

# **Ethical Guidelines for Intervention Studies: Revised edition**

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## Foreword to the 2012 edition

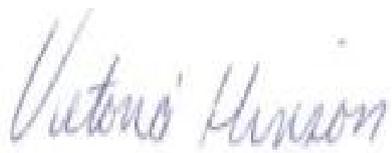
These *Guidelines* were first released in November 2009; the current document is a revision. The Health Committee's inquiry into improving New Zealand's environment to support innovation through clinical trials (June 2011) resulted in significant changes to the ethics review process, as reflected in the revised *Standard Operating Procedures* (SOPs) for Health and Disability Ethics Committees.

This 2012 revision aims to provide consistency with the SOPs. These *Guidelines* have been updated to remove process guidance, and ensure that policy previously included in the *Operational Standard for Ethics Committees* is now addressed by these *Guidelines*. The revision did not fundamentally change the existing ethical standards and principles set out in these *Guidelines*.

As previously, the *Guidelines* are directed primarily to investigators, who have the main ethical responsibility for good study conduct. But the *Guidelines* also continue to be directed to others with a role in health and disability research ethics – particularly the ethics committees that review studies against established ethical standards. The key objectives of developing national ethical guidelines are to:

- safeguard the rights and interests of participants in research and innovative practice
- promote high-quality ethical research for the social, cultural and economic wellbeing of society
- reflect the principles of the Treaty of Waitangi and protect Māori cultural interests, promote the wellbeing of Māori and ensure mechanisms for Māori participation in both research and ethical review
- foster awareness of ethical principles and practices among health care providers, researchers and the wider community
- give due consideration to local and national community views and perspectives on ethical review.

The 2012 revision was subject to a targeted consultation and the Committee is grateful to all who have contributed.



Victoria Hinson  
**Chair, National Ethics Advisory Committee**  
**Kāhui Matatika o te Motu**

## Foreword to the 2009 edition

Health professionals offer ‘interventions’ to prevent, diagnose or treat illness or disease. Intervention studies are their main source of reliable information about the safety and benefit of such interventions. These studies have been key sources for the large improvements in health care during the last 30 years.

In an intervention study, the investigator intervenes and then studies the effects of the intervention. This is usually done before a new intervention is approved for clinical use. A clinical trial of a new blood pressure medicine is an example of an intervention study. Through intervention studies, investigators can exercise the sort of critical thinking, innovation and evidence-based development of practice that improves patient care. This means that high-quality intervention studies are good for patient care.

For participants in an intervention study, the overall benefits and risks of the intervention being studied are uncertain. Most studies evaluate novel interventions that are thought likely to be improvements over current practice, but a study participant may or may not benefit from the intervention. There is also the potential for harm. It is therefore essential that intervention studies be ethically sound. One aspect of this involves weighing risks and benefits. Studies must also be scientifically sound, so that the results can reliably guide future health care.

In general, intervention studies involve higher risk than other kinds of studies. One reason for this is that two different roles and motivations are involved. A clinician wishes to provide the best care and an investigator wishes to add to knowledge, so; for the clinician-investigator there is some potential for conflict between these two roles. Another reason for the higher risk is that in intervention studies the investigator controls, and in many cases alters, the interventions that study participants receive, and this has the potential for both benefit and harm.

There is also greater potential for commercial influence in some intervention studies than in other sorts of study, with consequently greater potential for conflict between commercial interests and the interests of the participants and the public. Any potential conflict of interest for the investigators and/or sponsors of the study needs to be declared and steps taken to ensure possible conflicts do not undermine the ethical or scientific integrity of the study. There is a particular need to pay attention to non-therapeutic intervention studies, in which participants receive interventions that are not intended to benefit them.

These *Ethical Guidelines for Intervention Studies* (the *Guidelines*) aim to contribute to better health outcomes and reduced health inequalities for New Zealanders by assisting researchers to perform sound intervention studies. They aim to help investigators to think through and take responsibility for the ethical issues in their studies. The *Guidelines* may also be useful for training potential investigators. They bring together in one document, and build on, the best current national and international guidance on intervention studies. Some technical language is used, and this is defined in the Glossary at the end of the *Guidelines*.

In producing these *Guidelines*, the National Ethics Advisory Committee has undertaken a thorough and inclusive process. This has included discussion with key informants, public consultation, consultation with key stakeholders and multiple peer review. The *Guidelines* reflect the significant improvements suggested by a wide range of stakeholders through this process, and the Committee is grateful to all who have contributed.



Andrew Moore  
**Chair (2001–2010), National Ethics Advisory Committee**  
**Kāhui Matatika o te Motu**

## Note

If you wish to comment on your experience with using these *Guidelines*, please contact the National Ethics Advisory Committee at the address below. The Committee intends to review the *Guidelines* by the end of 2015 and would be grateful for your comments to inform that process.

Email: [neac@moh.govt.nz](mailto:neac@moh.govt.nz) (with 'Intervention Studies' in the subject line)

Postal address: Intervention Studies, National Ethics Advisory Committee Secretariat, PO Box 5013, Wellington 6145.



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# 1 Introduction

- 1.1 These *Ethical Guidelines for Intervention Studies* (the *Guidelines*) are issued in accordance with the statutory function of the National Advisory Committee on Health and Disability Support Services Ethics (the National Ethics Advisory Committee – Kāhui Matatika o te Motu, or NEAC), under the New Zealand Public Health and Disability Act 2000, section 16 to ‘determine nationally consistent ethical standards across the health sector’.
- 1.2 The *Guidelines* accord with the expectation stated in NEAC’s terms of reference that NEAC will:
- ... develop and promote national ethical guidelines for health research ... and innovative practice in an ethical manner and should establish parameters for, and provide guidance on, the ethical review of such types of health research (NEAC 2008: 39–40).
- 1.3 The *Guidelines* constitute ethical standards for intervention studies, for the purposes of the Code of Health and Disability Services Consumers’ Rights 1996 (the Code of Rights), Right 4(2).
- 1.4 An intervention study may be a ‘clinical trial’ for the purposes of the Accident Compensation Act 2001, section 32.
- 1.5 An intervention study may be ‘medical or scientific experimentation’ or ‘medical treatment’ for the purposes of the New Zealand Bill of Rights Act 1990, sections 10–11.
- 1.6 Some intervention studies may be ‘human reproductive research’ for the purposes of the Human Assisted Reproductive Technology Act 2004 (the HART Act). The *Guidelines* may then constitute ‘applicable ethical standards’ for the purposes of the HART Act 2004, section 27(4).
- 1.7 The *Guidelines* are based on statements from New Zealand and international guidelines (see the References). They accord with key international guidance, including the *World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects* (WMA 2008), the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002) and the *ICH Harmonised Tripartite Guideline: Guideline for good clinical practice* (ICH 1996). Researchers should be familiar with relevant sources of international and domestic ethical guidance materials (see the References). In the domestic context, researchers should also be aware of guidelines relating to research involving Māori, such as the Health Research Council’s *Guidelines for Researchers on Health Research involving Māori*, and NEAC’s resource document *Māori Research Ethics: An overview* (in press).
- 1.8 These *Guidelines* are written primarily for investigators conducting intervention studies. They are structured and ordered around ethical issues relating to the process of designing and conducting a study, from the beginning stages of developing a study question through to the communication of study results and post-study access to interventions.

- 1.9 Detailed matters concerning health and disability ethics committee (HDEC) review of intervention studies are addressed in the standard operating procedures (SOPs) for HDECs established under the New Zealand Public Health and Disability Act 2000, section 11. The SOPs were created in 2012 in response to the Government response to a Select Committee inquiry into improving New Zealand's environment to support innovation through clinical trials. They provide procedural guidance to HDECs and researchers, and set out the scope of HDEC review and information about how HDECs process applications. These *Guidelines* set the ethical standards that must be met or exceeded in all health and disability research, whether or not it requires HDEC review. The SOPs apply to intervention studies, but these *Guidelines* have precedence over the SOPs on any point of conflict relating to ethical standards and principles that must be met or exceeded in all health and disability research.
- 1.10 These *Guidelines* include references to legislation. It is the investigator's responsibility to comply with all relevant legal requirements, including those set out in the:
- Accident Compensation Act 2001
  - Care of Children Act 2004
  - New Zealand Bill of Rights Act 1990
  - Protection of Personal and Property Rights Act 1988
  - Health and Disability Commissioner Act 1994
  - Health Practitioners Competence Assurance Act 2003
  - Code of Rights
  - Privacy Act 1993
  - Health Information Privacy Code 1994
  - Human Tissue Act 1998 (particularly sections 9, 14, 19, 21, 22, 24 and 31).
- 1.11 The Code of Rights is a regulation issued under the Health and Disability Commissioner Act 1994, section 74. It sets out 10 rights of health and disability services consumers, including those involved in research. Investigators conducting intervention studies should be familiar with their responsibilities under the Code of Rights, and should consider their study in light of the rights of (proposed) participants. The Code of Rights is available on the Health and Disability Commissioner's website ([www.hdc.org.nz](http://www.hdc.org.nz)). Particular rights are referenced at relevant points throughout these *Guidelines*.

## 2 Definitions and scope of the *Guidelines*

- 2.1 These *Guidelines* are intended primarily to guide investigators conducting intervention studies, and to assist them to conduct high-quality studies.
- 2.2 Scientific matters that raise specific ethical issues are discussed in these *Guidelines*, but the *Guidelines* do not contain a complete description of all scientific issues relating to intervention studies.
- 2.3 The *Guidelines* are designed to apply to intervention studies in health or disability settings, but they may also be relevant to similar studies (eg, some studies of interventions in educational, sociological or psychological settings).

### Definition of ‘intervention study’

#### Intervention study

- 2.4 An intervention study is a study in which the investigator controls and studies the intervention(s) provided to participants for the purpose of adding to knowledge of the health effects of the intervention(s). The term ‘intervention study’ is often used interchangeably with ‘experimental study’. Many intervention studies are clinical trials.

#### Intervention

- 2.5 In an intervention study, an intervention may be, for example:
- preventive, diagnostic or therapeutic
  - a new intervention (including medication, psychological treatment, health education, radiation therapy, a vaccine, a surgical device, or a surgical or other technique)
  - an intervention established in practice but not adequately substantiated by scientific evidence
  - an established intervention being used for a new purpose
  - the withholding or altered administration of an established intervention
  - a change in the method of delivering care designed to add to knowledge of the health effects of the change (eg, the use of directly observed therapy for the treatment of tuberculosis as opposed to patient-administered medication, a new model of care, use of guidelines or protocols, use of different information formats, or care undertaken by a different group of professionals)
  - a study that has no therapeutic value to the subject, conducted with healthy volunteers, giving them an intervention previously untested in humans to evaluate its safety.
- 2.6 Common types of intervention studies are explained in the Glossary. Not listed in the Glossary are emerging trial designs, for which specific ethical issues may arise.

## Features of intervention studies

### Participants

- 2.7 The primary participants in most intervention studies are volunteers who have given their informed consent to participate. In some studies the primary participants are grouped in communities (eg, geographical communities or organisations such as schools).

### Study groups

- 2.8 To enable comparison of outcomes for participants, most intervention studies include a 'control' group and an 'intervention' group. The control group receives a standard or established intervention, a placebo or no intervention. The 'intervention' group receives the intervention that is being studied. In some studies a participant may act as her or his own control.

### Allocation

- 2.9 Assignment of participants to study groups may be:
- randomised, by a method (eg, a random numbers table or computer-generated random sequence) that uses chance to assign participants, or groups of participants, with a predetermined probability to each study group
  - quasi-randomised (eg, through minimisation, or assignment by date of birth, day of the week, medical record number or order of recruitment to the study)
  - non-random.

### Allocation concealment

- 2.10 Allocation concealment involves preventing those assessing participants for entry into a study from knowing which study group the participant will be entered into. The aim of this practice, which is implemented prior to entering a participant in a study, is to prevent selection bias and to ensure the assignment of participants to study groups is truly random. This is particularly important in studies where blinding is not possible (see below). Examples of allocation concealment include using sequential sealed opaque envelopes, or allocation through an independent telephone service.

### Blinding

- 2.11 Blinding is valuable in studies where there is subjectivity in assessing an outcome (eg, reduction in pain). Blinding prevents people involved in the study from knowing which intervention a participant has been allocated to. It is used in some intervention studies to minimise bias and maximise the reliability of study findings. In a single-blind study one group is blinded. Usually this group is the participants, who do not know which study group they have been allocated to. In a double – blind study two groups are blinded.

Usually these two groups are the participants and the investigator(s) administering the interventions: neither group knows which intervention the participants have been allocated to. Other groups that may be blinded include the outcome assessors, data analysts and those writing the study report.

## Scope of these *Guidelines*

- 2.12 These *Guidelines* apply to intervention studies in New Zealand health and disability settings. Intervention studies differ from observational studies because, in the latter, the study investigator has no control over the study conditions and merely collects data. For guidance on observational studies, see the *Ethical Guidelines for Observational Studies* (NEAC 2012).
- 2.13 The *Guidelines* do not normally concern interventions in observational studies (eg, biopsies), where such interventions are carried out to obtain information rather than to study the effect of the intervention.
- 2.14 Intervention studies may involve the collection and use of human tissue. Specific guidance on the collection and use of human materials can be found in *Guidelines on Ethics in Health Research* (HRC 2005b).
- 2.15 All clinical research involving the manipulation of human genetic material must be approved by the Health Research Council's Gene Technology Advisory Committee. See also:
- *Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research* (Ministry of Health 2006a)
  - *Guidelines for the Use of Human Tissue for Future Unspecified Research Purposes* (Ministry of Health 2007)
  - the Human Tissue Act 2008 (in particular sections 9, 14, 19, 20, 21, 22, 24 and 31).
- 2.16 Some studies to evaluate health products are not intervention studies because their primary purpose is to study intervention presentation or marketing development, rather than health or disability outcomes.
- 2.17 There is an overlap between intervention studies and innovative practice. Innovative practice is practice that is a planned deviation from currently accepted practice.
- 2.18 The scope of these *Guidelines* includes innovative practice in the context of an intervention study.
- 2.19 When intending to use an innovative practice, health practitioners have an obligation to objectively evaluate its efficacy and safety. This is best done through an intervention study.

## 3 Ethics of intervention studies

- 3.1 This section concerns the worth of intervention studies, and responsibilities for their ethical review. Investigators are responsible for identifying and satisfactorily addressing ethical issues in their studies (see also section 4: 'Underlying ethical considerations'). Where there is more than one investigator, the coordinating investigator has overall responsibility for the ethics of the study.
- 3.2 The greater the potential harm from a study, the closer the scrutiny that is required of the ethical issues raised. All intervention studies require ethics committee review. The ethics committee should assess whether the researcher has ensured that the study will meet established ethical standards.

