Ethics of Intervention Studies

Discussion Document and Draft Ethical Guidelines for Intervention Studies

June 2008

Citation: National Ethics Advisory Committee. 2008. *Ethics of Intervention Studies: Discussion Document and draft Ethical Guidelines for Intervention Studies.* Wellington: Ministry of Health.

Published in June 2008 for the
National Ethics Advisory Committee – Kāhui Matatika o te Motu
by the Ministry of Health
PO Box 5013, Wellington, New Zealand

ISBN: 978-0-478-31766-4 (print)
ISBN: 978-0-478-31767-1 (online)
HP 4593

This publication is available on the National Ethics Advisory Committee website:
http://www.neac.health.govt.nz

National Ethics Advisory Committee
Kāhui Matatika o te Motu

Foreword

In this two-part publication, the National Ethics Advisory Committee – Kāhui Matatika o te Motu (NEAC) presents this Discussion Document (Part A) and the proposed *Ethical Guidelines for Intervention Studies* (the draft *Guidelines* – Part B).

Health professionals offer 'interventions' to prevent, diagnose or treat illness or disease. They need to know which interventions are safe and effective for the people who seek their help. Intervention studies are their main source of reliable information on this subject. In these studies, the investigator intervenes and then studies the effects of the intervention. A clinical trial of a new blood pressure medicine is an example of an intervention study.

Through intervention studies, clinician-investigators can exercise the sort of critical thinking, innovation and evidence-based development of practice that improves patient care. Facilitating high quality intervention studies can also help health care providers to attract and retain good staff. In short, high quality intervention studies are good for patient care.

There are strong reasons for health care providers and research funders to facilitate good intervention studies, but there are also significant issues that must be addressed. In general, intervention studies entail a higher risk than other kinds of studies. One reason for this is that two different roles and motivations are involved: the clinician wishes to provide the best care and the investigator wishes to add to knowledge. For the clinician-investigator, there is some potential for conflict between these two roles. Another reason for the greater risk is that in intervention studies, the investigator controls and in many cases alters the treatments that study participants would otherwise receive, which has potential for both benefit and harm. Further, there is greater potential for commercial influence on intervention studies than on other sorts of study, with consequently greater potential for conflict between commercial interests and participant and public interests. There is a particular need for attention to non-therapeutic intervention studies, in which participants receive interventions that are not intended to benefit them.

Some intervention studies (for example, with patients who are not capable of giving consent) are highly beneficial to current and especially future patients, but New Zealand law does not provide clear pathways for their conduct. One of the aims of this Discussion Document and the draft *Guidelines* is to identify ethically sound pathways, in accordance with best international standards, to help investigators and patients to conduct these beneficial studies.

Given their power for good and their potential for harm, it is important that intervention studies are scientifically and ethically sound. NEAC's Discussion Document and draft *Guidelines* on intervention studies aim to contribute to better health outcomes and reduced health inequalities for New Zealanders by assisting researchers to perform sound intervention studies. This Discussion Document and the draft *Guidelines* pursue these aims by:

- identifying ethical issues for intervention studies in New Zealand
- considering how these issues are currently addressed
- identifying which issues need to be addressed more effectively
- proposing options for addressing these issues more effectively by:
  - identifying the common-sense ethical basis for guidance (for example, that study participants should be treated fairly compared with people not in the study)
  - bringing the best available national and international guidance from many sources together in a single piece of New Zealand guidance
  - developing new guidance where best available national and international guidance does not fully address the issues
  - proposing guidance to address the New Zealand–specific features of issues (for example, concerning compensation for injury in studies)
  - providing only broad guidance on issues where there is current international debate but not yet consensus
  - providing paths for investigators to address challenging issues (for example, for studies whose participants do not have the capacity to consent) consistent with both international best practice and New Zealand law
  - providing an accessible resource to assist all who deal with intervention studies (for example, patients and their families, study participants, investigators, health care and disability support providers, and ethics committees) to facilitate good studies and address the ethical issues they raise.

NEAC now invites feedback on this Discussion Document and the draft *Guidelines* from individuals and groups with a particular interest in health and disability matters and from the wider public. In accordance with its statutory functions, the Committee proposes to build on insights gained during consultation by revising its draft *Guidelines*, making recommendations to the Minister of Health, and establishing agreed national ethical standards.

Andrew Moore
Chair
National Ethics Advisory Committee
Kāhui Matatika o te Motu

How to respond

Ethics of Intervention Studies

Discussion document and draft *Guidelines*

The National Ethics Advisory Committee – Kāhui Matatika o te Motu (NEAC) is seeking your feedback on this Discussion Document to help make the *Ethical Guidelines for Intervention Studies* as useful as possible.

NEAC is interested in your comments on any aspect of the Discussion Document (Part A) and draft *Guidelines* (Part B). There are some questions stated at the end of this publication ('Questions for feedback') that you might like to use to help organise and present your feedback. Please also feel free to make additional comments.

There are two ways you can respond to this publication.

1. Complete the questions as an electronic Word document and either email it, or print it out and send it by post, to NEAC at the relevant address below.
2. Write your comments as an email or as a letter that you can send to NEAC at the relevant address below.

There is also a tear-out page at the end of this publication you may like to send us with your response.

This publication is available on the NEAC website, http://www.neac.health.govt.nz

Please respond by 23 July 2008.

Contact details

Postal address: NEAC – Intervention Studies
PO Box 5013
WELLINGTON

Email: neac@moh.govt.nz
(Please put 'Intervention Studies' in the subject line.)

Contents

Glossary of terms and abbreviations

For more detailed discussion of key definitions see 'Definitions and scope of the *Guidelines*' in Section 2 of the draft *Guidelines* (Part B).

