

CHAPTER 3.3: INTERVENTIONS AND THERAPIES, INCLUDING CLINICAL AND NON-CLINICAL TRIALS, AND INNOVATIONS

INTRODUCTION

Clinical research

Clinical research increasingly involves a range of different health professionals studying a wide range of matters, including disease prevention and causation, diagnostic methods, treatments, and effects of and response to illness. Such research can occur in a number of settings, including public and private hospitals and clinics, other institutions or organisations, community settings, and general or specialist medical practices.

This chapter focuses especially on randomised clinical trials, even though clinical trials are not always randomised. Further, as noted below, randomisation may be used in other areas of human research (eg education research) and therefore some of the ethical issues outlined will be relevant to such research.

At times it may be difficult to distinguish clinical and related research from quality improvement and clinical audit. In such situations, guidance is available from the NHMRC publication *When does quality assurance need review by a Human Research Ethics Committee?* (NHMRC 2003).

Innovations in clinical practice

Innovations in clinical practice and complementary medicine include new diagnostic or therapeutic methods that aims to improve health outcomes but have not yet been fully assessed for safety and/or efficacy. The spectrum of innovations may range widely from minor variations or extensions of existing methods, to new indications, through to completely novel technologies. Where a proposed intervention is innovative and/or experimental, this should always be made clear to those who might be subject to it.

Whether a change in an individual's investigation or treatment is simply an innovation or actually constitutes clinical research is generally a matter for the responsible clinician's judgement, guided by institutional policies. Systematic evaluation of an innovation is research and requires ethical review.

Clinical and other trials

A clinical trial is a form of human research designed to find out the effects of an intervention, including a treatment or diagnostic procedure. A clinical trial can involve testing a drug, a surgical procedure, other therapeutic procedures and devices, a preventive procedure, or a diagnostic device or procedure.

Clinical trials of new therapeutic substances are typically categorised into Phase I, II, III or IV trials. The following definitions, adapted from the Therapeutic Goods Administration (TGA), describe these phases in trials of medications:

- Phase I studies involve the first administration of the medicine to humans. Medicines are usually given to small numbers of healthy volunteers, but sometimes to people affected by the disease the medicine is intended to treat. The purpose may be to determine the medicine's safety, pharmacokinetics, pharmacological activity, side effects, preferred routes of administration, or appropriate doses (for later studies). The studies are usually undertaken in centres equipped for specialised monitoring and a high degree of surveillance.

- Phase II studies are typically the first trials of the medicine in people with the health condition for which the medicine is intended. The principal aim is to determine efficacy and safety and establish an appropriate dosing regimen. These studies are undertaken in a small number of closely supervised patients and conducted by researchers regarded as specialists in the health condition and its treatment.
- Phase III studies are undertaken if the Phase II studies indicate the medicine has potential benefits that outweigh any hazards. The studies involve greater numbers of patients with the health condition under study, and aim to determine whether the medicine confers clinical benefit in that health condition and whether the incidence and nature of adverse effects are acceptable.
- Phase IV studies are those undertaken after the medicine has been approved for marketing for the treatment of a particular disease or for a particular indication. They may include studies to compare the medicine with a wider range of therapies, and may also further investigate the use of the medicine in the normal clinical setting of the disease (which may differ markedly from the conditions under which pre-marketing trials were conducted). Such studies also gather more comprehensive safety data, adding to the information known from the pre-marketing studies.

In pharmaceutical and medical device trials there are established codes of good clinical research practice that define clearly what is meant by a clinical trial for those purposes (see the *Australian code for the responsible conduct of research*). This chapter's main application is to biomedical clinical trials, but it also applies to any other interventions claiming therapeutic benefit. Trials involving experimentation with therapeutic goods, whether drugs or devices, that are not yet registered, listed or entered on the Australian Register of Therapeutic Goods (ARTG) are subject to regulation by the TGA.

Application of randomised trial methods to other areas of human research

Research methods intended to avoid or reduce bias include randomisation and 'blinding' participants and researchers to the identity of agents being compared. These research methods were first applied to the study of new therapies, and are now used in various other fields including, for example, psychology and education. Researchers who propose to use such methods should be aware of the ethical issues that may arise in the design and conduct of such research. In particular, paragraphs 3.3.3 and 3.3.6 will apply in all situations, while other paragraphs may be relevant depending on the nature of the research and the relationship between the researcher and potential participants.

