial background, rationale, objectives, methodology (design, experimental and control interventions, blinding, patient selection, outcome measures), procedures (visit schedule, patient recruitment, patient consent, registration and randomization, allocation concealment, treatment plan and modifications, monitoring), laboratory procedures and investigation, routine sample handling and storage, substudy plans, data management, quality assurance, statistical considerations (including sample size calculations and a statistical analysis plan), ethical considerations, trial organization and publication policy. The document may need to be supplemented by a separate manual of operations providing more specific procedural detail. The investigator's brochure is an adjunct to the protocol and is a compilation of the clinical and non-clinical data on the trial intervention. Its purpose is to provide the investigators and others involved in the trial with the information needed to facilitate their understanding of the rationale for the trial, and their compliance with the protocol.

Successful trial protocols often have relatively simple designs, non-onerous visit and investigation schedules, and clearly defined eligibility (inclusion and exclusion) criteria, which ideally strike a balance between being sufficiently broad and inclusive to optimize trial feasibility and generalizability, and sufficiently narrow and exclusive to optimize trial safety (by excluding patients who might be adversely affected by the intervention) and enhance trial power (by selecting populations with high event rates for the outcome in question). Table 2 describes the common barriers to recruitment in randomized trials, that need to be specifically anticipated, monitored for, and addressed by the sponsor and the trial management committee. It is also very useful when planning for recruitment to develop a trial schema that pictorially represents the primary design features (Fig. 2).

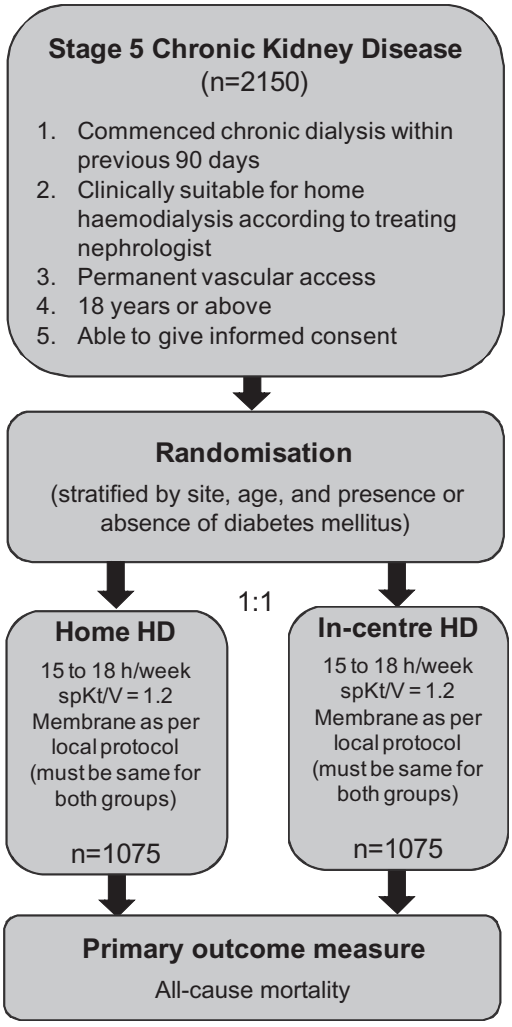

Fig. 2 Possible schema for a trial of home *versus* in-centre haemodialysis (HD).

Patient information sheet and consent forms

The patient information sheet and consent form is created following the study protocol development and submitted to the ethics committee for approval before participant enrolment. Patient information sheet and consent forms help volunteers understand the key aspects of the research of which they are considering taking part. In general, a patient information sheet and consent form will describe the background to the trial ('why is the trial necessary and what it aims to find') and explain the risks and benefits of study intervention. Information about reimbursement for time and expenses are also detailed in the patient information sheet and consent form. There is also a space for the participant (or legal representative where appropriate), the investigator, and a witness where required by state legislation or hospital practice, to sign the form to confirm that each participant gave voluntary, informed consent to participate in the research. The forms are most appropriately written in plain language[25] aiming for a reading age of between 10 and 14 years.[26]