Adverse event

An adverse event is any undesirable event occurring to a participant during an intervention study, whether or not it is considered to be related to participation in the study.

Bioavailability studies

Bioavailability studies examine 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 studies

Bioequivalence studies involve showing that the bioavailability of one formulation of a drug is equivalent to another formulation of the same drug (Chow 2003: 83).

CIOMS *Guidelines*

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

Community intervention studies

Community intervention studies investigate strategies designed to improve the health of individuals and populations. They do this by promoting wider adoption of prevention; detecting and treating disease early; increasing the availability of, and reducing barriers to, services that influence healthful behaviours; and improving psychological status through information, counselling or services (Glanz et al 1996: 156).

Data monitoring committee

A data monitoring committee is an independent 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).

Declaration of Helsinki

World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects (WMA 2004).

DSMB

Data and Safety Monitoring Board.

The Code

Health and Disability Commissioner (Code of Health and Disability Services Consumers' Rights) Regulations 1996 (the Code).

HRC *Guidelines*

Health Research Council's *Guidelines on Ethics in Health Research* (HRC 2005a).

Innovative practice

Innovative practice is 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. (Ministry of Health 2006b: paragraph 121).

Intervention study

In an intervention study, 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.

IPRC Act

Injury Prevention, Rehabilitation, and Compensation Act 2001.

Non-therapeutic research

Non-therapeutic research examines interventions that do not offer direct diagnostic, therapeutic or preventive benefit to the individual participant in the study. Types of non-therapeutic trials include some phase I trials, bioequivalence studies and bioavailability studies.

Operational Standard

Ministry of Health's *Operational Standard for Ethics Committees* (Ministry of Health 2006b).

Phase I trials

Phase I trials are the first trials of a new active ingredient or new formulations in humans. They are often carried out in healthy volunteers. Phase I trials aim to establish a preliminary evaluation of safety, a first outline of the pharmacokinetic profile and, where possible, a pharmacodynamic profile of the active ingredient in humans (WHO 1995: 6).

Phase II trials

Phase II trials are performed in a limited number of participants and are often, at a later stage, of a comparative design. Their purpose is to demonstrate therapeutic activity and to assess the short-term safety of the active ingredient in patients with a disease or condition for which the active ingredient is intended. These trials also aim to determine the appropriate dose ranges or regimens and (if possible) to clarify dose–response relationships in order to provide an optimal background for the design of extensive therapeutic trials (WHO 1995: 6).

Phase III trials

Phase III trials are performed in larger (and possibly varied) patient groups with the purpose of determining the short- and long-term safety/efficacy balance of formulation(s) of the active ingredient, and to assess its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored, such as clinically relevant drug interactions, or factors such as age that lead to differences in effect. The design of phase III trials should preferably be randomised and double-blind, but other designs may be acceptable, for example, long-term safety studies. Generally, the conditions under which phase III trials are carried out should be as close as possible to normal conditions of use (WHO 1995: 6).

Placebo

A placebo is an inactive or 'dummy' intervention used in some studies to help assess the comparative safety and effectiveness of an active intervention.

PPPR Act

Protection of Personal and Property Rights Act 1988.

Primary end-points

Primary end-points (or primary outcome measures) are the pre-specified outcome variables of interest in the study. Differences in outcome variables between groups are believed to be the result of the differing interventions. The primary end-point is the most important outcome. Data on secondary outcomes are used to evaluate additional effects of the intervention (Altman et al 2001).

Randomised controlled trial

A randomised controlled trial is 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. The study findings are assessed by comparing the rates of disease, death, recovery or other appropriate end-points in the intervention and control groups.

RMI *Guidelines*

Researched Medicines Industry Association of New Zealand's *Guidelines on Clinical Trials: Compensation for Injury Resulting from Participation in an Industry-sponsored Clinical Trial* (RMI 1997).

Serious adverse event

A serious adverse event is a 'significant hazard, contraindication, side effect or precaution [and] ... [i]ncludes any event that is fatal or life-threatening, is disabling, requires or prolongs in-patient hospitalisation, (except where death or hospitalisation is a defined end-point of the study), or is a congenital anomaly, malignancy or overdose' (Medsafe 1998: 48).

Study

A study in this publication means an intervention study, unless otherwise specified.

Therapeutic research

Therapeutic research examines interventions that offer direct diagnostic, therapeutic or preventive benefit for the individual participant.

Treatment

Treatment is 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

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

WHO *Operational Guidelines*

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

Part A

Ethics of Intervention Studies – Discussion Document

1 Introduction

Health professionals offer 'interventions' to prevent, diagnose or treat illness or disease. They need to know which interventions are safe and effective for the people who seek their help. Intervention studies are their main source of reliable information on this subject. In these studies, the investigator intervenes and then studies the effects of the intervention. A clinical trial of a new blood pressure medicine is an example of an intervention study.

For intervention studies to be beneficial, they need to meet high ethical standards. They must be done in ways that are safe and effective, and that reliably generate new knowledge. There are significant ethical issues that investigators, with the support of study sponsors, ethics committees and others, must address to ensure that intervention studies are conducted in ways that respect people, maximise benefit and minimise harm, and are seen to incorporate all these principles.

1.1 This NEAC project

Investigators conduct intervention studies, and good study conduct is their core professional responsibility. For this reason, it is also their primary responsibility to address the ethical issues in intervention studies. A way to help investigators address these issues, which has been established both nationally and internationally, is to develop ethical guidelines for the conduct of intervention studies; for example, the *Declaration of Helsinki* (WMA 2004).