### Worth of intervention studies

- 3.3 Intervention studies, especially randomised controlled trials, are often the best way of evaluating the worth of a treatment or a preventive intervention such as health promotion, screening or immunisation. They are valuable for this purpose. Without intervention studies, the quality of health care would advance more slowly, and opportunities to improve public health would be lost. For this reason, the ethical issues for these studies need to be widely understood and well addressed.
- 3.4 The potential benefits of intervention studies include:
- providing objective results that establish the safety, efficacy, effectiveness or cost-effectiveness of new and established interventions
  - developing practitioners' skills in critical thinking, innovation and evidence-based practice.
- 3.5 To make an optimal contribution, intervention studies must be of high scientific quality, and their ethical issues must be well understood and addressed.
- 3.6 The public are entitled to health and disability support services that are safe and effective. Organisations that provide health care and disability support should foster high-quality intervention studies, because these contribute both directly and indirectly to service safety and quality.

### Benefits to participants

- 3.7 People have a range of motives for participating in intervention studies. These can include gaining benefit for themselves or for other individuals in the future, helping to contribute to knowledge, and contributing benefit to communities, including benefit sharing and reciprocity.

## Risk in intervention studies

- 3.8 In general, close ethical scrutiny is appropriate for intervention studies because the potential harms are generally greater than with other types of study, due to the intervention itself. In addition, intervention studies may involve conducting research in the context of clinical care, and this creates the potential for conflict between the roles of investigator and clinician.
- 3.9 The level of risk that is acceptable is primarily a matter for potential participants to decide. For this reason, informed consent is a central concept (see also 'Free and informed consent', paragraphs 6.6–6.22).
- 3.10 Potential harms to participants in intervention studies can include physical harms such as adverse events or lack of efficacy from the intervention as well as psychological harm. The potential for harm is particularly important in non-therapeutic studies, where there is no expected compensatory benefit from the intervention provided. At a community level, potential harms may involve an inequitable burden without commensurate benefit to the community. Sometimes the benefits and harms may accrue to different individuals in an intervention study (eg, in randomised controlled trials of screening).
- 3.11 The potential risks of an intervention study must be proportional to the potential benefits.

## 4 Underlying ethical considerations

- 4.1 The ethical considerations stated in this section are important to the design and conduct of intervention studies. The application and weighting of these considerations will vary depending on the nature and circumstances of the intervention study in question.
- 4.2 Investigators should consider the features of a proposed study in light of these ethical considerations, and should then satisfactorily resolve any ethical issues raised by the study. Not all ethical considerations weigh equally.

### Respect for persons

- 4.3 Every person has the right to be treated with respect. (See also the Code of Rights, Right 1(1).)
- 4.4 Respect for people, and for their rights, incorporates at least two fundamental principles.
- (a) Respect for autonomy requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self – determination. This may apply on an individual or collective basis.
  - (b) Protection of people, particularly those with impaired or diminished autonomy, requires that those who are dependent or vulnerable be afforded security against harm. (See also the Code of Rights, Right 7(2) and (3); and ‘Vulnerable people’, paragraphs 5.28–5.35.)

### Justice

- 4.5 Justice requires that, within a population, there is a fair distribution of the benefits and burdens of participation in a study and, for any participant, a balance of burdens and benefits. Accordingly, investigators must:
- (a) avoid imposing on particular groups an unfair burden of participation in intervention studies (eg, vulnerable members of a community should not bear disproportionate burdens of studies from which other members of the community are intended to benefit)
  - (b) design studies so that the inclusion and exclusion conditions for participants are fair. (See also the criteria in ‘Inclusion and exclusion of participants’, paragraphs 5.26–5.27.)
- 4.6 Justice involves reducing inequalities. Decision-making about study questions and processes should include consideration of the potential to reduce health inequalities.
- 4.7 The Treaty of Waitangi is the founding document of New Zealand. The principles of partnership, participation and protection implicit in the Treaty should be respected by all researchers, and, where applicable, should be incorporated into all health research proposals (HRC 2005b). The principles can be explained as follows:

- partnership: working together with iwi, hapū, whānau and Māori communities to ensure Māori individual and collective rights are respected and protected in order to achieve health gain
  - participation: involving Māori in the design, governance, management, implementation and analysis of research, particularly research involving Māori
  - protection: actively protecting Māori individual and collective rights, and Māori data, cultural concepts, norms, practices and language in the research process.
- 4.8 There should be due recognition of Māori as the tāngata whenua and indigenous people of Aotearoa New Zealand.
- 4.9 Any potential cultural and ethical issues pertaining to Māori must be addressed through appropriate engagement with Māori, which may include discussions with appropriate representatives of specific whānau, hapū and iwi as determined by the scope and method of the study.
- 4.10 Comprehensive, high-quality Māori health research and information can inform both the Government and iwi on the matter of health priorities, and can assist whānau, hapū and iwi to be involved in meeting these priorities.

## Beneficence and non-maleficence

- 4.11 The principle of beneficence refers to a moral obligation to act in a way that will benefit others. ‘Non-maleficence’ refers to an obligation not to inflict harm on others (Beauchamp and Childress 2001).
- 4.12 In an intervention study the risks of the study should be reasonable in light of the expected benefits. The greatest risk is the potential for harm to study participants. This is particularly significant given that benefits often accrue to society but only in some cases to study participants. The greater the risk of harm from the study, the greater should be the care in addressing the ethical issues raised.
- 4.13 A study is within the range of minimal risk if potential participants can reasonably be expected to regard the probability and magnitude of possible harms from participation in the study as no greater than those encountered in everyday life (eg, where the only foreseeable risk is discomfort).
- 4.14 A study warrants greater provision for the protection of participants if they are to be exposed to more than minimal risk.

## Integrity

- 4.15 The investigator’s commitment to the advancement of knowledge entails a duty to conduct honest and thoughtful inquiry and rigorous analysis, and to accept responsibility for her or his activities in relation to research participants and communities.

- 4.16 In intervention studies there is the potential for personal bias in the analysis and presentation of results. All investigators need to be aware of this potential and conduct studies with objectivity, free from any influences that might compromise the scientific credibility of the study. The potential for personal bias or expectation is also a reason for blinding investigators and data analysts (see also 'Blinding', paragraph 2.11).

## Diversity

- 4.17 As they conduct intervention studies, investigators should understand, respect and put in place processes that recognise diversity among participants and their communities. (See also the Code of Rights, Right 1(3).)

## Addressing conflict of interest

- 4.18 Conflict of interest occurs when professional judgement concerning a primary interest, such as a patient's welfare or the validity of a study, tends to be influenced by a secondary interest, such as financial gain, special loyalties or protection of career advancement opportunities.
- 4.19 If an investigator has a conflict of interest, it can compromise study design or conduct, or the reliability of study findings. It can also expose study participants to (risk of) harm or inconvenience.
- 4.20 In intervention studies, potential for conflict of interest may arise when the investigator:
- is remunerated for participant recruitment (eg, with per capita payments)
  - has a commercial interest in the intervention or financial links to the study sponsor
  - will benefit in professional or academic terms from involvement in the study.
- 4.21 Investigators should disclose to relevant other parties (including the ethics committee, funder, employer, sponsor and study participants) any perceived potential or actual conflict of interest she or he has in relation to any others involved with the study. As appropriate to the circumstances, any conflict of interest should be avoided. Where this is not practicable, conflicts should be minimised and managed, using strategies such as oversight and disclosure.
- 4.22 Conflict of interest may also arise when the investigator is a participant's usual health or disability service provider. This may cause a conflict between the investigator role and the clinician role. In some circumstances this dual role will be appropriate. However, this possible conflict should always be disclosed and discussed with any potential participants.
- 4.23 Other members of the study team, such as research nurses, may also be placed in positions of conflict of interest if their employment prospects, job continuation or remuneration depend directly on their recruiting participants into studies.

## 5 Study and protocol design

### Study question

- 5.1 Investigators should undertake studies that address important health and/or disability problems.
- 5.2 Investigators should develop clear study questions that identify the participant population, the intervention and the main outcome of interest. Normally the outcome(s) to be studied should be clinically significant.
- 5.3 Every study question should be based on a thorough review of the relevant literature.

### Study design

- 5.4 The study design should be the one best suited to answer the study question, while minimising harm, maximising benefit and meeting other ethical standards.
- 5.5 Scientific soundness is ethically important. Projects without scientific merit needlessly expose participants to risk and misuse their time, and waste resources.
- 5.6 The intended number of participants in an intervention study should be sufficient to generate reliable study findings, and the consequent recruitment targets should be realistic. Statistical issues relating to trial design, sample size and analysis can be complex, and usually require expert advice.
- 5.7 The study protocol should contain an overview of the planned statistical analyses, and these planned analyses should be adhered to in conducting the study.
- 5.8 Assignment of participants to study groups is best done by randomisation. This process tends to make study groups reliably comparable and minimises biases, especially uncontrolled confounding. Quasi-randomised or non-random methods are generally less reliable in this regard because of their potential to allow other factors to influence the assignment of participants to study groups. Allocation concealment also improves study validity and design through preventing selection bias (see also 'Features of intervention studies', paragraphs 2.7–2.11).
- 5.9 Use of blinding is desirable in an intervention study design when it can be shown that it has methodological advantages and minimal risks (see also 'Blinding', paragraph 2.11).
- 5.10 Every effort should be made to ensure complete follow-up of all study participants. Incomplete follow-up means there is data missing from the study. This will be for non-random reasons and has the potential to compromise the reliability of the study findings (see also paragraph 6.20).

- 5.11 Peer review of the scientific validity of a study's protocols is beneficial, and is advised for all studies that pose more than minimal risk. Further advice about features of robust peer review is provided in Appendix 1.

## Comparison groups

- 5.12 Investigators should treat actual and potential study participants fairly, both in relation to one another and in relation to similarly placed non-participants.

## Best intervention standard

- 5.13 An intervention study meets the best intervention standard if the intervention(s) in the study are tested against the best proven intervention(s) available outside the study. In many settings there might be more than one intervention that is equivalent to the best, according to the current evidence.
- 5.14 All intervention studies should meet the best intervention standard, unless there are only temporary and minimal departures from the best intervention standard and the departure (and any risk posed) is justified in relation to the overall potential benefits of the study.
- 5.15 Withholding a proven intervention for a short time, whether or not it is replaced by a placebo, can sometimes be ethically justified to validate a measurement technique or to confirm the sensitivity of a therapeutic study design. An investigator who proposes any such approach should justify this to an ethics committee and explain how it can be undertaken without significant risk of harm to participants.
- 5.16 In some cases, one or more interventions provided in an intervention study are equivalent to the best proven intervention available locally outside the study but are known to be inferior to the best proven intervention available internationally. In such cases, the study can be justified only if the world-best intervention is unlikely to be available locally for the duration of the study and if the study can be justified in terms of its potential benefit to the community from which the participants are drawn. The same considerations apply to New Zealand-sponsored studies conducted in countries with less access to health interventions than New Zealand.
- 5.17 Investigators should ensure that participants understand that their participation in an intervention study is not designed to benefit them more than the benefit they would gain if they were instead receiving the best proven intervention available outside the study. (See also 'Equipose standard', paragraphs 5.18–5.21.)

## Equipoise standard

- 5.18 An intervention study meets the equipoise standard if the evidence is 'equally poised' as to the overall balance of risks and benefits of each of the interventions offered in the study, so that it cannot be determined in advance which of the groups in a proposed study will be better off.
- 5.19 Any intervention study to compare two or more interventions should be designed to meet the equipoise standard. For example, study participants may not be assigned to different interventions when the available evidence demonstrates that one intervention has a better expected overall balance of benefits over risks than the other(s).
- 5.20 Equipoise is a matter of the evidence that should inform the decisions of study designers and study investigators. In the case of some proposed studies there may be reasonable professional debate about whether or not the evidence is in equipoise. However genuinely felt, an individual feeling of certainty or uncertainty is not enough to demonstrate the presence or absence of equipoise.
- 5.21 In addition to equipoise of evidence, the preferences of individual participants are important. For example, a potential participant might have a strong preference for the less radical of two alternative interventions that are in equipoise. If a potential participant has a strong preference for one of the options over the other(s), they may wish to decline to participate once given full information about the study.

## Use of a placebo

- 5.22 Use of a placebo or no intervention as a control may be ethically acceptable in an intervention study when:
- there is no proven effective intervention, or
  - withholding a proven intervention would not expose the participant to any additional risk of serious or irreversible harm but, at most, would expose them only to temporary discomfort or delay in relief of symptoms, or
  - there are compelling methodological reasons to believe that using an established effective intervention as comparator would not yield reliable findings on safety or efficacy, and use of a placebo would not add any risk of serious or irreversible harm to participants.
- 5.23 In some intervention studies all participants receive the best proven current intervention, and are given either a placebo or the study intervention as well. This approach does not raise any particular ethical issues, because the best proven current intervention is still given to all participants. A similar situation may also arise with other study designs.

- 5.24 When a placebo control is used, the investigator should ensure that each participant is fully informed about:
- any intervention that will be withdrawn or withheld for the purposes of the study
  - the consequences that can reasonably be expected from not having this intervention
  - the scientific justification for proceeding with a placebo-controlled study.
- 5.25 A placebo control study should also meet other ethical requirements, such as the best intervention standard (see 'Best intervention standard', paragraphs 5.13–5.17).

## Inclusion and exclusion of participants

- 5.26 Inclusion of participants in intervention studies must be equitable. Investigators may not exclude participants on the basis of sex, ethnicity, national origin, religion, education or socioeconomic status, except where such exclusion or inclusion is essential to the purposes of the study.
- 5.27 Inclusion and exclusion of participants affect the extent to which study findings can be generalised. To contribute to an equitable distribution of study benefits and burdens, investigators should, when practicable, consider including all those who may benefit from the study findings.

## Vulnerable people

- 5.28 Vulnerability is a broad category. It describes people who have restricted capability to make independent decisions about their participation in the study (ie, who might traditionally be regarded as lacking the capacity to consent to participate). It also encompasses people who may lack the ability to consent freely or may be particularly susceptible to harm either because of their health status, physical or mental capacity or employment status, or as a result of imprisonment. Non-exhaustive examples of potentially vulnerable people include:
- children and young people
  - people with mental illness
  - people with serious intellectual disability
  - people with English as a second language and/or a different cultural background to the investigators (for studies whose details are primarily, or only, stated in English)
  - people whose freedom to make independent choices is restricted (eg, prisoners, employees of a sponsoring company or students)
  - people with serious illness for which the study treatment offers potential benefits that substantially exceed those of any other available treatment.
- 5.29 It is important to remember that even if a group is identified as likely to be vulnerable, the label may not apply to all individuals in such groups, and even where it does apply, it may do so only intermittently.