Ethics committee/institutional review board approval

All clinical trials need approval from an ethics committee before patient enrolment. An ethics committee generally is responsible under good clinical practice guidelines for reviewing as a minimum the trial protocol, investigator's brochure, informed consent forms and patient information documents, procedures for patient recruitment, and the

investigator(s) qualifications. In Australia, ethics approval is provided by human research ethics committees (HREC) under the auspices of the National Statement on Ethical Conduct in Human Research (2007) issued by the NHMRC. The National Statement requires that all research involving human participants be reviewed and approved by a HREC. More information can be obtained from the Australian Government NHMRC website (www.nhmrc.gov.au/health_ethics/hrecs/hreclist.htm). In Australia, the development and implementation of a national system where the single ethical review of a HREC can be recognized by all institutions participating in a collaborative research project (Harmonization of Multicentre Ethical Review (HoMER)) is still ongoing. In New Zealand, applications for ethics approvals are made to the local health and disability ethics committees established by the Ministry of Health. When a proposed trial is to be conducted in more than one region, a single application is made to the dedicated multi-regional ethics committee. More information is available from the New Zealand Health and Disability Ethics Committees website (www.ethicscommittees.health.govt.nz/). In addition to ethics approval, the trial should be designed in accordance with the Guideline for Good Clinical Practice (GCP) of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) (www.ich.org/LOB/media/MEDIA482.pdf). Changes to the trial protocol need to be approved by the appropriate ethics committee before implementation. Even after obtaining ethics approval, PI at each research site still need to engage with their institutional research governance processes to obtain the authorization to commence research.

Clinical trial registration

This step involves the registration of the trial with a recognized trial registry. International bodies including the revised Declaration of Helsinki, the World Health Organization and member journals of the International Committee Medical Journal Editors (ICMJE) require registration of the clinical trial in a publicly accessible registry before the onset of patient enrolment. A trial must be registered before patients are enrolled if it prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome. A medical intervention is any intervention used to modify a health outcome and includes, but is not limited to, drugs, surgical procedures, devices, behavioural treatments and process-of-care changes. A trial must have at least one prospectively assigned concurrent control or comparison group in order to trigger the requirement for registration, but does not need to be randomized. The trial can be registered through any of the following websites, free of charge: the International Standard Randomized Controlled Trial Number Register (http://isrctn.org); the Australia and New Zealand Clinical Trials Registry (ANZCTR) (www.anzctr.org.au/); and the US National Institutes of Health's website (http://clinicaltrials.gov/). The Food and Drug Administration (FDA) Amendment Act of 2007 also requires the disclosure of results within 12 months of trial completion for all FDA-approved drugs and devices. Registering a trial not only helps investigators meet the requirements of the ICMJE but also facilitates collaborative efforts between investigators working on similar topic.[27]

Case report form development

Case report forms (CRF) are designed and piloted at the beginning of the trial to collect the relevant data in a standardized manner. Most often, study data are collected in paper form in the participating centres and transcribed into a centralized electronic database. Therefore, the CRF should have clear questions that are consistent with the protocol together with clear instructions and definitions for completing the required fields. The CRF should be carefully monitored against the primary data (source data) collected at participating centres. Any changes or corrections made to the case report form should be documented and signed by the study staff at the participating institutions.

CONCLUSION

In summary, a well-designed, adequately-powered randomized trial will provide a definitive answer to a specific clinical question. Critical factors for a successful trial design include finding or performing a formal systematic review of the intervention question, undertaking a careful assessment of trial feasibility (including anticipated recruitment relative to calculated sample size requirements), obtaining adequate financial support, establishing appropriate trial infrastructure, developing a clear and unambiguous study protocol (paying particular attention to simple trial design and non-restrictive patient selection), registering the trial and developing CRF. Clinical trial networks, such as the Australasian Kidney Trials Network (www.aktn.org.au), can help facilitate trial design and conduct.

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