This project on intervention studies accords with the statutory function of the National Ethics Advisory Committee – Kāhui Matatika o te Motu (NEAC) to 'determine nationally consistent ethical standards across the health sector', and to advise the Minister of Health on 'ethical issues of national significance'. This work also accords with NEAC's Terms of Reference, which state that NEAC should:

> ... develop and promote national ethical guidelines for ... how to conduct different types of health research ... in an ethical manner and should establish parameters for, and provide guidance on, the ethical review of such types of health research ... (NEAC 2007: 29).

As required by its Terms of Reference, NEAC has also agreed its intervention studies project with the Minister of Health.

NEAC has identified ethical issues for intervention studies through review of current literature and discussions with key informants. The Committee has also had its draft work peer reviewed and has received comment from key public agencies. NEAC has made substantial revisions in response to this feedback. It is now undertaking wide sector and public consultation on its revised work. This consultation will include further peer review of the work.

1.2 This Discussion Document and draft *Guidelines*

This publication is divided into two parts: a Discussion Document (Part A) and draft *Ethical Guidelines for Intervention Studies* (Part B). Part A identifies central ethical issues in intervention studies, and core ethical ideals that are important in addressing those issues. Key New Zealand and international guidance is outlined and, in particular, New Zealand-specific issues are discussed.

Part B of this publication provides draft *Ethical Guidelines for Intervention Studies* (the draft *Guidelines*), which seek to achieve the aims outlined in the Discussion Document (see 1.3 below). These draft *Guidelines* parallel NEAC's *Ethical Guidelines for Observational Studies*, which were developed through inclusive and thorough public consultation between 2002 and 2005 and have been in operation since 2006 (NEAC 2006).

New Zealand guidance

New Zealand guidance relevant to the ethics of intervention studies includes:

- Health Research Council of New Zealand, *Guidelines on Ethics in Health Research* (HRC 2005a)
- Ministry of Health, *Operational Standard for Ethics Committees* (Ministry of Health 2006b)
- National Ethics Advisory Committee, *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities* (NEAC 2006)
- New Zealand Medicines and Medical Devices Safety Authority, *Interim Good Clinical Research Practice Guideline* (Medsafe 1998).

International guidance

Key international guidance documents relating to the ethics of research include:

- Council for International Organizations of Medical Sciences, *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002)
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice* (ICH 1996)
- World Medical Association, *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (WMA 2004).

Where New Zealand guidance needed to be developed further to address all aspects of an issue, this was undertaken primarily with reference to the above international documents. National guidelines from other countries and published works are also referred to in the draft *Guidelines* as appropriate.

Definitions and conventions used in this document

There is a list of definitions of some terms in paragraphs 2.2–2.15 of the draft *Guidelines* (Part B, Section 2: 'Definitions and scope of the *Guidelines*'). We encourage readers to refer to these definitions and to the others provided in the Glossary.

To assist readability, this Discussion Document uses the following terms based on the conventions described.

- **Ethics committee** refers to an approved ethics committee in New Zealand. Such committees include the Health Research Council Ethics Committee (HRCEC) and other ethics committees approved by the HRCEC, in accordance with section 25 of the Health Research Council Act 1990. The standards being established in these draft *Guidelines* may also be of assistance to other ethics committees.
- **Study** refers to an intervention study, unless otherwise specified.
- **Treatment** refers to any type of intervention that may be studied, including medicines, tests, methods of health care delivery and other health or disability support interventions.

1.3 Scope and aims of the *Guidelines*

Scope

The draft *Guidelines* contained in Part B of this publication relate to intervention studies. Intervention studies may trial medicines, radiation therapies, devices, methods of health care delivery or other types of interventions. The draft *Guidelines* are applicable to all types of intervention studies but focus primarily on randomised controlled trials and especially on phase III trials – those designed to generate definitive results about the safety and benefit of interventions. Where randomised controlled trials or other kinds of intervention studies include ethical features of particular note, these are also addressed specifically in both parts of this publication. Studies of this sort include phase I trials and non-consensual studies. See the Glossary and Section 2 of the draft *Guidelines*, Part B, for definitions.

Innovative practice can overlap with intervention studies. Innovative practice has been defined as:

> ... 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. Innovative practice includes the application of known procedures in new or novel circumstances in which they have not previously been tested. It may involve new delivery practices by health practitioners, new devices, new investigative procedures, or clinical management options (Ministry of Health 2006b: paragraph 121).

Although some innovative practice can be the subject of an intervention study, not all innovative practice will be. Innovative practice that occurs outside the context of an intervention study is outside the scope of these draft *Guidelines*. NEAC is carrying out a separate project on ethical issues for innovative practice.

Aims

The draft *Guidelines* are directed at both experienced and novice investigators. They are being developed with the aim of assisting investigators in undertaking high quality studies that protect the interests of participants and that benefit society. Other aims are to:

- establish a shared ethical basis for all parties, including investigators, patients and their families, ethics committees, and organisations where intervention studies are conducted
- foster the highest ethical standards in studies that add to knowledge and benefit New Zealanders.

Because the draft *Guidelines* are primarily directed at investigators, they address issues that investigators are able to influence. NEAC recognises that there are also some wider issues in relation to intervention studies (for example, research governance arrangements that are capable of giving independent oversight of study conduct). NEAC is currently undertaking related work to address some of these wider issues, including a project on governance in health and disability research ethics.

1.4 Implications for other guidance

Establishing NEAC's *Ethical Guidelines for Intervention Studies* could have implications for other New Zealand guidance. Some agencies may wish to update their guidance in light of NEAC's finalised *Ethical Guidelines for Intervention Studies*.

The guidance NEAC has identified that could be updated is listed below.