- 5.30 Vulnerable people should have the opportunity to be included in high-quality studies on questions that might affect their health, taking the following into account.
- The study should ask questions that matter to the participant’s community, and the answers should benefit the community.
  - Studies should not be performed with vulnerable groups if they can be adequately performed with other groups.
  - Where a study with a vulnerable group is conducted, it should involve the least vulnerable people in that group (eg, older rather than younger children).
  - Intervention studies should be conducted only if the risk to vulnerable people is at an acceptable minimum. (See also paragraph 5.35 below.)
  - Study participation should be a matter of free and informed decision-making by study participants wherever possible. (See also the Code of Rights, Right 7(2) and (3); and the guidance referred to in paragraph 5.35 below.)
- 5.31 The interests of vulnerable individuals must be protected, and these individuals must not be exploited for the advancement of knowledge. Adherence to this principle is especially important if any of the interventions being studied are invasive.
- 5.32 When a vulnerable person is competent to decide on participation in a study for himself or herself, that person’s decision should be respected. Even when a vulnerable person is competent to decide her or his own study participation, it is often appropriate to notify and seek advice from a person or persons with knowledge of, or responsibilities for, that vulnerable person. (See also ‘Non-consensual studies’, paragraphs 6.24–6.29.)
- 5.33 Where a study involving vulnerable people is conducted, additional support (often in the form of extra time, resources – such as modified information sheets or means of information delivery – and assistance) might need to be provided to ensure that such people can participate fully.
- 5.34 If the competence of a vulnerable person to decide her or his own study participation is unclear, it may be appropriate for an investigator to seek both the informed consent of that person and the informed agreement of another person who is interested in, or has responsibilities for, that person’s welfare. (See also ‘Non-consensual studies’, paragraphs 6.24–6.29.)
- 5.35 Further specific guidance for research involving particular vulnerable groups (eg, children, people with intellectual disabilities, unconscious people, people with a terminal illness and older persons) is provided in the appendices to this document.

## Skills and resources

- 5.36 Studies should be undertaken only by investigators and research teams with the necessary skills and resources to do so. These skills and resources include those needed to deal with any contingencies that may affect participants.

- 5.37 Necessary skills include competence in:
- the field of study, demonstrated by knowledge and experience
  - administering study interventions
  - monitoring the health of participants throughout and after the study
  - identifying and applying relevant study methods, with the ability to take full responsibility for proper study design, conduct and analysis
  - ethical conduct of research, with the ability to take full responsibility for ethical considerations.
- 5.38 An investigator should proceed with a study only when the locality (eg, staff, facilities and equipment) is known to be adequate. This includes the capability to provide emergency medical care of an acceptable standard, if required. An acceptable standard is to be determined having regard to the anticipated risk of the study to participants, and is the standard reasonably to be expected of the facility in which the study is undertaken, or at least the standard expected of a competent general practitioner working in her or his surgery. (See also ‘Study locality’, paragraphs 5.45–5.47.)
- 5.39 All those responsible for study conduct must be provided with enough information to ensure the safety of participants.
- 5.40 Investigators must operate under professional standards or employment requirements that oblige them to maintain the confidentiality of patient data.

## Study protocol

- 5.41 All intervention studies should be conducted according to written protocols. The amount of detail in the written protocol and the extent of protocol review processes should be sufficient to ensure appropriate conduct of the study and to cover the level of risk the study presents to participants.

## Registering studies

- 5.42 The purposes of study registration are to avoid duplication of studies and to foster the publication of key study outcomes. All clinical trials (this includes Phase I to Phase IV trials) should be registered with a World Health Organization (WHO)-approved register. Such registers include, but are not limited to, the Australian and New Zealand Clinical Trials Registry (ANZCTR), the International Standard Randomised Controlled Trial Number (ISRCTN) Register and the ClinicalTrials.gov trial registry maintained by the United States National Institutes of Health.
- 5.43 Registered trial details should include the data items identified by the WHO Trial Registration Data Set, including:
- public and scientific titles
  - the sponsor(s)

- the study intervention(s)
- the primary and secondary outcomes
- the target sample size.

~~5.44 — New Zealand-based clinical trials must be registered on the ANZCTR ([www.anzctr.org.au](http://www.anzctr.org.au)). International trials that have a New Zealand arm should likewise be registered with an appropriate register.~~

## Study locality

- 5.45 Investigators should ensure that they comply with internal organisational requirements when conducting intervention studies. The appropriate approach will vary from organisation to organisation; as such, organisations might also specify their own processes regarding notification or approval.
- 5.46 The appropriateness of the study locality should be considered in terms of the following factors.
- The facility must be of an adequate standard to ensure safe and appropriate conduct of the study. Meeting this standard requires appropriate expertise of staff to conduct the study and manage any adverse events that may result.
  - The facility must be of an adequate standard to implement the study without any adverse effect on access to treatment at that facility.
- 5.47 For information on locality authorisation required as part of HDEC approval, see the SOPs ([www.ethics.health.govt.nz](http://www.ethics.health.govt.nz)). Early engagement in the locality authorisation process is desirable.

## Studies with distinctive features

### Non-therapeutic studies

- 5.48 Therapeutic intervention studies examine interventions or procedures that hold the prospect of direct diagnostic, therapeutic or preventive benefit for individual participants. Non-therapeutic studies examine interventions that do not hold the prospect of direct diagnostic, therapeutic or preventive benefit to individual participants. Types of non-therapeutic studies include some phase I studies (see also ‘Phase I studies’, paragraphs 5.50–5.51), bioequivalence studies and bioavailability studies (see Glossary).
- 5.49 A non-therapeutic intervention study is justified only when the importance of the objective outweighs the inherent risks and burdens to the participant, and participants are well informed of the possible risks (see also ‘Non-consensual studies’, paragraphs 6.24–6.29).

## Phase I studies

- 5.50 Phase I studies test interventions in human populations, often for the first time (see Glossary). These interventions may already have established risk profiles from other studies in humans (eg, a new combination of two established agents where the potential interaction between them is in question rather than the tolerability of either used on its own). Some phase I studies are ‘first-in-human’ studies, where subjects are administered an intervention that has not previously been given to humans. In these circumstances the investigators rely on pre-clinical data and, where available, previous human experience with similar interventions. Some first-in-human studies therefore may be of significantly higher risk to subjects.
- 5.51 Following a first-in-human phase I study in the United Kingdom where six volunteers required intensive care support due to severe adverse reactions, an independent report on these events was commissioned (Expert Scientific Group on Phase I Clinical Trials 2006). The report focused on the study of higher risk compounds such as those that may have a novel mechanism of action, a highly species-specific action, or that directed towards immune system targets. Although risk assessment of individual phase I studies in New Zealand is the role of regulatory bodies such as the Standing Committee on Therapeutic Trials (SCOTT), phase I study investigators should be familiar with the 22 recommendations made in the Expert Scientific Group’s report (pp 6–11) in order to evaluate their capability to conduct the study in an ethically acceptable manner. These recommendations cover:
- pre-clinical and early clinical development
  - the process of preparation and review of clinical trial applications, and early access to advice for both regulators and sponsors
  - determining and administering initial doses in humans
  - the clinical environment for first-in-human studies
  - developing the skills and training to meet future needs.

## Community intervention studies

- 5.52 In a community intervention study, interventions are allocated primarily to whole communities or groups (see Glossary). Before undertaking a community intervention study the investigator must make every effort to ensure that:
- the study is responsive to the health needs and priorities of the population
  - any intervention or product developed will be made reasonably available for the benefit of that population or community.
- 5.53 Individual consent to participate in a community intervention study should not be required if gaining that consent is impracticable, and if the benefits from the study are sufficient and the potential harms minimal. An example of such a study might be one examining the effects of a media campaign to reduce adolescent tobacco use.

- 5.54 In general, where there is some engagement with affected communities before and during the conduct of the study, there is more likely to be long-term benefit to study participants and to the community.
- 5.55 To the extent possible, and whenever appropriate, investigators should involve community representatives in the planning and conduct of studies, and give community members the opportunity to contribute (eg, through submissions or public meetings).

## Collective consultation

- 5.56 When an intervention study focuses on an intervention for a whole community, rather than for individuals, it is normally appropriate for the community as a whole, rather than individuals, to be consulted about participation in the study.
- 5.57 Some intervention studies are conducted within identifiable communities but with the intervention(s) targeted at individuals. For example, a primary care study may allocate schools or hapū to study groups, while individual members of those groups receive the intervention(s). In such cases, investigators should consult with the community about conducting the study, and obtain informed consent from individuals to receive the intervention.
- 5.58 In consulting a community or group about participation in a study, the investigator should approach its representative(s) in accordance with the group's practices and shared values. Agreement given by a community representative should be consistent with general ethical principles. In general, investigators should consider collective entitlements and protection as they would individual entitlements and protection.
- 5.59 In studies involving Māori where the investigators include one or more members from a whānau, hapū or iwi to be studied, it may be preferable to include a statement in the study protocol that group agreement for individuals to be approached to participate was obtained from the representatives/participants at a hui.
- 5.60 In studies involving Māori where no investigator is a member of the whānau, hapū or iwi to be studied, a system of investigator accountability to the whānau, hapū or iwi concerned should be instituted after full discussion and agreement between the participants and investigators.

## 6 Study processes

### Recruitment of participants

- 6.1 Adequate recruitment is important to ensure that the number of participants is sufficient to reliably answer the study question(s).
- 6.2 The investigator should choose a method of approaching participants that meets applicable ethical and scientific standards. Depending on the study question and design, the approach may be made directly to the potential participant (eg, by advertisement, telephone or letter) or indirectly (eg, through the participant's own doctor or relevant health practitioner).
- 6.3 In some circumstances the investigator may also be a potential participant's own doctor or other relevant health practitioner. In this case it is important for the investigator to recognise the potential for conflict of interest this creates and to remove any element of coercion into, or inappropriate discouragement from, participation in the study (see also 'Addressing conflict of interest', paragraphs 4.18–4.23). On the other hand, the regular practitioner may be the best person to approach their patient (eg, because of patient preference, ability to reduce poorly judged approaches, or the need to maintain continuity of care) rather than transferring this task and the patient's management to a second practitioner.
- 6.4 If a patient (or her or his family or friends) approaches her or his health practitioner or an investigator about study participation, this situation needs to be managed using the same principles outlined in paragraph 6.3 above.
- 6.5 Where intervention studies are designed as non-therapeutic, group-based or community-based studies (with the exception of phase I studies), the prospective involvement of the participant's regular doctor is not mandatory, although subsequent communication about participation is desirable, if the participant agrees to this. (See also 'Clinical responsibilities', paragraph 6.68–6.71).

### Free and informed consent

#### General principles

- 6.6 Informed consent is best understood in terms of decision-making that is based on good communication between people, rather than simply as a transfer of information from one person to another (Manson and O'Neill 2007).
- 6.7 Informed consent has two basic components.
- (a) The decision is informed by adequate understanding of any information that is relevant to that decision.
  - (b) The decision is voluntary, and is therefore free from undue influence such as manipulation or coercion.

- 6.8 People are entitled to make free and informed decisions about their participation in a study. The purposes of this are to ensure that such decisions express the will of potential and actual participants and to protect them from coercion, manipulation and other undue influence.
- 6.9 The person making the decision must have sufficient competence to make that decision, in terms of their ability to understand and weigh the information.
- 6.10 Verbal information provided should be tailored to the individual, taking into account the participant's level of knowledge and understanding and the amount of detail they desire. Written information provided should be tailored to the study population (for example, it should be culturally appropriate for that study population), and should have a reading age appropriate to that population.
- 6.11 Consent provisions should include establishing access to an ongoing dialogue about the study and give the opportunity for any questions to be asked and answered throughout the duration of the study. Providing such ongoing access to information is often a better way to communicate than providing a lot of extra written material.
- 6.12 Investigators should effectively communicate to participants the purpose and practical implications of all key study features, including any randomisation, placebo control or blinding (see also 'Features of intervention studies', paragraphs 2.7–2.11).
- 6.13 Investigators are responsible for designing and conducting studies to maximise the validity and quality of participants' informed consent. Ethics committees are responsible for checking that proposed study information sheets and consent forms enhance informed consent of this nature.
- 6.14 Providing information that is too detailed or complex can frustrate rather than assist free and informed consent. If a consent form or information sheet for a study is very long and complex, participants may be overwhelmed by the information and may not be able to process the critical information. Further detail about informed consent for specific groups is located in the appendices to this document.
- 6.15 It is preferable that participants provide in writing their consent to participate in an intervention study. There may be some situations where this is not possible; for example, due to a participant's illiteracy or physical inability. The principles of justice and non-exclusion imply that prospective participants should not be excluded from research purely on the basis of illiteracy or physical inability. However, any exceptions to obtaining written informed consent should be justified to an ethics committee. In all cases where consent is not provided in writing, the procedures used to seek free and informed verbal consent and the fact that consent was given, should be documented. (See also the Code of Rights, Right 7(6).)
- 6.16 The purposes of consent are normally best served by decision-making that occurs prior to a participant's inclusion in a study. Any exception requires justification to an ethics committee on grounds that prior consent is one or both of the following:
- impracticable (eg, for studies in emergency care or community intervention studies)
  - undesirable (eg, when any delay of the intervention(s) to be studied would harm the person). (See also 'Non-consensual studies', paragraphs 6.24–6.29.)

- 6.17 People are ethically entitled to be informed about their participation in a study, whether their participation occurs with their consent or without it. (For example, participants should be informed once they have sufficient competence to understand what the study involves.) Any exception requires justification to an ethics committee on grounds that informing participants is impracticable and/or undesirable. (See also paragraph 6.16.)
- 6.18 During the initial consent discussion about the study, due regard should be paid to the circumstances of the potential participant. If a potential participant is in pain or under stress, a short discussion may suffice. This brief dialogue should be followed up with more detailed information about the study once the participant is more comfortable.
- 6.19 People are entitled to refuse to participate in intervention studies and to withdraw their consent to participate. They may make either of these decisions whenever practicable and without experiencing any disadvantage. (See also the Code of Rights, Right 7(7).)
- 6.20 Those who ask to withdraw from a study may wish only to withdraw from any interventions they are yet to receive, rather than from all aspects of the study. Normally, those who withdraw should be asked whether they are willing for their data to remain in the study, and whether they are willing to have further data recorded, particularly data on study end-points (see the Glossary). Any new data or data that have already been collected could provide beneficial information for the study. (See also paragraph 5.10.)
- 6.21 If a study is amended significantly, or if new information becomes available after informed consent has been obtained, participants must be notified. It may also be appropriate to seek their consent to continue to participate. The ethics committee should review any proposal to make significant amendments to the study protocol.