Research to which this chapter applies must be reviewed and approved by a Human Ethics Research Committee (HREC) rather than by one of the other processes of ethical review described in paragraphs 5.1.7 and 5.1.8 (page 78).

Values, principles and themes that must inform the design, ethical review and conduct of all human research are set out in Sections 1 and 2 of this National Statement. The guidelines and headings below show how those values, principles and themes apply specifically in research that is the subject of this chapter.

GUIDELINES

Research merit and integrity

- 3.3.1 Health care and medical institutions should establish standards to determine when an innovative intervention requires systematic investigation to determine its safety and efficacy.
- 3.3.2 When such systematic investigation is required, it should be treated as clinical research needing formal consideration by an HREC.

3.3.3 Researchers should show that:

- (a) the research is directed to answering a specific question or questions;
- (b) there is a scientifically valid hypothesis being tested that offers a realistic possibility that the interventions being studied will be at least as beneficial overall as standard treatment, taking into account effectiveness, burdens, costs and risks;
- (c) the size and profile of the sample to be recruited is adequate to answer the research question; and
- (d) the research meets the relevant requirements of the *CPMP/ICH Note for Guidance on Good Clinical Practice (CPMP/ICH-135/95)*, *ISO 14155 Clinical Investigation of Medical Devices*, and the TGA.

3.3.4 Researchers must inform the HREC of:

- (a) any business, financial or other similar association between a researcher and the supplier of a drug or surgical or other device to be used in the trial;
- (b) any other possible conflicts of interest; and
- (c) any restrictions on publication.

3.3.5 In any clinical research, especially clinical trials, an HREC should be satisfied that:

- (a) funding is sufficient to conduct and complete the trial as designed;
- (b) any payment in money or kind, whether to institutions, researchers or participants, will not adversely influence the design, conduct, findings or publication of the research; and
- (c) the facilities, expertise and experience available are sufficient for the trial to be conducted safely.

Justice

- 3.3.6 The research methodology should provide a rationale for the selection of participants and a fair method of recruitment (see paragraph 1.4, page 12).

Risks

- 3.3.7 In research without likely benefit to participants, any known risk to participants should be lower than would be ethically acceptable where there are such likely benefits. In 'first-time-in-humans' research projects, risks are uncertain, and recruitment into the study should therefore be gradual and monitored with special care.
- 3.3.8 In clinical research, where patient care is combined with intent to contribute to knowledge, any risks of participation should be justified by potential benefits to which the participants attach significance.
- 3.3.9 The prospect of benefit from research participation should not be exaggerated, either to justify to an HREC a higher risk than that involved in the participant's current treatment or to persuade a participant to accept that higher risk.
- 3.3.10 The use of a placebo alone or the incorporation of a non-treatment control group:
- (a) is ethically unacceptable in a controlled clinical trial where:
 - (i) other available treatment has already been clearly shown to be effective; and
 - (ii) there is known risk of significant harm in the absence of treatment;
 - (b) may be considered if there is genuine uncertainty as to whether currently available treatments have a net clinical benefit.

Records

- 3.3.11 Data should be accurately recorded in a durable and appropriately referenced form that complies with established legislation, policies and guidelines. Where a trial is using materials of biological origin, or other materials where there is limited experience of their long-term use, records should be preserved for long enough to enable participants to be traced in case evidence emerges of late or long-term effects (see *Australian code for the responsible conduct of research*, paragraph 3.1.1).
- 3.3.12 Before beginning the clinical phase of the research, researchers should register clinical trials in a publicly accessible register.

Respect

- 3.3.13 Due to the potential complexity of information to be provided to participants, the requirements of paragraphs 2.2.2 to 2.2.6 (page 19) should be carefully considered and followed. Written information should not be unduly long or complex. Adequate time should be allowed for prospective participants to read and take in what is proposed, and they should be encouraged to ask questions.
- 3.3.14 Particular care should be taken in clinical trials to make it clear to participants whether there is intended to be any therapeutic benefit to them from the trial.
- 3.3.15 It should always be made clear to those who might be subject to a proposed intervention whether it is innovative and/or experimental.
- 3.3.16 In clinical research, where patient care is combined with an intent to contribute to knowledge, the following matters should be carefully weighed:
- (a) the seriousness of the condition being treated;
 - (b) the risks involved in the proposed research; and

- (c) the possible effects of an unequal or dependent relationship between the treating health professional or researcher and the potential participant (see *Chapter 4.3: People in dependent or unequal relationships*).