- National Ethics Advisory Committee, *Ethical Guidelines for Observational Studies* (NEAC 2006)
- Ministry of Health, *Operational Standard for Ethics Committees* (Ministry of Health 2006b)
- Health Research Council, *Guidelines on Ethics in Health Research* (HRC 2005a)
- Ministry of Health, *National Application Form for Ethics Committees* (NAF-2005 v1)
- Ministry of Health and ACC, *Compensation for Injuries Caused as a Result of Participation in a Clinical Trial and the Role of Ethics Committees: Guidelines* (Ministry of Health and ACC 1993)
- Researched Medicines Industry Association of New Zealand, *Guidelines on Clinical Trials: Compensation for Injury Resulting from Participation in an Industry-sponsored Clinical Trial* (RMI 1997).

2 Key issues

This section identifies and considers some of the main areas in which guidance is provided in the draft *Guidelines* in Part B. Each area is discussed with reference to:

- an outline of the main issues in this area
- existing New Zealand guidance
- issues with existing New Zealand guidance
- how the draft *Guidelines* address the issues.

Particular reference is made to the *Operational Standard for Ethics Committees* (the *Operational Standard*) (Ministry of Health 2006b), because of its currently high profile among the established ethical standards.

The following issues are discussed in this section.

Question for the Discussion Document – Section 2 ('Key issues')

- Have the key issues been identified and well addressed?

See also page 90 for further questions you might find helpful in providing your feedback.

2.1 'Best intervention' standard for the comparison group

See draft Guidelines (Part B): 'Comparison groups – "Best intervention" standard' (paragraphs 5.8–5.13).

In an intervention study, investigators often compare one intervention with another. For example, a study might compare an established intervention (or treatment) with a new one. The 'best intervention' standard refers to the idea that one or more interventions (or treatments) are better than all others, or are in a person's 'best equal' interests, in a particular setting. A person would normally be offered one of these treatments if he or she were not participating in a study.

Outline of the main issues

In general, any new interventions being studied should be compared with a current 'best intervention'. This approach ensures that participants in the comparison group are not disadvantaged by taking part in the study. Meeting the 'best intervention' standard is also part of ensuring that information gained from a study will add to the body of knowledge about the best option for patients.

A further issue arises in studies where the best intervention that is available locally differs from the best that is available internationally.

Existing New Zealand guidance

NEAC is not aware of any New Zealand guidance on the 'best intervention' standard.

Issues with existing New Zealand guidance

The 'best intervention' standard is central to ethical conduct of intervention studies. A statement of the 'best intervention' standard in New Zealand guidance would therefore be helpful. That statement should also address the distinction between what is 'best' nationally and what is 'best' internationally, as New Zealand patients do not always have access to the most effective treatments that are available internationally (for example, some cancer treatments). Issues about local versus international 'best intervention' also potentially arise for studies that recruit patients from multiple countries, including developing countries.

The *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects* (the *Declaration of Helsinki*) states:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods ... (WMA 2004: paragraph 29).

This statement is helpful, but does not indicate whether this 'best' is to be understood on a local or international scale.

How the draft *Guidelines* address the issues

The relevant ideal is that participants in intervention studies should be treated fairly compared with similarly placed non-participants. As part of achieving this ideal, the draft *Guidelines* apply the principle outlined in the *Declaration of Helsinki* above when addressing the 'best intervention' standard. The aim is to protect participants by requiring that they be offered interventions as good as the best they would receive if they were having best standard care outside a study.

In any assessment of whether the 'best intervention' standard should be based on the best option internationally or the best one available locally, an important consideration is that studies should be conducted in a population only if that population stands to benefit in a meaningful way. Therefore, a study that offers interventions that are inferior to the best proven intervention available internationally, but are the best that is available locally, can be justified only if the world-best intervention is unlikely to be available in the foreseeable future and if the study can be justified in terms of its potential benefit to the community from which the participants are drawn.

(See paragraphs 5.8–5.13 of the draft Guidelines (Part B): 'Comparison groups – "Best intervention" standard'.)

2.2 Equipoise standard

See draft *Guidelines* (Part B): 'Comparison groups – Equipoise standard' (paragraphs 5.8, 5.14–5.17).

'Equipoise' describes a state where the evidence from the comparative overall risk–benefit equation of two or more treatments is 'equally poised'. That is, it is not **known** if one of the treatments is better overall.

Outline of the main issues

When two or more treatments are compared in a study, there is often reason to think that one **may** be better than the other but, according to a systematic review of best current evidence, there is still a state of equipoise. Intervention studies of two or more treatments should be done only where this equipoise exists, and they should aim to 'break' the equipoise by adding to our knowledge of the treatments they compare. Although in some cases there is scope for reasonable professional disagreement about whether equipoise exists, in many cases there is not.

In some situations a departure from the requirement for equipoise can be ethically justified. Such a situation might arise when the superiority of one treatment over the other is only minor or temporary. Any such departure from the equipoise standard would need to be justified to an ethics committee.

Existing New Zealand guidance

The *Operational Standard* mentions equipoise only in relation to the evaluation of established clinical practice. Equipoise is defined there as the situation:

> ... where, based on the available evidence, the comparative safety and efficacy of two or more alternative therapeutic practices is uncertain (Ministry of Health 2006b: paragraph 315).

The Health Research Council's *Guidelines on Ethics in Health Research* (the HRC Guidelines) state:

> ... when the administration of effective treatment is important for the wellbeing of the patient, a controlled trial can only be undertaken where there is genuine uncertainty about whether the trial treatment is more effective (or has less risk) than the standard treatment with which it is being compared (HRC 2005a: 16).