## Features of informed consent

- 6.22 Informed consent is essentially a matter of good communication between people. Information should be provided to potential participants in a form and in a way that assists their informed decision-making. For example, the information should as far as possible be provided in lay terms. In general, such information should:
- explain the study, including:
    - the purpose of the study, including its expected contribution to knowledge and its potential benefits to communities
    - how the study meets the best intervention and equipoise standards
    - the purpose and practical significance of the use of randomisation, blinding or placebos, as relevant
    - the nature and sources of funding of the study, the institutional affiliations of the investigator(s), and who can be contacted to answer questions and how to contact them
    - the study's status, with a current approval from an ethics committee

- describe what the study involves, including:
  - what will be done in the study, including how participation in it will differ from not being in the study
  - the time involved in participation (eg, the number and duration of any visits to the research centre, and the expected finishing date of the study)
  - the purpose and expected number of any extra tests to be performed during the study
- outline potential benefits, risks and compensation, covering:
  - foreseeable risks, side-effects, discomforts and possible direct benefits of study participation, including any risks or benefits to the health of a participant's family members
  - arrangements for personal compensation for injury, including whether the study is covered by the Accident Compensation Act 2001
  - payments or other forms of reimbursement, if any, provided in recognition of participation
  - the extent of the investigator's responsibility to ensure that care is provided to participants during the study
- explain the rights of participants, covering:
  - the voluntary nature of participation, including that they are free to decline to participate or to withdraw from the research at any practicable time, without experiencing any disadvantage
  - the fact that participants have the right to access information about themselves collected as part of the study
  - the fact that participants will be told of any new information about adverse or beneficial effects related to the study that becomes available during the study that may have an impact on their health
  - what provision will be made for the privacy and confidentiality of individuals
- describe what will happen after the study, covering:
  - whether any study intervention will be available to participants after the study and, if so, under what conditions (including any cost to them)
  - how study data will be stored and for how long, whether the data will be retained for possible future use, who will be responsible for their secure storage and how they will be destroyed
  - whether any biological specimens collected during the research will be destroyed at its conclusion and, if not, details of their storage and possible future use
  - how the study findings will be communicated on completion of the study, including to participants, and in what expected timeframe.

6.23 Paragraph 6.22 is subject to the principles stated in 'Free and informed consent – General principles', paragraphs 6.6–6.21, and 'Vulnerable people', paragraphs 5.28–5.35. For a pro forma consent form, see the Application Form for Health and Disability Ethics Committees. For an example of an information sheet, see the WHO consent form templates ([www.who.int/rpc/research\\_ethics/informed\\_consent/en](http://www.who.int/rpc/research_ethics/informed_consent/en)).

## Non-consensual studies

- 6.24 Some people who have diminished competence or no competence at the time a study is conducted (eg, potential participants in a study of the care provided in an intensive care unit after major elective procedures) may be competent to make decisions about study participation at an earlier time. In such cases investigators should make all reasonable efforts to obtain prior consent to participate by the person, and to identify any prior consent or refusal to participate by the person, and should give effect to any such prior decision. (See also the Code of Rights, Right 7(5) and clause 4 and the Health and Disability Commissioner Act 1994, section 2, definition of 'health care procedure'.)
- 6.25 People who have diminished competence to make decisions about their participation in a study are entitled to make informed decisions to the extent appropriate to their level of competence. (See also the Code of Rights, Right 7(3).)
- 6.26 In non-consensual studies it is the investigator's responsibility to ensure that all applicable legal standards are met. New Zealand law substantially limits the powers of health practitioners to offer treatment without consent in the context of research. It also substantially limits the powers of others to consent to such treatment on behalf of any person who is not competent. (See, in particular, the New Zealand Bill of Rights Act 1990, the Protection of Personal and Property Rights Act 1988 and the Code of Rights, particularly Right 7(4).)
- 6.27 The ethical standards for non-consensual studies that are stated in these *Guidelines* are intended for application only to studies that are lawful.
- 6.28 Intervention studies with no therapeutic intent should be undertaken only with the prior informed consent of the competent individual, unless a legal proxy can consent for an incompetent individual. (See also 'Studies with distinctive features – Non-therapeutic studies', paragraphs 5.48–5.49.)
- 6.29 If a person is not competent to make an informed decision about participating in a therapeutic study, then the decision may be made by an individual who is legally entitled to decide on behalf of that person. If no such individual is available, and the investigator can legally undertake the study, then study participation must:
- meet appropriate ethical standards, which include the best intervention standard (see 'Best intervention standard', paragraphs 5.13–5.17) and the equipoise standard (see 'Equipoise standard', paragraphs 5.18–5.21)
  - be consistent with the views of other suitable people who are interested in the person's welfare and available to advise on this
  - be in accordance with a study protocol approved by an ethics committee.

## Study conduct

### Deception and concealment

- 6.30 To maintain study validity, it may sometimes be appropriate to withhold information from participants until after study completion, or to conceal certain aspects of study design. Some examples of these circumstances are where:
- participants are not told the purpose of tests performed to monitor their adherence to the study protocol
  - prospective participants are asked to consent to remain uninformed of the purpose of some procedures until the study is completed
  - participants are not told that some information has been withheld until the study has been completed, because their knowledge of this aspect of the study would jeopardise its validity.
- 6.31 When an investigator believes deception or concealment is scientifically justified, the following criteria apply.
- There are no suitable alternative methods.
  - Participants are not exposed to increased risk of harm.
  - The extent of deception or concealment is defined in the study protocol.
  - Adequate and prompt disclosure is made, and debriefing is provided, as soon as appropriate and practicable.
  - Participants are entitled to require the withdrawal of study data that were obtained from them without their knowledge or consent.
  - The deception or concealment will not compromise the relationship between the community and the investigators or research.
  - The investigator justifies the deception or concealment to an ethics committee.

### Payments to participants

- 6.32 Payments or inducements for study participants can normally be ethically acceptable only if the study would be ethically acceptable in the absence of the inducement. Investigators may seek to create legitimate motivation for participation in studies, but may not exert undue influence by offering inappropriate inducements.
- 6.33 Inducement can take many forms. For example, it can occur directly or indirectly through financial or other recognition, or offers of treatment that would otherwise not be available. Inducement can be in the form of the influence and status of the health professional or investigator. As a result there is potential for inducement to exploit the vulnerability of individuals and to be inappropriate.

- 6.34 Appropriate payment may include:
- reimbursement of the incurred expenses of participants (eg, travel costs)
  - payment in recognition of time, inconvenience and/or discomfort for participants, especially in phase I trials
  - free health services
  - koha that accords with the cultural norms of the study participants (it is generally not appropriate to discuss koha prior to agreement to participate).

(In Māori tradition, koha is a gift presented by visitors as part of a welcoming ceremony. However, contemporary meanings include a gift or donation in response to some good provided, such as participation in research.)

- 6.35 Payments or free health services should not be of such value that they induce prospective participants to consent against their better judgement. Risks involved in participation should be acceptable to participants even in the absence of any inducement.
- 6.36 All payments, reimbursements and health services provided to study participants must be disclosed to an ethics committee.
- 6.37 When payments are used, it should be stated at the outset of the study if withdrawal on health grounds or for any other reason, or wilful non-adherence to the study protocol, will affect any payments and, if so, what the effect will be.

## Study monitoring and adverse event reporting

- 6.38 Every intervention study should have appropriate oversight of the conduct of the study to ensure the safety of the participants and the integrity and validity of the study data (National Institutes of Health 1998).
- 6.39 Every intervention study should include documentation of the planned monitoring arrangements (a 'monitoring plan') for the study.
- 6.40 The overall goals of study monitoring are to ensure that:
- the rights and wellbeing of human subjects are protected
  - the reported study data are accurate, complete and verifiable from source documents
  - the conduct of the study adheres to the study protocol, and is consistent with appropriate good clinical practice guidelines.
- 6.41 The nature and extent of monitoring should depend on the level of study risk, and should be based on considerations such as the study objectives, design (including patient population, intervention and study outcome measures), complexity, size and duration, and the experience of the investigators.

## Monitoring arrangements

- 6.42 Mechanisms for meeting the monitoring goals outlined in paragraph 6.40 range from committees with responsibility for oversight to day-to-day monitoring of data on site. The study's monitoring plan should state all appropriate monitoring arrangements. These will depend on the nature of the study.
- 6.43 Study monitoring arrangements may include one or more of the following.

### Trial oversight committees

- 6.44 Trial oversight committees may include one or more of:
- a trial steering committee (TSC), the role of which is to provide overall supervision of the trial and to ensure that it is being conducted in accordance with the principles of good clinical practice, and which may have members who are independent of the study investigators
  - a trial management group (TMG) – every trial should have a TMG (although in small, simple studies this may comprise just the principal investigator), which is responsible for the day-to-day management of the trial, and often also includes the statistician, the trial coordinator, the data manager and the research nurse(s)
  - a data monitoring committee (DMC), the purpose of which is to protect the safety of the study participants, the credibility of the study and the validity of the study results (Ellenberg et al 2003: 1), and which is generally an independent body, although in some circumstances it may be internal to the study, including representation from the TSC and/or the study sponsor (factors determining the need for an independent DMC are outlined in paragraphs 6.51–6.58 below).

### A coordinating centre/database monitoring

- 6.45 A trial coordinating centre monitors data as they enter the database during the course of the trial. This monitoring includes: checking the data against the protocol and for internal logic; and checking eligibility, recruitment rates, withdrawals, missing data and loss to follow-up. This monitoring should be done for all trials to ensure integrity of study data.

### On-site monitoring

- 6.46 Monitors visit study sites to check adherence to study protocol and good clinical practice guidelines. This normally includes checking informed consent and eligibility, checking data on study case report forms against source data, and checking adverse event reporting. The appropriate extent of on-site monitoring depends on factors such as the degree of risk, the complexity of the study, blinding and the experience of sites (ICH 1996).

## Data monitoring committee

- 6.47 A DMC is an advisory body responsible for monitoring emerging safety and efficacy data, reviewing trial conduct and making recommendations to the trial steering committee and study sponsor(s). Normally, the DMC should have sole access to the data emerging in the study. The DMC makes recommendations on early termination of the study if there is convincing evidence of benefit, unfavourable results ruling out benefit, safety concerns or a low probability of the trial achieving its objectives. (For an example of DMC operating guidelines, see [www.hrc.govt.nz](http://www.hrc.govt.nz).)
- 6.48 The primary responsibilities of a DMC are to:
- safeguard the interests of the study participants
  - preserve the integrity and credibility of the study so that future patients may be treated optimally
  - ensure definitive and reliable results are available in a timely way to the health care community.
- 6.49 Where the risks of a study are low, it may be appropriate for there not to be a DMC.
- 6.50 Where a DMC is appropriate, the following criteria apply.
- The DMC's monitoring plan should specify the DMC membership, with a brief indication of the expertise of the members, both in the study area and on DMCs.
  - The DMC should have operating guidelines, including statements as to the data to be reviewed, the timing and form of meetings, and reporting policy (HRC 2005a).
  - Plans for any interim analysis of both efficacy and safety data and criteria for early termination should be specified in the study protocol, and agreed between the study sponsor, the trial steering committee and the DMC. These plans should be appropriate to the setting. They should indicate the statistical approach for preserving overall error rates when multiple analyses are carried out, and should give appropriate recognition to the unreliability of early results due to random fluctuations.

## The independence of the data monitoring committee

- 6.51 All intervention studies need monitoring, but not all studies need an independent DMC (Ellenberg et al 2003: 153–6).
- 6.52 An independent DMC is independent of those conducting the study the DMC is monitoring. It has a multidisciplinary membership, including physicians from relevant medical specialties and biostatisticians. In many cases its membership also includes others with relevant expertise, including ethicists, epidemiologists and basic scientists. At least some members, especially the chair and the biostatistician, should have prior DMC experience.

- 6.53 An independent DMC should have its membership limited to individuals free of any significant conflict of interest in relation to the study being monitored, whether financial, intellectual, professional or regulatory in nature.
- 6.54 For studies with an independent DMC, that DMC should ideally be the only party to whom the data analysis centre provides interim results on the relative efficacy and safety of the study interventions. This protects the study from inappropriate early termination, which can be caused by premature judgement based on potentially misleading early results.
- 6.55 An independent DMC is most needed for an intervention study that aims to provide definitive data on treatments intended to save lives or prevent serious disease (Ellenberg et al 2003: 153–6).
- 6.56 An independent DMC should also be considered in early phase studies, whether or not randomised, of a high-risk intervention; for example:
- where there is risk of non-preventable, potentially life-threatening complications
  - where the intervention is novel and there is very limited information on clinical safety, or where prior information raises concern regarding potential serious adverse events
  - where professional or financial goals may be perceived to unduly influence the sponsor and/or investigators
  - where interim analyses of efficacy (allowing planning for the possibility of early study termination) and safety are considered essential to ensure patients' safety
  - where vulnerable populations, such as children or people with mental illness, are studied
  - where there is potential for a large public health impact
  - where studies are carried out in emergency settings (Ellenberg et al 2003: 153–6).
- 6.57 In settings other than those stated in paragraphs 6.55–6.56, some aspects of the oversight provided by a DMC may still be valuable, and could be carried out by a group that is not fully independent of the study, sometimes termed an 'internal' DMC (Ellenberg et al 2003: 157–8). An internal DMC can significantly improve patient safety and trial integrity through regular meetings to review data on study conduct and relative efficacy and safety. Its membership should be multidisciplinary, and may include the principal (clinical) investigator for the study and the study statistician.
- 6.58 The table below gives an indication of the most appropriate form of DMC monitoring for an intervention study (Ellenberg et al 2003: 160).

## Appropriate form of DMC monitoring

Type of setting <sup>1</sup>	Imperatives		Need for DMC	
	Ethical integrity	Credibility	Independent DMC	Internal DMC
<b>Setting 1</b>				
Randomised trials (phases IIb, III, IV)	Yes	Yes	Yes	–
Randomised trials (phases I, IIa)	Yes	Likely	Maybe	Likely <sup>2</sup>
Non-randomised trials	Yes	Maybe	Unlikely	Likely <sup>2</sup>
<b>Setting 2</b>				
Randomised (any phase trial)	Unlikely	Likely	Unlikely <sup>3</sup>	Maybe <sup>2</sup>
Non-randomised	Unlikely	Unlikely	No	Unlikely

- 1 Setting 1 includes: life-threatening diseases (treatment, palliation and prevention); diseases causing irreversible serious morbidity (treatment, palliation and prevention); novel treatments for life-threatening diseases (treatment, palliation and prevention) with potential for significant adverse events; and vulnerable populations. Setting 2 includes trials not included in setting 1.
- 2 An internal DMC would be advised if an independent DMC is not established.
- 3 Integrity/credibility issues could motivate use of an independent DMC; for example, if a trial in this setting were to impose interim monitoring of comparative data.