3.3.17 Where the researcher is also the treating health professional, it should be considered whether an independent person should seek the consent of potential participants.

3.3.18 An HREC should be satisfied that:

- (a) payment in money or incentives of any kind, whether to researchers or participants, does not result in pressure on individuals to consent to participate (see paragraphs 2.2.10, and 2.2.11, page 20);
- (b) research participants are adequately informed of the funding arrangements of the research and given the option of knowing the details of any capitation payments to researchers or clinicians; and
- (c) it has been made clear to participants whether they will have continued access after the trial to treatments they have received during the trial, and on what terms.

Monitoring of approved clinical research

3.3.19 The ultimate responsibilities of institutions for monitoring the conduct of approved research are described in *Chapter 5.5: Monitoring approved research* (page 91–92). In clinical research, and especially clinical trials, research sponsors also have such responsibilities.

3.3.20 Institutions responsible for the conduct of clinical research should require that:

- (a) monitoring arrangements are commensurate with the risk, size and complexity of the trial;

- (b) for each project, there are mechanisms for reporting and reviewing:
 - (i) serious adverse events at any site for which the institution is responsible;
 - (ii) serious adverse drug reactions (ADRs), serious unexpected suspected adverse reactions (SUSARs), and serious adverse device events from any site for which the institution is responsible;
- (c) for a large multi-centre trial, a Data and Safety Monitoring Board (DSMB) is used and there is a mechanism for informing the HREC of any relevant emerging data from the DSMB;
- (d) for a local trial, there is an identified person/s or committee with suitable expertise to assist and advise the HREC about reports of serious adverse events.

3.3.21 HRECs should review approved projects in light of information provided to them under paragraph 3.3.20.

3.3.22 In addition to the requirements outlined in *Chapter 5.5: Monitoring approved research* (page 91–92), the granting and continuation of ethical approval of clinical research must be on the condition that, for any trial site under the HREC's responsibility, the researcher:

- (a) conducts the trial in compliance with the approved protocol;
- (b) provides reports of the progress of the trial to the HREC, at a frequency directed by the HREC (but at least annually), and related to the degree of risk to participants;
- (c) informs the HREC, and seeks its approval, of amendments to the protocol including amendments that:
 - (i) are proposed or undertaken in order to eliminate immediate risks to participants;

- (ii) may increase the risks to participants; or
- (iii) significantly affect the conduct of the trial;

- (d) notifies, in the manner and form specified by the HREC, any serious adverse events at any of those trial sites;
- (e) informs the HREC as soon as possible of any new safety information from other published or unpublished studies that may have an impact on the continued ethical acceptability of the trial or may indicate the need for amendments to the trial protocol;
- (f) informs the HREC, giving reasons, if the trial is discontinued before the expected date of completion; and
- (g) for trials with implantable medical devices, confirms the existence of, or establishes, a system for
 - (i) tracking the participant, with consent, for the lifetime of the device; and
 - (ii) reporting any device incidents to the TGA.

Discontinuance of trials

3.3.23 It may be unethical for a researcher to continue a trial if:

- (a) there are or have been substantial deviations from the trial protocol;
- (b) side-effects of unexpected type, severity, or frequency are encountered; or
- (c) as the trial progresses, one of several treatments or procedures being compared appears to be so much better or worse than the other/s that the continuation of the trial would disadvantage some of the participants.

The clearer it becomes that one treatment is substantially better or worse than the others, the stronger the need to consider discontinuing the trial.

Insurance

- 3.3.24 Institutions must be satisfied that sponsors of trials have made the indemnity or insurance and compensation arrangements required by *CPMP/ICH Note for Guidance on Good Clinical Practice* (CPMP/ICH-135/95), *ISO 14155 Clinical Investigation of Medical Devices* and the TGA.
- 3.3.25 In addition to the requirements in paragraph 3.3.24, institutions must also have arrangements to compensate participants for harm resulting from negligence in research to which this chapter applies.