Issues with existing New Zealand guidance

Although equipoise is often discussed in the context of uncertainty, the fundamental principle concerns the state of the best current evidence. When understood as an issue about the state of the evidence, equipoise is central to the good conduct of all intervention studies that compare two or more interventions. Existing guidance does not give equipoise prominence, nor make clear its wide scope. In general, the importance of equipoise is also not clearly expressed in international guidance, though it is widely discussed in the research literature.

How the draft *Guidelines* address the issues

The relevant ideal is for participants in intervention studies to be treated fairly in relation to each other. The ethical principle of non-maleficence (not causing harm) also requires that participants are not given an intervention that is known to be inferior, with the exception of departures from equipoise that are minor and temporary, which can sometimes be ethically justified. Within-study fairness and non-maleficence thus require equipoise. The draft *Guidelines* build on the ideal stated in the HRC *Guidelines* about ensuring the wellbeing of the patient by not knowingly giving a person an inferior intervention. Judgements about equipoise in particular cases should be made about the group of participants as a whole. Any professional disagreement about the relative merits of the treatments proposed for study should be addressed on the basis of the best current evidence.

(See paragraphs 5.8 and 5.14–5.16 of the draft *Guidelines* (Part B): 'Comparison groups – Equipoise standard'.)

Even if the evidence is equally poised between the interventions in a study, each individual participant may have a preference for a particular treatment. For example, if a study compares a surgical with a medical intervention, some individuals may have a strong preference for one or the other, based on their personal experience or situation. This personal preference may be relevant to each individual's decision about whether to participate in a trial.

(See paragraph 5.17 of the draft *Guidelines* (Part B): 'Comparison groups – Equipoise standard'.)

2.3 Placebo

See draft *Guidelines* (Part B): 'Use of placebo' (paragraphs 5.18–5.20); 'Comparison groups' (paragraph 5.8).

Some studies use a placebo or 'dummy' intervention (that is, no active treatment) to help assess the comparative safety and effectiveness of an active intervention.

Outline of the main issues

It is important that the use of a placebo still allows all participants to receive the 'best intervention', and also allows the study to achieve a state of equipoise between comparison groups.

(For relevant definitions, see paragraphs 2.6–2.15 of the draft *Guidelines* (Part B): 'Features of intervention studies'.)

Existing New Zealand guidance

The use of a placebo is not directly addressed in the *Operational Standard* (Ministry of Health 2006b).

The HRC *Guidelines* recommend ethical review of placebo-controlled studies on a case-by-case basis, encompassing all relevant considerations, in deciding whether to give approval for a placebo arm in a randomised controlled trial. The HRC *Guidelines* also note the overriding principles of the *Declaration of Helsinki* (see 'Issues with existing New Zealand guidance' below) (HRC 2005a: 29).

Issues with existing New Zealand guidance

Using a placebo in clinical trials raises several issues. First, studies need to meet the 'best intervention' standard (see Section 2.1 above (Part A): '"Best intervention" standard for the comparison group)'. Where an effective intervention is known, participants should not be offered a placebo unless all treatment arms are being offered a placebo plus either a new intervention or standard treatment.

If there is no 'best intervention', including in situations where there is inadequate scientific validation for what is considered routine treatment, it may be justifiable to test the new intervention against a placebo.

The *Declaration of Helsinki* provides guidance on the use of a placebo, stating:

> The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists (WMA 2004: paragraph 29).

A note of clarification on this paragraph, added in 2002, specified:

> ... a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:
>
> - Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
> - Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm (WMA 2004: note of clarification on paragraph 29).

In addition to endorsing the above principles, the Council for International Organizations of Medical Sciences (CIOMS), in its *International Ethical Guidelines for Biomedical Research Involving Human Subjects* of 2002 (the CIOMS *Guidelines*), recommends that where a placebo is used, consideration should be given to using a standard treatment as well (Commentary on Guideline 11).

How the draft *Guidelines* address the issues

The draft *Guidelines* aim to strengthen existing New Zealand guidance by incorporating the principles of the *Declaration of Helsinki* and the CIOMS *Guidelines*. The draft *Guidelines* currently state that the 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 participants 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 use of an established, effective intervention as comparator would not yield reliable findings on safety or efficacy **and** use of placebo would not increase the risk of serious or irreversible harm to participants.

(See paragraphs 5.18–5.20 of the draft *Guidelines* (Part B): 'Use of a placebo'.)

This standard aims to ensure that participants are treated fairly. Participants within the same trial (but in different treatment groups) should be treated fairly in relation to each other. Participants should also be treated fairly in relation to non-participants. Achieving this ideal means that participants should not be exposed to undue risk through being denied adequate treatment for the purposes of participating in a study. Participants in placebo-controlled trials should be informed of other available therapy and the consequences, if any, of deferring such therapy.

(See paragraph 5.8 of the draft *Guidelines* (Part B): 'Comparison groups'.)

2.4 Vulnerable people

See draft *Guidelines* (Part B): 'Vulnerable people' (paragraphs 5.23–5.27).

Vulnerable people are those who:

> ... are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests (CIOMS 2002: Commentary on Guideline 13).

Groups who are generally considered to be vulnerable include young children, unconscious people, and those with severe intellectual disability or dementia. Other groups may be vulnerable because of their current situation. These groups may include people in institutional care, prisoners, some ethnic minority groups, refugees, those with life-threatening illnesses, and junior or subordinate members of a hierarchical group.