## Adverse event monitoring

6.59 Key terms relating to adverse event monitoring are defined in the box below.

Term	Definition
Adverse event (AE)	Any untoward medical occurrence in a patient administered a study product and which does not necessarily have a causal relationship with this product
Adverse drug reaction	Any untoward and unintended response in a subject to an intervention that is related to any dose administered to that subject
Unexpected adverse reaction	An adverse reaction, the nature and severity of which are not consistent with information about the intervention in the investigator's brochure (or, for a product with marketing authorisation, in the summary of product characteristics for that product)
Serious adverse event (SAE), serious adverse drug reaction or unexpected serious adverse reaction	An adverse event, adverse drug reaction, or unexpected adverse reaction, that: <ul style="list-style-type: none"><li>• results in death, or</li><li>• is life-threatening, or</li><li>• requires inpatient hospitalisation or results in prolongation of existing hospitalisation, or</li><li>• results in persistent or significant disability or incapacity, or</li><li>• consists of a congenital anomaly or birth defect, or</li><li>• is a medically important event or reaction</li></ul>
Suspected unexpected serious adverse reaction (SUSAR)	Any unexpected serious adverse reaction that is suspected to be related to the intervention under study

Source: MHRA 2009

## Responsibilities for monitoring adverse events

- 6.60 The protocol and/or monitoring plan of any intervention study should state the processes and responsibilities for identifying, coding, analysing and reporting adverse events. Reliable interpretation of AEs requires coding according to body system and severity (eg, using the *Medical Dictionary for Regulatory Activities* (MedDRA 2009) or *Common Terminology Criteria for Adverse Events* (CTEP 2009)) and comparison of grouped data across intervention arms (with consideration of the benefit and risk profile). An independent DMC is best placed to reliably interpret such safety data.
- 6.61 Prompt reporting of serious adverse events is especially important for SUSARs (see paragraph 6.59).
- 6.62 A mechanism should be in place for responding to any potential safety concerns. In general, reliable interpretation of the safety signals would require an interim report on safety and efficacy, in a form unblinded by intervention arm. Any interventional study with potential for serious treatment-related adverse events should have a mechanism in place for prompt reporting, recognition, and response to SAEs and SUSARs.

## Terminating a study

- 6.63 There are some circumstances (eg, a major deviation from study protocol) that may make it appropriate to terminate an intervention study early.
- 6.64 For any study with a DMC, any issues about early termination of the study should be addressed in the study's monitoring plan (see also paragraphs 6.39, 6.42, 6.47, 6.50), and any early termination of the study should be in accordance with the study's monitoring plan and under the advice of the DMC. For any study without a DMC, the study's monitoring plan should include comment on whether (and if so under what conditions) early termination of the study would be considered.
- 6.65 Studies should not be terminated simply for reasons of commercial interest or public relations.

## Care of participants

- 6.66 Investigators have an obligation to ensure the availability of health care services that are essential to the safe conduct of a study and for any participants who suffer injury as a consequence of study interventions.
- 6.67 Ideally, phase III intervention studies should be designed to assure that every participant has post-study access to the best-proven intervention. The minimum requirement is that investigators make clear to all participants the post-study access arrangements, including any uncertainties in this regard. The sponsor and investigator should also pursue matters of access to effective interventions for study and target populations with relevant authorities. In most intervention studies it cannot be known which intervention is best until after the study has been completed.

## Clinical responsibilities

- 6.68 Responsibilities to inform other health professionals of a participant's study involvement depend on the nature of the study. For some studies the investigator should inform professionals responsible for the health care of participants of their participation in a study, usually at the time of enrolment in the study, and provide information about the possible health implications of this involvement. For other studies, informing other health professionals is desirable, with the participant's consent. There are also some studies (eg, where risk is minimal – see paragraph 4.13) for which it is not necessary to inform any other professional of the participant's study participation. (See also paragraphs 6.5 and 7.9–7.11.)
- 6.69 Participants (and their main care provider) must be informed of any clinically significant abnormal laboratory results or clinical observations that develop or are detected during the course of a study. Appropriate follow-up must be arranged.

- 6.70 Where participants are found through the conduct of a study to have a previously undetected health care need that is not directly related to the study, arrangements should be made for them to receive that care. Investigators and study sponsors have a responsibility to take all reasonable steps to ensure that appropriate care is provided.
- 6.71 If it is reasonably foreseeable that health problems previously unknown to the individual participant could be identified during the study process, then arrangements for referral, with the individual's consent, should be made.

## 7 Confidentiality, disclosure and publication of results

- 7.1 The information collected or determined by a study must be used in a way that does not disadvantage any participant.
- 7.2 Investigators should make arrangements for protecting the confidentiality of study data. The data can be identified, potentially identifiable, partially de-identified, de-identified or anonymous. These terms are defined below.
- **Identified data:** Identified data allow a specific individual to be identified. Identifiers may include the individual's name, date of birth or address. In particularly small sets of data even information such as a postcode may be an identifier.
  - **Potentially identifiable (key-coded, re-identifiable) data:** Key coding is the technique of separating personally identified data from substantive data, maintaining a potential link by assigning an arbitrary code number to each data-identifier pair before splitting them. Held securely and separately, the key allows the re-associating of the substantive data with the identifiers, under specified conditions, if that is ever necessary (Lowrance 2002). Data may be single-coded, or double-coded if extra security is required. Data can also be potentially identifiable if it is possible to infer an individual's identity from them.
  - **Partially de-identified (AIDS-type code) data:** Data coded with abbreviated identifiers (for example, initials, date of birth, sex) are used for reporting AIDS, HIV and some other conditions. This allows re-identification by the clinician reporting, but is anonymous to the recipient, although duplicates can be linked.
  - **De-identified (not re-identifiable, anonymised, anonymous, unlinked) data:** The process of de-identification can be irreversible if the identifiers have been removed permanently. These data are referred to as 'de-identified' data. It should be recognised that the term 'de-identified' is used frequently in other documents to refer to sets of data from which only names have been removed; in fact such data may remain 'potentially identifiable'.
  - **Anonymous data:** Anonymous data have been collected without personal identifiers, and no personal identifier can be inferred from them.
- 7.3 Investigators must ensure the adequate physical and electronic security of data.
- 7.4 For studies involving the collection of information about illegal activities (eg, the use of illegal substances), potential participants should be made aware of whether investigators can or cannot ensure confidentiality.
- 7.5 In the unusual event that individual or group confidentiality cannot be maintained or is violated – for example where the researcher is legally or ethically obliged to disclose information to protect the safety of a participant or another person – investigators should take all reasonable steps to maintain or restore the good name and status of the individual(s) or group concerned.

- 7.6 Note that ‘privacy’ is the status of information about aspects of a person’s life over which she or he claims control and may wish to exclude others from knowing. Privacy is a relative status, and claims to it must be negotiated against countering claims, such as the rights of others or collective societal goods. ‘Confidentiality’ is the respectful handling of information disclosed within relationships of trust, especially as regards further disclosure (Lowrance 2002).
- 7.7 If study data are to be used for any purpose, or by any people, other than as specified in the approved protocol, investigators should ascertain whether they need to submit a proposed revision of the study protocol or a new protocol to an ethics committee (see *Ethical Guidelines for Observational Studies* and the SOPs for HDECs).
- 7.8 See also the Health Information Privacy Code 1994, Rules 5 and 11 and the Privacy Act 1993, Principles 5 and 11.

## Disclosure of information obtained by intervention studies

- 7.9 Where findings obtained by an intervention study suggest serious disease, study participants who have not already given permission for the transfer of the information to their medical advisor should be urged to seek further advice and advised of any potential consequences of not seeking such advice.
- 7.10 Care should be taken not to interfere with health professional–patient relationships, and investigators should usually refrain from giving an opinion about how a particular finding should be dealt with by a participant’s doctor.
- 7.11 Individuals’ privacy and confidentiality of information need to be protected unless there is an overriding concern (eg, health or safety) justifying the release of such information. If privacy or confidentiality must be breached, the investigator should first make a reasonable attempt to inform participant(s) of the event and the reasons for it.
- 7.12 Investigators have an obligation to advocate for the release of information that is in the public interest, even when data are retained by governmental, commercial or other sponsors.
- 7.13 Investigators should strive to ensure that, at a minimum, study results are interpreted and reported on accurately. Where possible, they should also anticipate and avoid any misinterpretation of study results that might cause harm.
- 7.14 Investigators have an obligation to disclose to participants and their legal proxies, where applicable, any unforeseen risks discovered during the course of a study, and any other new information that might reasonably affect their consent to participate or their future health and safety. Participant rights in this regard should be indicated in the informed consent process and in the study’s monitoring plan.
- 7.15 Investigators should not normally enter into contracts with clauses that restrict or prohibit disclosure of risks or lack of benefit of research products to participants, other members of the research group, ethics committees, regulatory agencies or the scientific or general community.

- 7.16 There should not be contractual restrictions to investigator access to study data. Where a study has a DMC, that committee should normally have sole unblinded access to emerging data.

## Publishing study results

- 7.17 Investigators have a responsibility to study participants, future patients and the wider scientific and general community to publish the results of their studies.
- 7.18 Investigators should not normally enter into contracts that limit, or apply unreasonable time restrictions to, the publication of study results.
- 7.19 Full publication of study results helps to prevent publication bias and allows for additional information to be gleaned through meta-analyses. All end-points stated in the study protocol – including positive, negative, significant and non-significant results – should be published. Results from all participants in the trial, including all arms of the trial, should be published. Where such a comprehensive approach is not practicable, the published report should acknowledge and explain any departures, including any omissions or additions, from the end-points specified in the study protocol.
- 7.20 It is normally not appropriate to publish incomplete results from intervention studies (eg, publication of early results only, of secondary end-point results only or results from only some study centres), because incomplete results have the potential to be misleading.
- 7.21 Study protocols should include a provision for communicating results in a timely, understandable and responsible way by suitable means, so that the widest possible community stands to benefit. The optimal time at which to disseminate the results of intervention studies can be difficult to determine. Both premature release and unnecessary delay in the release of study results can be more harmful than beneficial to individuals and to society. It may be necessary to balance the need for cautious communication of results to other investigators with appropriate peer review and the need for expeditious communication of results to other interested parties. Where availability of the results would lead to immediate benefit to patients, investigators are responsible for making these results available to the relevant parties in an expeditious manner.
- 7.22 Study results should be published in a form that gives due regard to cultural and other sensitivities. This normally implies that they should not be published in a form that permits the identification of individual participants. (See also paragraph 7.5.)
- 7.23 In the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and editing for biomedical publication*, the International Committee of Medical Journal Editors (ICMJE) states:

When reporting experiments on human subjects, authors should indicate whether the procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.  
(ICMJE 2004: section II.F)

7.24 Any New Zealand intervention study should abide by the ICMJE requirements.

## 8 Compensation for injury

- 8.1 Section 32 of the Accident Compensation Act 2001 sets out the limited circumstances in which there will be cover for 'personal' (physical) injury suffered as a result of treatment provided as part of an intervention study. This cover is provided through the Accident Compensation Corporation (ACC).
- 8.2 Participants in clinical trials are excluded from cover under the general provisions of the Accident Compensation Act 2001 if they agreed in writing to participate in the trial and an approved ethics committee did not approve the clinical trial. Participants are also excluded if *all* of the following conditions are met:
- the participant's personal injury results from medical treatment
  - this injury occurs during or after his or her participation in a clinical trial
  - the medical treatment is provided as part of the study
  - the medical treatment is provided by a registered health practitioner
  - the participant agreed, in writing, to participate in the study
  - an approved ethics committee approved the trial, and was satisfied that the trial was to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled.
- 8.3 Investigators and sponsors should ensure that the extent of each participant's compensation entitlements in the event of adverse consequences arising out of their participation in an intervention study are outlined clearly to him/her as part of the informed consent process. Where personal injury suffered as a result of treatment given as part of a clinical trial is covered under the accident compensation scheme, participants must be advised that compensation may not be available, or may be modest.
- 8.4 If cover under the Accident Compensation Act 2001 will be excluded for the intervention study, investigators and study sponsors have responsibilities to ensure alternative compensation cover for study participants to at least ACC-equivalent standard. This may include earnings-related compensation.
- 8.5 HDECs have a responsibility to check that at least ACC-equivalent compensation is available to participants in clinical trials that are not covered by the accident compensation scheme.

# Glossary

**Adverse drug reaction:** any untoward and unintended response in a subject to an intervention which is related to any dose administered to that subject (MHRA 2009).

**Adverse event:** any untoward medical occurrence in a patient administered a study product and which does not necessarily have a causal relationship with that product (MHRA 2009).

**Bias:** the tendency of a measurement or a statistic to deviate from the true value of the measure or statistic (Brownson and Petitti 1998: 50).

**Bioavailability study:** a study examining the rate and extent at which a drug, when administered in a pharmaceutical dosage form, becomes available, either at the site of pharmacological effect or systemically within the body (Chow 2003: 83).

**Bioequivalence study:** a study aiming to show that the bioavailability of one formulation of a drug is equivalent to another formulation of the same drug (Chow 2003: 83).

**CIOMS guidelines:** the Council for International Organizations of Medical Sciences *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002).

**Clinical trial:** any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate effects on health outcomes. Clinical trials may also be referred to as interventional trials. Interventions include but are not restricted to drugs, cells and other biological products, surgical procedures, radiologic procedures, devices, behavioural treatments, process-of-care changes and preventive care, etc. This definition includes Phase I to Phase IV trials (WHO 2009).

**Code of Rights:** the Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996, issued under the Health and Disability Commissioner Act 1994, section 7.

**Community intervention study** (or cluster intervention study): a study in which interventions are allocated primarily to whole communities or to groups (such as schools, households or groups of patients), other communities serving as comparison. For example, such a study might focus on a mass media campaign to prevent smoking in young people, or a school-based programme of antibiotic treatment of throat infections to prevent rheumatic fever, or a new model of care.

**Crossover trial:** in a crossover trial each subject is randomised to a sequence of two or more treatments, and hence acts as her or his own control for treatment comparisons. This design reduces the number of subjects and usually the number of assessments needed to achieve a specific power, sometimes to a marked extent. In the simplest  $2 \times 2$  crossover design, each subject receives each of two treatments in randomised order in two successive treatment periods, often separated by a treatment-free period (ICH 1998: 11).

**Data monitoring committee (DMC):** a body that advises the study team and study sponsor, and is responsible for monitoring emerging data during the course of a study. The purpose of these roles is to ensure both that the participants are safe and that the study is conducted to a high quality so that it generates reliable answers to its study question(s). The DMC may be independent or may be constituted from those conducting the study. Another term for a DMC is 'data and safety monitoring board'.

**Declaration of Helsinki:** the *World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects* (WMA 2008).

**End-point** (outcome measure): a pre-specified outcome variable of interest to a study. The primary end-point is the most important outcome, and should reflect clinically relevant effects and the principal objective of the study. Data on secondary outcomes (secondary end-points) are used to evaluate additional effects of the intervention (ICH 1997: 10–11).

**Ethics committee:** any ethics committee approved by the Health Research Council Ethics Committee (HRCEC) in accordance with the Health Research Council Act 1990, section 25, or the HRCEC itself. The standards established in these *Guidelines* may also assist other ethics committees.