Outline of the main issues

Vulnerable people can benefit from inclusion in research through findings that improve treatment or other interventions for them. It is important that measures intended to protect vulnerable participants do not reduce these benefits. It is also essential that vulnerable groups are not exploited in research, as has happened in some cases. For example, in the Tuskegee Syphilis Study, African American males were used in an exploitative way to monitor the natural history of syphilis, without being offered effective treatment, even when it became available (Gamble 1997).

The challenge is to include vulnerable people in research that is of benefit to them, while also strongly protecting their interests against exploitation and other harms. Any guidance must recognise that due to their capabilities or situation at the time, vulnerable individuals may be coerced into taking actions or making decisions that are not in their best interests.

Existing New Zealand guidance

New Zealand guidance seeks to protect the interests of vulnerable people. The *Operational Standard* states:

> Respect for persons requires that greater protection be provided to those persons with diminished autonomy ... to ensure that they are not subjected to abuse, exploitation or discrimination ... (Ministry of Health 2006b: paragraph 27).

In appendices, the *Operational Standard* provides further guidance regarding particular participant groups, including children, older persons, those with a terminal illness, and those with intellectual disability (Ministry of Health 2006b). It also acknowledges that distributive justice (the fair distribution of the benefits and burdens of research within a given population) imposes duties to neither neglect nor discriminate against individuals or groups who may benefit from advances in research (Ministry of Health 2006b: paragraph 73).

NEAC's Ethical Guidelines for Observational Studies state:

> Ethical consideration of studies involving individuals or groups who have diminished competence to give free and informed consent on their own behalf (for example, children) must seek to balance:
>
> a) the vulnerability that arises from their diminished competence; with
>
> b) the injustice that would arise from their exclusion from the benefits of [observational] studies in these groups (NEAC 2006: paragraph 6.17).

Issues with existing New Zealand guidance

Current New Zealand guidance protects vulnerable people, but does not emphasise the benefits to vulnerable people of being included as participants in research.

In general, it is desirable to include vulnerable people in research relevant to their situation, because much of the improvement in services for patients is identified through research. Vulnerable participants should be protected from exploitation and risks from unnecessary research while their opportunities for participation in studies are maintained where there is potential to benefit them, and where the benefit can be generated only with their participation.

The *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* states:

> ... members of society should neither bear an unfair share of the direct burdens of participating in research, nor should they be unfairly excluded from the potential benefits of research participation ...
>
> Unfortunately, the history of research involving human subjects contains chapters on the misuse or serious abuse of research subjects. Continuing concerns about such abuses have sharpened ethical focus on the relative levels of benefits and harms that research would impose on prospective subjects ... Sometimes the harms have resulted from intentional exclusion, such as that inspired by concerns about the misuse or abuse of research subjects ... In attempting to avoid the moral problem of exploiting vulnerable research subjects, such practices may incur the moral problem that individuals in need of the benefits of research may be denied them (CIHR, NSERCC and SSHRCC 1998: Section 5).

International best practice supports involving vulnerable people in research as long as key ideals are met. The CIOMS *Guidelines* outline some requirements:

- the research could not be carried out equally well with less vulnerable subjects
- the research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class – either the actual subjects or other similarly situated members of the vulnerable class
- research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research

- the risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless an ethical review committee authorises a slight increase over this level of risk ... (CIOMS 2002: Commentary on Guideline 13).

How the draft *Guidelines* address the issues

The draft *Guidelines* recognise the importance, for vulnerable people, of both conducting valuable research with their participation and ensuring their protection within these studies.

The following are some ideals that are especially relevant for research involving vulnerable people.

- The study should ask questions that matter to the participants' communities; the answers should benefit those communities.
- Research should only be performed in vulnerable groups if it cannot be adequately performed in other groups.
- Where research in a vulnerable group is conducted, it should use the least vulnerable members of that group (for example, older rather than younger children).
- Intervention studies should be done only if the risk to vulnerable participants is at an acceptable minimum.
- Study participation should be established through free and informed decision-making by study participants wherever possible.

Vulnerable people should have the opportunity to be included in high quality studies on questions that matter to their health. As well as the above issues, there are issues about consent for some vulnerable people. When a vulnerable person is competent to decide on his or her own study participation, this decision should be respected. Where vulnerable people are not able to give fully informed consent, it is generally recommended to both obtain the consent of a legally recognised representative where possible, and inform the vulnerable people to the degree possible given their ability. Any refusal to participate should be respected. See also Sections 2.7 and 2.8 of this discussion document (Part A): 'Consent' and 'Non-consensual studies' respectively.

(See paragraphs 5.23–5.27 of the draft *Guidelines* (Part B): 'Vulnerable people'.)

2.5 Registering trial protocols

See draft *Guidelines* (Part B): 'Study protocol: Registering trial protocols' (paragraphs 5.33–5.36).

Registering trial protocols involves assigning a unique identification number, and recording and publicly releasing protocol information. Some people also advocate that trial registries should require the recording and public release of trial results; and some advocate that trial protocols should also be published.

Outline of the main issues

There are ethical and scientific reasons to register trials. Registration of trial protocols is advised to reduce duplication of studies and to inform the planning of new trials. Another aim of trial registration is to ensure that the results of unpublished trials become part of the body of new knowledge. Trial registries also assist in reducing the bias in results that are published, by identifying, before the study begins, the study end-points that will be reported on. Finally, trial registries provide some transparency that assists researchers and industry to demonstrate that they are meeting the relevant standards.

There is international debate about which trials should be registered and about the exact amount and nature of information that should be made publicly available.

Existing New Zealand guidance

NEAC is not aware of any current New Zealand guidance on these issues.

Issues with existing New Zealand guidance

Part of the reason for the lack of guidance in this area in New Zealand is because this issue is currently under active debate internationally. There is tension between the desire to share knowledge and the concern about making publicly available information that may be commercially sensitive. The *Declaration of Helsinki* states:

> ... The design of all studies should be publicly available (WMA 2004: paragraph 16).