**Health and disability ethics committee (HDEC):** an ethics committee established under section 11 of the New Zealand Public Health and Disability Act 2000 and approved by the HRCEC.

**HRC guidelines:** the Health Research Council *Guidelines on Ethics in Health Research* (HRC 2005b).

**Indication:** a condition for which the use of a certain intervention (eg, a certain medicine) is indicated or is appropriate.

**Informed consent:** a process through which a subject voluntarily agrees to participate in a particular trial, having been informed of all aspects of the trial that are relevant to their decision to participate (ICH 1996: 5).

**Innovative practice:** a planned deviation from the currently accepted practice of a New Zealand body of health professionals involving an untested or unproven clinical intervention intended to be used on an ongoing basis.

**Intention-to-treat principle:** a principle asserting that the effect of a treatment can be best assessed by evaluating on the basis of the intention to treat a subject (ie, the planned treatment regimen) rather than the actual treatment given. This means that subjects allocated to a treatment group should be followed up, assessed and analysed as members of that group irrespective of their compliance to the planned course of treatment (ICH 1998: 33).

**Intervention study:** a study in which the investigator controls and studies an intervention(s) provided to participants for the purpose of adding to knowledge of the health effects of that intervention(s). The term 'intervention study' is often used interchangeably with 'experimental study'. Many intervention studies are clinical trials.

**Investigator:** any qualified individual who may be involved in the study design and who conducts all or part of an investigation.

**Non-consensual study:** a study conducted without the consent of its participants.

**Non-therapeutic study:** a study that examines interventions that do not hold the prospect of direct diagnostic, therapeutic or preventive benefit to the individual study participant. Types of non-therapeutic studies include some Phase I trials, bioequivalence studies and bioavailability studies.

**Phase I study:** a study involving the initial administration of a new investigational intervention into humans. Although human pharmacology studies are typically identified as Phase I, they may also be later phase studies. Phase I studies usually have non-therapeutic objectives, and may be conducted in healthy volunteer subjects, or in patients with a specific disease (particularly in the case of studies of cytotoxic drugs). Studies in this phase can be open or baseline controlled, or may use randomisation with blinding to improve the validity of observations. Studies conducted in Phase I typically involve one or a combination of: estimation of initial safety and tolerability, pharmacokinetics, assessment of pharmacodynamics and early measurement of drug activity (ICH 1997: 6–7).

**Phase II study:** a study usually considered to start exploring the therapeutic efficacy of an intervention in patients. Initial therapeutic exploratory studies use a variety of study designs, including concurrent controls and comparisons with baseline status. Subsequent Phase II studies are usually randomised, and use concurrent controls to evaluate the efficacy of an intervention and its safety for a particular therapeutic indication. Studies in Phase II are usually conducted in a group of patients who are selected by relatively narrow criteria, leading to a relatively homogeneous population that is closely monitored. One important goal for this phase is to determine the dose(s) and regimen for Phase III studies. Additional objectives may include evaluation of potential study end-points, therapeutic regimens (including concomitant medications) and target populations (eg, mild versus severe disease) for further study in Phase II or III (ICH 1997: 7). Phase II studies are sometimes further categorised as Phase IIa studies, where the focus is on assessing dose requirements, or Phase IIb studies, which are designed to evaluate efficacy.

**Phase III study:** a study with the primary objective of demonstrating or confirming therapeutic benefit. Phase III studies are designed to confirm the preliminary evidence accumulated in Phase II that an intervention is safe and effective for the intended indication and recipient population. Studies in Phase III may also further explore the dose–response relationship, or investigate the intervention’s use in wider populations, in different stages of disease or in combination with another intervention. For interventions intended to be administered for long periods, studies involving extended exposure to the intervention are usually conducted in Phase III, although they may be started in Phase II (ICH 1997: 7).

**Phase IV study:** a study (other than routine surveillance) performed after an intervention’s approval, related to the approved indication. Phase IV studies are studies that were not considered necessary for approval but can be important for optimising the intervention’s use. They may be of any type of study design, but should have valid scientific objectives. Studies in this phase commonly examine additional drug–drug interaction or the dose–response relationship or safety, or investigate use under the approved indication, such as mortality/morbidity studies and epidemiological studies (ICH 1997: 8).

**Placebo:** an inactive or ‘dummy’ intervention used in some studies to help assess the comparative safety and effectiveness of an active intervention. Using a placebo assists blinding, as participants (and, in some studies, investigators) are unaware to which group each participant has been allocated.

**Principal investigator:** the qualified health professional or qualified researcher with primary responsibility for the design and conduct of a particular investigation (referred to as a ‘co-ordinating investigator’ in the SOPs for HDECs).

**PPPR Act 1988:** the Protection of Personal and Property Rights Act 1988.

**Protocol:** a protocol document describes the objective(s), design, methodology, statistical considerations and organisation of a trial. The protocol often gives the background and rationale for the trial, but these could be provided in other documents referenced by the protocol (ICH 1996: 6).

**Randomised controlled trial:** the general term for a study in which participants are randomly assigned to intervention and control groups to receive or not receive a diagnostic, preventive or therapeutic intervention. Findings in such a study are assessed by comparing rates of disease, death, recovery or other appropriate end-points in the intervention and control groups.

**Serious adverse drug reaction:** an adverse drug reaction that results in death, or is life-threatening, or requires inpatient hospitalisation or results in prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, or is a medically important event or reaction (MHRA 2009).

**Serious adverse event:** an adverse event that results in death, or is life-threatening, or requires inpatient hospitalisation or results in prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, or is a medically important event or reaction (MHRA 2009).

**SOPs:** standard operating procedures for HDECs.

**Sponsor:** any individual, company, institution or organisation that has responsibility for the initiation, management and/or financing of a clinical trial (ICH 1996: 7).

**Standing Committee on Therapeutic Trials (SCOTT):** a committee of the Health Research Council, responsible under the Medicines Act 1981, section 30 (HRC 2005b) for assessing the scientific validity and safety of clinical trials.

**Study:** in this context, an intervention study, unless otherwise specified.

**Suspected unexpected serious adverse reaction (SUSAR):** any unexpected serious adverse reaction that is suspected to be related to an intervention under study (MHRA 2009).

**Therapeutic study:** a study that examines interventions that hold the prospect of direct diagnostic, therapeutic or preventive benefit for the individual participant. This includes studies undertaken in the context of clinical care.

**Treatment:** any type of intervention that may be studied, including medicines, tests, methods of health care delivery and other health or disability support interventions.

**Trial management committee** (or trial steering group): a group formed to provide overall supervision of a trial. Membership should include one or more investigators, the trial biostatistician and, in some cases, one or more independent people.

**Unexpected adverse reaction:** an adverse reaction, the nature and severity of which are not consistent with information about the intervention in the investigator's brochure (or, for a product with marketing authorisation, in the summary of product characteristics for that product) (MHRA 2009).

**Unexpected serious adverse reaction:** an unexpected adverse reaction that results in death, or is life-threatening, or requires inpatient hospitalisation or results in prolongation of existing hospitalisation, or results in persistent or significant disability or incapacity, or consists of a congenital anomaly or birth defect, or is a medically important event or reaction (MHRA 2009).

**WHO Operational Guidelines:** the World Health Organization *Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards* (TDR 2005).

# Appendix 1: Joint Health Research Council and NEAC guidance on features of robust peer review for assessing the scientific validity of research

## Background

This document seeks to outline the principles of peer review that might be undertaken to assure New Zealand's Health and Disability Ethics Committees (HDECs) of the scientific validity of a research proposal. Scientific validity of a research project is one component of the research being ethically sound. Research with insufficient scientific validity will waste scarce resources, will misuse the trust and commitment of participants, and may needlessly expose them to risk for no appropriate return.

The term 'scientific validity' is used in the 2012 *Standard operating procedures* (SOPs) for HDECs, without definition. NEAC's *Ethical Guidelines for Observational Studies* (2012) and these *Guidelines* refer to studies being 'scientifically sound', which encompasses the expectation that a proposal's objectives can reasonably be expected to be achieved. *Standards and Operational Guidance for Ethics Review of Health-Related Research with Human Participants* (WHO 2011) refers to 'valid scientific methods' as part of Standard 7: Ethical basis for decision-making in research ethics committees. Important factors in this standard include how the study will be conducted, the qualifications of the researcher(s), the adequacy of provisions made for monitoring and auditing, and the adequacy of the study site (eg, availability of qualified staff and appropriate infrastructures).

The Government, in its response to the Health Committee's 2011 Inquiry into improving New Zealand's environment to support innovation through clinical trials (Health Committee, June 2011), decided that researchers and research sponsors will be 'responsible for ensuring that their research has been peer-reviewed for scientific quality' (response to recommendation 14). The SOPs state that HDECs will check that appropriate peer review (of scientific validity) has been carried out, but will not conduct it themselves. HDECs may not require specific, defined changes to research protocols on the grounds of lack of scientific validity as a condition of HDEC approval.

This guidance does not explain *how* review of a research proposal can be obtained, but lays out the features of a fit-for-purpose peer review process. It is anticipated that these guidelines will be of use both to those seeking ethical approval for their health and disability research, and to those undertaking ethical review of research proposals, to verify that the scientific validity of proposed research has been assured through an appropriate peer review process.

## Peer review

The role of New Zealand's HDECs is to check that proposed health and disability research meets established ethical standards that aim to protect participants (see the SOPs). The SOPs require that researchers and sponsors ensure that the scientific validity of proposed research has been peer-reviewed before an application is made to an HDEC. In this context, peer review is the process by which an applicant can assure an HDEC that a proposal has an appropriate degree of scientific merit, feasibility and likelihood of impact.

## Areas of focus during peer review

Peer review can be tailored to deliver opinions on a variety of matters relating to a health and disability research proposal. In order to determine scientific validity, the following factors should specifically be determined:

- **The relative merit of the research:** A key consideration is whether the proposed work is important, worthwhile and justifiable. The research should address a health issue that is important for health and/or society. The aims, research questions and hypotheses will build on and address gaps in existing knowledge.
- **The design and methods:** The quality of study design and methods should be reviewed to assess its robustness. This might include study methodology, a description of sample recruitment and characteristics (including number, gender and ethnicity where relevant) and proposed methods of data analysis. Indication of timelines for the research should be included.
- **The feasibility of the research:** This includes whether the overall strategy, methodology and analyses are well reasoned and appropriate to achieve the specific aims of the project. It should determine whether the research has the likelihood, on balance, of improving scientific knowledge, concepts, technical capacity or methods in the research field, or of contributing to better treatments, services, health outcomes or preventive interventions. The research will be achievable within the specified timeframe and the research team has the appropriate experience and expertise to undertake the research.

## Core features of the peer review process

A peer review process should be commensurate with the type of proposal, the potential risk to participants and where the research will be undertaken. The type of peer review process that is used must be fit-for-purpose and justifiable. For example, the mechanism for delivering peer review of a graduate student project carried out largely within a tertiary institution will differ from that of a multi-centre clinical trial. Opinions from one or more peers may be sought; again, the extent of peer review should be fit-for-purpose. Despite potential differences, an appropriate process for ensuring scientific validity will have the following features:

- **Peer review delivers an informed opinion:** An effective peer review process provides perspectives from subject matter experts. It may be suitable for informed perspectives to be sought from individuals in the same organisation as the researcher, as long as the requirements of freedom from bias, equity and fairness can be met. An appropriate peer is one who can deliver an informed opinion on some or all of a proposal. Reviewers will be knowledgeable about the topic and/or context for the research, have the appropriate expertise relative to the breadth and scope of research under review and, as a result, will be well placed to make a statement as to whether the research in question has verifiable scientific merit. Peer review of scientific validity may include consideration of cultural relevance and appropriateness.
- **Peer review delivers an objective opinion:** Those acting in the capacity of reviewers are charged with delivering a balanced and considered analysis of the research. Generally, the success of the peer review process is determined by the extent to which these evaluations can be considered free of bias, equitable and fair. Objectivity can be compromised if peer reviewers have conflicts of interest, and so appropriate peer reviewers typically will not be materially connected to the researcher(s) in a way that might undermine objectivity, and be free from either positive or negative inducements.
- **A consensus opinion on scientific validity is formed:** An HDEC will need to receive assurance that the peer review process has delivered support for the scientific validity of the proposed research. When a peer review process has engaged a range of experts, there needs to be a process that leads to a consensus opinion about the quality of the research.
- **Intellectual capital in the research proposal is respected:** A peer reviewer is in a privileged position through having access to the unexploited ideas and intellectual capital of the researcher. A peer review process should require that reviewers do not disclose the substance of any research proposal, unless there is explicit permission to do so.

## Limitations of peer review

Peer reviewers typically are not privy to the operational details of a proposed research study. Research proposals usually will outline a methodology, but not explain its implementation in detail. For example, a proposal might state how many patients will be recruited, but will not necessarily explain how patients will be approached, how they might be compensated for participation, nor what information any participant information sheet might contain. Similarly, the detailed clinical trial protocols are not typically included in a peer review. (Detailed examination of a trial protocol is often undertaken by the independent data and safety monitoring committee associated with the trial.) Ethics committees should be aware that studies can be of satisfactory scientific quality as judged by peer review, but still pose ethical concerns because of how the research is to be operationalised. Necessarily, consideration of the safety of participants and researchers, and the balance of risk and benefit, by ethics committees is likely to involve scrutiny of study design and execution.

## Appendix 2: Research papers

**Note:** This appendix derives from the Ministry of Health's 2006 *Operational Standard for Ethics Committees: Updated Edition* (Wellington: Ministry of Health).

### Research involving children and young people

This section presents the ethical guidelines developed by Nicola Peart and David Holdaway on health research with children and young people (for full references refer to the original article).<sup>1</sup> For further information on issues relating to research with children, refer to the following publications.

- Peart N, Holdaway D. 1998. Legal and ethical issues of health research with children. *Children's Issues* 2: 42–6.
- Peart N. 2000. Health research with children: the New Zealand experience. *Current Legal Issues* 3: 421–39.
- Ministry of Health. 1999. *Consent in Child and Youth Health: Information for practitioners*. Wellington: Ministry of Health.

The special vulnerability of children makes consideration of involving them as research participants particularly important. To safeguard their interests and to protect them from harm, special ethical considerations should be in place for reviewing research with children.

### Principles

These guidelines are based on six principles, based on the Guidelines of the Royal College of Paediatrics and Child Health 1999 and the European Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine 1996.

- Research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner.
- Children are not small adults; they have their own unique set of interests.
- Research should only be done with children if comparable research with adults could not answer the same question and the purpose of the research is to obtain knowledge relevant to the health needs of children.
- A research procedure which is not intended directly to benefit the child participant is not necessarily unethical.
- Legally valid consent should be obtained from the child, parent or guardian as appropriate. When parental consent is obtained, the assent or consent of the children should, wherever possible, also be obtained by the researcher.