Investigators also need to be aware of the expectations of journal editors. In 2004 the International Committee of Medical Journal Editors (ICMJE) published a joint editorial in member journals that made the following points.

- Clinical trials starting enrolment after 1 July 2005 will be considered for publication only if registered in a public trial registry prior to enrolment of the first participant.
- Ongoing trials (which began enrolment before this date) will be considered for publication only if registered before 13 September 2005.

The ICMJE requirements excluded trials whose primary goal was to assess major toxicity or study pharmacokinetics, from the requirement (such as phase 1 trials) (De Angelis et al 2004). However, the ICMJE has revised its requirements for clinical trials that must be registered, effective 1 July 2008, to include "any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes" (Laine et al 2007).

How the draft *Guidelines* address the issues

Ethically-sound research should answer important unanswered questions. Trial registries play an important role in enabling investigators to determine what is already known and to keep current with this information. Knowing about current research is relevant to study design, implementation of stopping rules (see Section 2.9 (Part A): 'Data monitoring') and dissemination of study results. To assist in these processes, the draft *Guidelines* recommend registering all intervention studies.

(See paragraphs 5.33–5.36 of the draft *Guidelines* (Part B): 'Study protocol: Registering trial protocols'.)

New Zealand–based clinical trials can now be registered without charge on the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au), administered by Australia's National Health and Medical Research Council. When submitting an application for ethics committee approval, evidence of trial registration should be provided. Alternatively, a statement should be given to the ethics committee that the registry in question, which should be named, requires ethics committee approval prior to registration.

2.6 Non-therapeutic studies

See draft *Guidelines* (Part B): 'Studies with distinctive features – non-therapeutic trials' and 'Phase 1 trials' (paragraphs 5.38–5.42).

Therapeutic intervention studies examine interventions that offer direct diagnostic, therapeutic or preventive benefit for the individual participant. Non-therapeutic studies examine interventions that do not offer direct diagnostic, therapeutic or preventive benefit to the individual participant in the study. Types of non-therapeutic studies include some Phase 1 trials, bioequivalence studies and bioavailability studies (see the Glossary).

Outline of the main issues

Given that the interventions offered in non-therapeutic studies do not offer direct benefit to individual study participants, particular attention to ethical issues in these studies is justified.

In many non-therapeutic studies, the participants are healthy volunteers. The nature of their motivation to participate may differ from that of patient-participants. In some countries (for example, the United States), money is the primary motivation for many participants in non-therapeutic studies (Elliott 2008). There is potential for this to be an undue influence on individuals' decisions about their study participation. These points do not necessarily generalise to New Zealand non-therapeutic studies, but consideration of their potential to do so is nevertheless justified.

For each non-therapeutic study, as for all intervention studies, there should be organisational oversight that is independent of those conducting the study. It is also important that the organisation conducting the research is committed to principles that assist good research practice; for example, a well-functioning hospital is committed to patient care or a well-functioning academic institution is committed to adding to the general body of knowledge.

In addition, most existing guidance on intervention studies is written with a focus primarily on therapeutic studies. As a consequence, relatively little ethical guidance is focused on the issues for non-therapeutic studies.

Existing New Zealand guidance

There is currently little New Zealand guidance relating to non-therapeutic studies.

Issues with existing New Zealand guidance

Specific guidance for this area in New Zealand would be useful. It would be desirable for such guidance to recognise the often distinctive features of phase 1 trials, and state that particular attention to the ethical issues in such studies is consequently justified.

A further issue is that of credentialing research institutions, particularly those involved in phase I and phase II trials. For example, it is important that all such institutions have high levels of access to resuscitation and intensive care services, consistent with best international practice. The question of credentialing raises issues beyond the scope of these draft *Guidelines*, however, and such issues are considered in NEAC's separate project on research ethics governance.

The severe adverse events experienced by volunteers in the United Kingdom trial of a drug called TGN1412 in March 2006 drew attention to the potential risks of exposing humans to certain new pharmacologic agents. A report by the Early Stage Clinical Trial Taskforce of the Association of the British Pharmaceutical Industry and the BioIndustry Association, written in response to this experience, made several recommendations to help prevent such an event occurring again (ABPI and BIA 2006). These recommendations included the following.

- Where an early clinical study of novel biologic or chemical agents has the potential to cause harm:
  - the study should be performed in a research facility that is on the site of a hospital with intensive care facilities
  - only one subject should receive the active drug on the first day ('staggered dosing')
  - investigators should have appropriate training or significant experience in phase 1 (first-in-human) trials, with close involvement of a medical monitor.
- Protocols for early studies of this nature should be reviewed by a group with the appropriate technical, scientific and medical expertise (ABPI and BIA 2006: 10–11).

The CIOMS *Guidelines* state that risks of interventions that do not offer the prospect of direct diagnostic, therapeutic or preventive benefit for the individual must be justified in relation to the expected benefits to society (generalisable knowledge). The risks of such interventions must be reasonable in relation to the importance of the knowledge to be gained (CIOMS 2002: Guideline 8). In assessing the risks and benefits that a study protocol presents to a population, it is appropriate to consider the harm that could result from foregoing the research.

How the draft *Guidelines* address the issues

The draft *Guidelines* recognise that non-therapeutic studies entail some distinctive and significant ethical issues. They make recommendations to ensure that non-therapeutic trials are scientifically robust and that there is adequate medical monitoring, in terms of both the medical team and the medical facilities, to protect the health of study participants. Non-therapeutic studies should be conducted only if the importance of the objective outweighs the inherent risks and burdens to the participant.