<sup>1</sup> Peart N, Holdaway D. 2000. Ethical Guidelines for Health Research with Children. *New Zealand Bioethics Journal* 1(2): 3–9.

## Nature and design of research

Before undertaking research with children, the investigator must ensure that:

- children will not be involved in research that might equally well be carried out with adults
- the purpose of the research is to obtain knowledge relevant to the health needs of children
- if a choice of age groups is possible, older children should be involved in preference to younger ones
- the research is designed or supervised and carried out by people experienced in working with children
- the number of children involved is limited to the number which is scientifically and clinically essential.

## Risk

Research procedures or interventions which are intended to provide direct therapeutic benefit to the child participants may be undertaken if:

- the risk is justified by the anticipated benefit to the child participants
- any ratio of the anticipated benefit to the risk is likely to be at least as favourable to the child participant as any available alternative.

Research procedures or interventions which are not intended to be of direct benefit to the child participants, but which are likely to yield generalisable knowledge about the child's disorder or condition which is of vital importance for the understanding or amelioration of the child's disorder or condition, may be undertaken if:

- any risk represents a minor increase over minimal risk
- the interventions or procedures present experiences to the child participants which are reasonably commensurate with those inherent in their actual or expected medical, psychological, social or educational situations.

Research procedures which are not intended to be of direct benefit to the child participants, and do not come within the scope of research set out in the paragraphs above, may be undertaken only if the risk presented by the interventions to the child participant is:

- minimal; and
- commensurate with the importance of the knowledge to be gained.

## Informed consent

### Information

When inviting children to participate in any research, the investigator must ensure that the children and, where appropriate, the children's parents, guardians or caregivers have been fully informed about the research in a manner best suited to their needs.

- Each child must be given full information about the research in a form that he or she can readily understand.
- Children must be advised of their right to decline participation and their right to withdraw from the research at any time without giving a reason.
- Investigators must give the children an opportunity to ask questions and to have those questions answered to the children's satisfaction.
- If proxy consent is required, the proxy must also be given full information about the research and be advised of the child's right to decline participation or withdraw from the research at any time.
- The proxy must be given an opportunity to ask questions and have them answered to the proxy's satisfaction.

## **Consent**

Before undertaking research with children, the investigator must ensure that appropriate consent is sought on the basis of the information provided.

- The consent of a child of or over the age of 16 must be obtained, and has the same effect as if the child were of full age.
- If the child is below the age of 16, but has the competence to understand the nature, risks and consequences of the research:
  - the consent of the child must be obtained; and
  - that consent will have the same effect as if the child were of full age.
- If the child is below the age of 16, and lacks the necessary competence to give legally effective consent:
  - the child's parent or legal guardian must give permission for the child's participation
  - the child's assent must be obtained unless the child is unable to communicate
  - the refusal of a child to participate in research must be respected unless, according to the research protocol, the child would receive therapy for which there is no medically acceptable alternative.
- Care must be taken to ensure that no pressure is placed upon a child to consent to participate in research, especially if the procedures are not intended to be of direct benefit to the child participants.
- The requirement for written consent should take into consideration the age and competence of the child.

## **Inducements**

Families and children must not receive any financial payments or other reward for participating in the research. Only expenses resulting from participation may be reimbursed.

## Health research data

Retention and use of personally identifiable health research data.

- Research data pertaining to the child participants should be retained by the researcher for ten years after the child has attained the age of 16.
- Children have the right to withdraw consent to the continued use or retention of personally identifiable health research data once they attain the age of 16.

## Applicable laws and regulations

Section 36 of the Care of Children Act 2004 governs consent to any medical, surgical or dental procedures in relation to a child. Right 7 of the Code of Health and Disability Services Consumers Rights 1996 is also applicable in relation to consent to treatment and/or research.

## Research involving people with intellectual disabilities

This section draws extensively on the 1998 paper 'Research Involving People with Intellectual Disabilities: Issues of Informed Consent and Participation' by Anne Bray, Director, Donald Beasley Institute Inc (for full references refer to the original paper).

### Introduction

The predominant ethical concern in research involving individuals with intellectual disabilities relates to the extent to which such individuals are able to give informed consent to participate in research. People with intellectual disabilities may be at risk of information not being provided at an appropriate level, of not being able to understand or reason adequately about the information, or of being easily coerced into taking part.

People with intellectual disabilities have the same rights as other members of New Zealand society. These rights include the right to choose whether to participate in research and the right to be protected from any undue risks from participation in research.

Historically, they have experienced disadvantage, over-protection and abuse. Their right to give informed consent has typically been ignored, and unwarranted assumptions have been made about their lack of legal competence.

Research evidence and changing conceptions of individual rights have led to statutory changes which recognise a continuum of competence and its specificity to particular situations for a particular individual.

Research involving people with intellectual disabilities should:

- be designed and focuses on an issue of significant importance to people with intellectual disabilities
- respect the rights of people with intellectual disabilities to make their own choices and give informed consent
- protect people with intellectual disabilities from undue risks, exploitation and abuse.

## Capacity to give informed consent

It has often been assumed that anyone who has any degree of intellectual disability is therefore incapable of giving informed consent to treatment or involvement in research. The capacity to give informed consent is a continuum, and a person's capacity to make decisions may vary depending on the specific topic or area of life under consideration.

People with intellectual disabilities vary widely in their degree of intellectual disability and in their ability to understand, reason and communicate. Many people with intellectual disabilities will be capable of making decisions or giving informed consent, depending on the nature of the specific decision in question. The capacity of an individual to give informed consent should be assessed on a case-by-case basis.

When considering the competence of a person with an intellectual disability to give informed consent it should be recognised that different decisions demand different levels of competence. In other words, a person with an intellectual disability may not be competent to give informed consent to participate in a clinical trial of psychoactive drugs but may well be competent to consent to be interviewed about his/her experiences of community living.

Issues of competence to consent are highly significant for people with intellectual disabilities in their daily lives. Questions arise in the provision of health and disability services, their rights to undertake legal contracts, criminal liability, ability to be a witness in a trial – to mention a few.

Factors to consider when researching with people with intellectual disabilities include the following.

- People with intellectual disabilities are not usually concerned about the implications of research for public policy, but are more likely to be interested in what changes the research can bring about for them personally.
- People with intellectual disabilities often have difficulty separating hypothetical situations from personal anxieties and concerns.
- People with intellectual disabilities often have fewer opportunities to acquire ordinary knowledge (for example, due to lack of or inappropriate education, segregation, over-protection or lack of access to information).
- The most difficult area for people with intellectual disabilities to understand is the area of legal rights. They may have limited experience of their voluntary decisions being respected.
- People with intellectual disabilities often have a tendency to comply with the perceived demands of an authority figure.
- Even persons with severe disabilities may be able to make decisions if given the opportunity, support and training to do so.

People with intellectual disabilities may have specific difficulties relevant to informed consent, including:

- a reduced vocabulary and understanding of abstract words and ideas
- shorter attention spans and reduced short-term memory capacity
- limited abstraction skills (that is, concrete and literal understanding of questions and situations)
- a reluctance to rarely say they do not understand unless directly asked
- difficulty following long, run-on sentences
- difficulty answering time-related questions.

Proposals for research involving people with intellectual disabilities should clearly describe:

- the proposed sample of participants and the possible range of intellectual disabilities to be included
- how the researcher will determine competence to give informed consent for each individual participant
- a rationale for the decisions on judgment of competence in terms of the complexity of the research and/or the possible risks to participants.

### **Providing information to potential participants**

Particular attention should be paid to how to provide information to potential participants with intellectual disabilities.

A person with an intellectual disability has the right to receive information that he or she can understand, and which takes account of his or her individual circumstances, such as level of understanding, reading ability, and knowledge about research and research requirements.

People with intellectual disabilities can be very valuable advisors to researchers on the wording of information sheets. Whenever possible, information sheets and consent forms should be trialled with a group of people who are similar to potential study participants.

Adequate time must be allowed for the process of obtaining informed consent from people with intellectual disabilities. Whenever possible, information about the research should be provided to each participant on an individual, face-to-face basis.

Careful consideration should be given to how other people who are concerned members of the person's support network will be informed about the research, while ensuring that potential participants experience no coercion in making their decision whether or not to take part in the research.

A permanent record of the process of information provision should be kept.

## Recording consent

While written consent is the usual method of recording informed consent in research, some people with intellectual disabilities may be unable to read and/or write, and other methods of obtaining and recording informed consent may be more appropriate.

The critical ethical issue relates to obtaining consent based on information and non-coercion. To assure other people that this has occurred, it is necessary to have a permanent record. An audiotape of an oral discussion of the researcher and a participant involving information provision and decision-making can provide an even fuller record of the validity of the consent obtained than a signature on a consent form.

## Applicable laws and regulations

Applicable legislation includes:

- sections 6 and 18 of the Protection of Personal and Property Rights Act 1988
- section 17 of the Judicature Act 1908
- Rights 7 and 7(3) of the Code of Health and Disability Services Consumers' Rights 1996.

Case law with regard to section 17 of the Judicature Act 1908 has said that the approval of the court is required when the:

- principal or a major aim of the surgical procedure has a non-therapeutic purpose
- medical procedure involves interference with a basic human right.

## Research involving unconscious participants

Research involving unconscious participants may involve the use of an innovative practice or the evaluation of an established therapeutic practice or treatment. In some circumstances, research may involve the delivery of therapeutic interventions in emergency situations (such as consumers requiring intensive care). Whatever the case, research involving unconscious participants raises special problems regarding informed consent.

This section addresses issues arising where individuals are unconscious at the time their participation in research is being considered. When it is foreseeable that treatment will be needed and participants can be identified in advance (for example, a study to be performed after elective major surgery), informed consent may be obtained well before the surgery.

## Ethical issues

There is a general expectation that research involving participants will not be conducted without first obtaining informed consent from each participant. Research involving unconscious participants differs from standard research because the participants are unable to provide informed consent.

In a situation where a therapeutic intervention is needed and there is no alternative method of approved or generally recognised therapy that provides an equal or greater likelihood of benefiting the consumer, either by saving the person's life or improving or preventing deterioration in their physical and mental health, an innovative practice might be used to treat a consumer who cannot give informed consent if, in the opinion of the health professional, it is the most promising treatment available and it is, in their opinion, in the best interest of the consumer.

Consumers, their families and/or legal representatives should be provided with pertinent information when, and if, it becomes possible and appropriate to do so.

Wherever possible, families and/or legal representatives should be informed and given the opportunity to express their views prior to undertaking any research. The health professional should take into account the views of those suitable persons who are interested in the welfare of the consumer and are available to advise the provider. In emergency situations, decisions about a consumer's treatment (and hence, in some cases, their participation in research) may have to be made too quickly to consult with families and/or legal representatives. Whatever the case, the health practitioner must always act in the best interests of the consumer.

When a consumer recovers consciousness and is able to give informed consent, researchers should seek their consent to continue with the research.

If the proposed treatment is contrary to the known wishes of the consumer, the consumer should be excluded from the study and provided with standard care.

### **Research involving the provision of health care**

Research involving unconscious participants may involve the provision of health care. Health practitioners are required to observe a standard of care and skill to be reasonably expected in the circumstances in which treatment is provided.

Except in specific circumstances, health practitioners are also required to obtain informed consent from the consumer or a person entitled to give consent on behalf of that consumer before providing treatment.

One of the exceptions is in an emergency situation, where a health practitioner may, out of necessity, treat a consumer where the consumer cannot give consent and it is not possible to obtain consent from a person entitled to give consent on behalf of that consumer. The action or treatment must be appropriate and reasonable in the circumstances and not more extensive than required. Any action or treatment must be in the best interest of the consumer's life or physical or mental health and must not be contrary to the known wishes of the consumer.

## Risks and benefits

The risks and benefits of studies involving unconscious consumers may vary from extremely high to negligible. At one extreme, where significant incapacity or death is almost certain, a new therapeutic measure may offer a reasonable chance for recovery, sustaining life or preventing serious and permanent deficits. In other situations, the potential benefits and risks may be equally great – one may not outweigh the other. Drugs given in an effort to save the lives of trauma victims might do so at the risk of preserving those lives in a persistent vegetative state. Many studies involving unconscious consumers may be almost without risk yet yield information useful in the treatment of the consumer (for example, monitoring certain physiological events by non-invasive means).

Researchers should design their studies in such a way as to minimise risks, be able to justify anticipated benefits and ensure that the risks are reasonable in relation to the anticipated benefits.

## The legality of research involving unconscious consumers

The legality of undertaking research on unconscious people is not completely clear, and until this particular situation is raised before the courts it will continue to remain so. The area of law is governed by a number of different pieces of legislation, together with the common law. Relevant references include:

- the Code of Health and Disability Services Consumers' Rights 4(4), 6(1)(d), 7(1), 7(2), 7(4), 7(5), and 7(6)
- the Accident Compensation Act 2001, section 33
- the Crimes Act 1961, sections 61 and 61A
- the New Zealand Bill of Rights Act 1990, sections 10 and 11.

Both the Bill of Rights and the Code of Health and Disability Services Consumers' Rights 1996 relate to a person being physically involved in the research. When considering the legality of research involving unconscious consumers it is therefore important to distinguish between research where individuals directly participate (such as with an innovative practice or a clinical trial) and research that utilises information normally gathered during the course of the delivery of a currently recognised health care practice or treatment (such as the clinical evaluation of a particular treatment).

If the latter is the case (the research does not involve any additional information gathering above what would normally be associated with a particular treatment), then research can proceed if conducted in compliance with the Health Information Privacy Code 1994.

Where research would require the physical involvement of a consumer, each specific case will need to be assessed to determine whether the proposed research is in compliance with the law. The following factors should form the basis of the assessment.

- What is the age of the unconscious person?
- Can another person legally consent (parent, legal guardian, holder of enduring power of attorney)?
- What kind of research is involved (eg, leading experimentation, audit or review of data)?
- Is the research in the best interests of the individual consumer?
- What orders has the consumer given in a power of attorney or otherwise?
- How long is the consumer expected to be unconscious?
- What do the consumer's relatives think?

The list is not exhaustive, and depending on the particular circumstances other considerations may be relevant.

Researchers should demonstrate that they have adequate procedures in place for determining in each specific case whether or not the unconscious person may legally be included as a participant of the proposed research.

## Research involving consumers with a terminal illness

This section has been largely based on the section on research involving consumers with a terminal illness presented in the Institutional Review Board's *Guidebook*, last updated in 1993.<sup>2</sup>

Consumers with a terminal illness are those suffering from a deteriorating life-threatening disease or condition for which no effective standard treatment exists. It is generally considered unacceptable to ask such persons to participate in research for which alternative, not similarly burdened, populations of participants exist.

Nevertheless, it may often be necessary to involve consumers with a terminal illness in research concerning their disease and its treatment. Further, consumers with a terminal illness should not be excluded, simply because of their status, from research in which they may want to participate. Individuals with a terminal illness are a vulnerable population of research participants, and therefore require additional protection against coercion and undue influence.

### Overview

In many contexts, research involving a terminal illness and its treatment requires the involvement of consumers with a terminal illness when alternative populations for study do not exist or when involving alternative populations would be ethically unjustifiable. Two important reasons for concern regarding research involving consumers with a terminal illness are: (1) they tend to be more vulnerable to coercion or undue influence than healthy adult research participants; and (2) research involving consumers with a terminal illness is likely to present more than minimal risk.

<sup>2</sup> United States Department of Health and Human Services. 1993. *Institutional Review Board Guidebook*. Washington: Office for Human Research Protections, Chapter VI: 'Special Classes of Subjects', Section G: 'Terminally Ill Patients'.

The risk of coercion and undue influence may be caused by a variety of factors. In addition to the fact that severe illness often affects a person's competence, consumers with a terminal illness may be vulnerable to coercion or undue influence because of a real or perceived belief that participation is necessary to receive continuing care from health professionals or because the receipt of any treatment is perceived as preferable to receiving no treatment. Although consumers with a terminal illness should be protected from an understandable tendency to enrol in research under false hopes, one should not take too protective an attitude toward competent consumers simply because they have a terminal illness. Some consumers with a terminal illness may find participation in research a satisfying way of imparting some good to others out of their own misfortune.

It is important to distinguish between risks that may be justified by anticipated benefits for the research participants and risks associated with procedures performed purely for research purposes.

A particularly difficult issue relating to research involving consumers with a terminal illness arises in connection with the conduct of Phase I drug trials in which the drugs involved are known to be particularly toxic (for example, a new form of cancer chemotherapy). In some of these studies, any benefit to the participant is, at best, highly unlikely. Despite the therapeutic intent of the investigators to benefit the participant, participants may in fact experience a decline in health status, no improvements in terms of quality of life or only a short extension to their lives. It is extremely important that prospective participants be clearly informed of the nature and likelihood of the risks and benefits associated with this kind of research. The challenge to the investigator and the ethics committees is to provide consumers with an accurate description of the potential benefits without engendering false hope.

The HIV epidemic has heightened awareness of mechanisms for including in research persons who have serious and life-threatening illness. Increasingly, individuals and advocacy groups have emphasised the need for opportunities for consumers with a terminal illness to exercise their right of autonomy: to weigh for themselves the risks and benefits of participating in research on drugs, even where relatively little is known about the safety or effectiveness of the drugs. Because they may be in the very early stages of the development of their illnesses, many desperately ill individuals would like to take investigational drugs that may not be available except through limited, well-controlled clinical trials.

### **General considerations**

Research involving consumers with a terminal illness should consider having special procedures for protecting the rights and wellbeing of these participants. The nature, magnitude, and probability of the risks and benefits of the research should be identified as clearly and as accurately as possible. Special attention should be paid to the consent process, both in terms of the accuracy of the information to be provided and the manner in which consent is sought. As a general rule, accurate information concerning eligibility for participation (diagnosis and prognosis), treatment options, and risks and benefits should be conveyed clearly and in a manner that will neither engender false hope nor eliminate all hope.

Participants should be told whether or not participation in the study is a condition for receiving treatment, and any costs to the consumer of the research should be stated explicitly. Any payment should not constitute an undue inducement, particularly if the participant population is economically disadvantaged. Consumers should be provided with relevant information well in advance of making a decision about participation, and consultation with others such as family members, close friends or medical consultants should be encouraged.

Ideally the clinical investigator should be someone other than the consumer's physician, emergency services should be readily available and there be frequent monitoring of the progress of the research. Factors to consider include:

- anticipated toxicity of the therapeutic interventions
- extent to which participants are likely to be debilitated by either their illness or their therapy
- the remaining life expectancy of the participants
- whether participation in the research would require a change in residence (for example, from home or hospice to a hospital or research institution).

The investigator should also be able to answer the following questions.

### Points to consider

- Must the research involve consumers with a terminal illness to achieve its objectives?
- Is a clear explanation of the consumers' eligibility for the study provided?
- Are specific treatment alternatives, including the option of no treatment, described?
- Are the potential benefits and risks (and their probability) realistically and simply stated?
- Are the ways in which participation may affect the consumer's lifestyle clearly described?
- Is the consumer assured that he or she can withdraw from the study at any time? If withdrawal from the research will result in a consumer's discharge from a research unit or end the consumer's access to health care that has been provided in conjunction with the research, is that fully explained?
- Should a witness or health and disability consumer advocate be present during consent negotiations?
- Is there reason to require that the consumer's physician not be the clinical investigator?
- If a drug is administered at the community level, does the participant's physician have access to information about the drug's potential usefulness and potential risks?

## Research involving older persons

This section has been largely based on the section on research involving older persons presented in the Institutional Review Board's *Guidebook*.<sup>3</sup>

As the New Zealand population ages, research on the ageing process and conditions and diseases that disproportionately affect older persons has become increasingly important. The participation of older persons in research poses several issues for researchers and ethics committees; primary among them is the question of whether and when older persons need special protections, without being over-protective.

### General considerations

It is generally agreed that older persons are, as a group, heterogeneous and not usually in need of special protections, except in two circumstances: cognitive impairment and institutionalisation. Under those conditions, the same considerations are applicable as with any other person in the same circumstances.

There is no age at which prospective participants should become ineligible to participate in research. Most older people are neither cognitively impaired nor live in institutional settings. Nevertheless, investigators may avoid older persons as participants because of difficulties in recruiting them to participate. Also, conducting research with older consumers may be more difficult and more costly.

A major problem is that older people tend to have multiple conditions/co-morbidities, and this may complicate research that tries to isolate a particular intervention for a particular condition. Older people have more complications than younger people from medical drugs. Because the likelihood of unfavourable drug interactions increases with the greater the number of drugs an individual takes, for older people it is important to limit the number and dose of drugs prescribed. Symptoms of many diseases in older age may also vary quite markedly from symptoms of the same disease in earlier life.<sup>4</sup>

Older persons may have hearing or vision problems and may therefore require more time to have the study explained to them. They also drop out of studies at a higher rate than do younger participants, so that investigators may need to recruit more participants initially to for this possibility.

Despite these difficulties, including older persons in research is important. Older persons should share in the benefits and burdens of research.

<sup>3</sup> United States Department of Health and Human Services. 1993. Chapter VI: 'Special Classes of Subjects', Section H: 'Elderly/Aged Persons'.

<sup>4</sup> Prime Ministerial Task Force. 1997. *Facing the Future: A Strategic Plan*. Wellington: Prime Ministerial Task Force. Reference from Appendix D: 'Disease Effects in Old Age'.

Cognitive impairment in older participants should be treated as it would be in any prospective participant. The participant population should comprise cognitively impaired persons only when competent participants are not appropriate for the study, if the study is related to a problem unique to persons with that disability and if the study involves minimal risk.

The use of age as the criterion of ability to consent and therefore participate in research is not valid. While memory may be a problem for some older participants (thus putting into question their ability to provide continuing consent), the question is whether, despite some impairment to competence, participants can make reasonable choices.

In the past, persons in nursing homes or other institutions have been selected as participants because of their easy accessibility. It is now recognised, however, that conditions in institutional settings increase the chances for coercion and undue influence because of the lack of freedom inherent in such situations. Research in these settings should therefore be avoided, unless the involvement of the institutional population is necessary to the conduct of the research (for example, the disease or condition is endemic to the institutional setting, persons who suffer from the disease or condition reside primarily in institutions, or the study focuses on the institutional setting itself). What may seem trivial to the average person in terms of risk, discomfort, disorientation or dehumanising effects may not seem so trivial to the potentially vulnerable populations in institutional settings.

### Points to consider

- Does the proposed consent process provide mechanisms for determining the adequacy of prospective participants' comprehension and recall?
- How will participants' competence to consent be determined?
- Will the research take place in an institutional setting? Has the possibility of coercion and undue influence been sufficiently minimised?
- If older people have been excluded from the research, are the reasons valid?
- Does the research methodology make adequate provision for older people (and others) with hearing and/or vision problems or with difficulty in communicating (eg, due to stroke, multiple sclerosis or Parkinsonism)?

## Research involving specific categories of healthy participants

### Students

Universities provide investigators with a ready pool of research participants: students. The problem with student participation in research conducted at the university is the possibility that their agreement to participate will not be freely given. Students may volunteer to participate out of a belief that doing so will place them in good favour with academic staff (for example, that participating will result in receiving better grades, recommendations or employment, or the like), or that failure to participate will negatively affect their relationship with the investigator or faculty generally.

Prohibiting all student participation in research, however, would be an over-protective reaction. An alternative way to protect against coercion is to require that researchers advertise for participants generally (for example, through notices posted in the school or department) rather than recruit individual students directly. As with any research involving a potentially vulnerable participant population, special attention should be paid to the potential for coercion or undue influence, and the possibility of exploitation should be reduced or eliminated.

Another concern raised by the involvement of students as research participants is confidentiality. Research involving the collection of data on sensitive topics such as mental health, sexual activity or the use of illicit drugs or alcohol presents risks to participants which they should be made aware of and from which they should be protected, to the greatest extent possible. The close environment of the university amplifies this problem.

## Employees

The risks for employees as research participants are similar to those applicable to students: coercion, undue influence and breach of confidentiality. Employees of drug companies are often seen by investigators as ideal participants, because of their ability to comprehend the protocol and to understand the importance of the research and compliance with the protocol.

Just as student participation raises questions of the ability to exercise free choice because of the possibility that grades or other important factors will be affected by decisions to participate, employee research programmes raise the possibility that the decision will affect performance evaluations or job advancement. It may also be difficult to maintain the confidentiality of personal medical information or research data when the participants are also employees; particularly when the employer is also a medical institution.

## Prison inmates

The involvement of inmates in research was once common because the stability of inmate life (controlled diet, ready availability of participants for follow-up) made prisons attractive research environments. However, the very fact of incarceration may make it difficult or impossible for inmates to give voluntary, informed consent.

Where a study proposes to use prison inmates as a study population a threshold question to be asked is whether that population was chosen simply out of convenience to the investigator.

Some procedures that would inconvenience free participants are not a burden to inmates. However, the nature of incarceration may conflict with the ethical principle of autonomy, which requires that the participant be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching or other ulterior form of constraint or coercion.

The primary issue surrounding the participation of inmates in research has always been whether inmates have a real choice whether to participate in research, or whether their situation prohibits the exercise of free choice. A secondary issue is whether confidentiality of participation and of data can be adequately maintained in the prison.

The circumstances common in prisons create environments in which the offer to participate in research is necessarily coercive or creates an undue influence in favour of participation. The desire to obtain the advantages offered to those who agree to participate may preclude their ability to weigh fairly the risks and benefits involved in participation. For example, the investigator may propose to move the research participants to special units where they are given medical care and where the living conditions are better than those provided to the general prison population. Even the opportunity to leave the prison cell and interact with people from outside the prison may act as an undue inducement to participate in research.

In addition to problems of coercion and undue inducement, the involvement of inmates in research raises questions of burden and benefit. Inmates should neither bear an unfair share of the burden of participating in research, nor be excluded from its benefits, to the extent that voluntary participation is possible.

Inmates' rights to self-determination (autonomy) should not be circumscribed more than required by applicable regulations. One should refrain from assuming, without cause, that prospective inmate-participants will lack the ability to make autonomous decisions whether to participate in research. To the extent that inmate-participants can voluntarily consent to participation, and to the extent allowable under applicable regulations, inmates should be allowed the opportunity to participate in potentially beneficial research.

Finally, confidentiality is extremely difficult to maintain in an environment such as prisons, in which there is no privacy. In prisons, people do not move about freely; the movements of inmates are carefully tracked. When inmates are moved around (for example, to go to a research appointment), everyone will know about it. Prison records, including medical records, are accessible to persons who in other settings would not have access to such personal information. Consider the inmate participating in HIV-related research. How will the sensitive nature of the research be kept secret? The investigator must be able to ensure that the necessary confidentiality can and will be maintained so that the participants are not subjected to any risk from participation.

# Appendix 3: The National Ethics Advisory Committee

The National Ethics Advisory Committee – Kāhui Matatika o te Motu (NEAC) is an independent advisor to the Minister of Health on ethical issues of national significance concerning health and disability matters. NEAC's statutory functions are to:

- advise the Minister of Health on ethical issues of national significance in respect of any health and disability matters (including research and services)
- determine nationally consistent ethical standards across the health sector and provide scrutiny for national health research and health services.

NEAC works in the context of the New Zealand Public Health and Disability Act 2000. The members of NEAC, appointed by the Minister, bring expertise in ethics, health and disability research, health service provision and leadership, public health, epidemiology, law, Māori health and consumer advocacy.

## Committee membership

Andrew Moore, Chair (to July 2010)

Victoria Hinson, Chair (from June 2011)

Robin Wray (from June 2009, appointed as Chair July 2010)

Allison Kirkman, Deputy Chair (to December 2007)

Geoffrey Fougere, Deputy Chair (to September 2011)

Robin Olds, Deputy Chair (from September 2008, appointed as Deputy Chair October 2011)

Michael Ardagh (to December 2007)

Dale Bramley (to December 2007)

Lorna Dyall (from June 2009)

Michael Findlay (from December 2006)

Adriana Gunder (from October 2011)

Andrew Hall (from November 2008, reappointed October 2012)

Elisabeth Harding (to December 2007)

John Hinchcliff (to June 2009)

Barbara Holland (to June 2009)

Te Kani Kingi (to June 2009)

Jacob Te Kurapa (from June 2009)

Robert Logan (from November 2008, reappointed October 2012)

Joanna Manning (to December 2011)

John McCall (from July 2010)

Charlotte Paul (to December 2007)

Ann Richardson (to September 2008)

Diana Sarfati (from October 2011)

Elizabeth Smales (to September 2011)

Fa'afatai Sopoaga (from October 2011)  
Martin Sullivan (to December 2007)  
Martin Wilkinson (from July 2010)

### **Secretariat for this project**

Annabel Begg, Public Health Medicine Registrar (2004–2005)  
Barbara Burt, Senior Analyst (to July 2011)  
Helen Colebrook, Senior Analyst (2011–2012)  
Fiona Imlach, Public Health Medicine Registrar (2006–2007)  
Gabrielle McDonald, Public Health Medicine Registrar (2007–2009)  
Vanessa Roberts, Analyst  
Olivia Stapleton, Senior Policy Analyst (2011–2012)

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**Note:** A bibliography of works consulted when preparing these *Guidelines* is available on NEAC's website ([www.neac.health.govt.nz](http://www.neac.health.govt.nz)) or by contacting the NEAC secretariat.

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