(See paragraphs 5.38–5.42 of the draft *Guidelines* (Part B): 'Studies with distinctive features – non-therapeutic trials' and 'Phase 1 trials'.)

2.7 Consent

See draft *Guidelines* (Part B): 'Free and informed consent' (paragraphs 6.5–6.23).

Consent is 'informed' when prospective participants are able to make a free and informed decision about whether or not to participate in a study, having received adequate information on which to base this decision. Informed consent is accepted internationally as an ethical prerequisite for including participants in most intervention studies.

Outline of the main issues

Consent should, wherever possible, be documented in writing by the participant. Instances in which oral consent may be more appropriate include where participants are illiterate or unable to write (for example, participants with a high spinal cord injury). If only oral consent is obtained, there should still be some written documentation of this event. It is also widely recognised that, although the documentation of consent is usually a discrete event, informed consent is part of a continuous process of good communication between the investigator and participant.

There are shared ideals for many issues related to consent. However, it is an ongoing challenge to set policy and to pursue practice that achieves rather than unintentionally compromises the shared ideals.

Existing New Zealand guidance

New Zealand guidance outlines some of the components that are required for informed consent. These components relate to the type of information that is required and the language and technical terms used in providing this information. The *Operational Standard* (Ministry of Health 2006b: paragraph 29) states that adequate information about studies should be provided to potential participants to enable them to make an informed judgement. Information should be provided in a way that each individual can understand. Consent must be voluntary.

There is a broader legal requirement for health and disability services providers to inform, and to obtain informed consent from, 'consumers', as defined in the Code of Health and Disability Services Consumers' Rights (the Code). See Rights 6(1) and 7(1) of the Code.

Issues with existing New Zealand guidance

Current New Zealand guidance focuses on the types of information that are required for a person to give informed consent. However, there is little guidance about the process of consent. There can be a tendency for consent to be viewed as a solitary act of information transfer. It is also recognised internationally that many participants find current consent forms incomprehensible (Wilets et al 2005); the same issue arises about participant information sheets.

It would be desirable to have further New Zealand guidance that:

- advises how to enable potential participants to understand the key information while still having access to the details of the study
- is built around the principle that consent is a matter of good communication between people, rather than just being a transfer of information and responsibility
- gives due emphasis to written consent without inappropriately excluding from studies those people who are not able to write.

International guidance highlights some aspects of informed consent that can assist in the process of informing prospective participants. The CIOMS *Guidelines* state that:

> ... Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation ... Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in doing so manifest respect for their dignity and autonomy ... (CIOMS 2002: Commentary on Guideline 4).

The aim of the consent process should be to inform prospective participants so that they have enough information and adequate understanding of this information to make an informed decision. Merely providing information does not necessarily fulfil this aim. Giving fully detailed and specific information is not always helpful, and is sometimes impossible (Manson and O'Neill 2007). It is also important that the provision of information does not preclude useful dialogue or confuse potential participants. There remains a need to find practical ways to help participants understand complex research tools, such as randomisation and blinding.

Consideration should be given to renewing informed consent under certain conditions. In particular, renewal may be appropriate if there are significant changes in the conditions or procedures of the research, if new information becomes available that could affect the willingness of subjects to continue to participate, or if the duration of the study is long.

Informed consent can be construed in three parts:

- **Consent process:** O'Neill (2002) argues that only key central information should be given on the consent form, but additional information on various aspects of the research, should be available in verbal and written form, if people wish to have it. Other process improvements might include minimum requirements for time available to consider participation, and guidance on who can consent. A two-step consent process may be preferred, where the prospective participant is given a verbal explanation of the research, which is later followed up with written information (Wilets et al 2005). In support of this possible approach, several studies have found that participants recall and understand oral information about the trial more readily than written information, and the majority prefer to receive oral information (Gammelgaard 2004).

- **Consent structure:** Structural improvements might include setting a maximum reading age for consent documents (information sheets and consent forms), and using standardised language with a standardised glossary. A shortened and simplified form of the information, supplemented by details for participants who wish to know more, could be another option. Lengthy consent forms have been criticised as being an obstacle to research and designed to protect researchers from legal liability rather than inform participants (Gammelgaard 2004).
- **Consent outcome:** Research tools have been developed to assess consent outcome, identify problems and evaluate potential improvements. These include the Informed Consent Evaluation Feedback Tool (Bankert and Amdur 2002) and the Quality of Informed Consent questionnaire (Joffe et al 2001). These tools provide evidence about the effectiveness of informed consent and are additional to the usual consent process.

How the draft *Guidelines* address the issues

The draft *Guidelines* aim to enhance New Zealand guidance by drawing on international guidance and literature about both the structure and the process of consent. The aim is to assist participant understanding through good two-way communication. The draft *Guidelines* provide guidance about the information to include in consent forms and information sheets, while recognising that this information should be neither too complex nor too lengthy.

The draft *Guidelines* also present ways for investigators to inform prospective participants using a process that maximises their understanding. Using such a process is important both prior to their decision about entering the study and throughout any study they enter. Relevant methods include tailoring the information provided and the way it is given to the individual, and not restricting consent to a one-off event.

In addition, there is a reminder to make allowances for different study settings. In some instances prospective participants may be in pain, under stress or in an urgent situation when the study is initially discussed. In any of these situations, the initial consent discussion may be relatively short. Such a discussion should be followed by further conversation when the participant is not acutely unwell.

(See paragraphs 6.5–6.23 of the draft *Guidelines* (Part B): ‘Free and informed consent’.)

2.8 Non-consensual studies

See draft *Guidelines* (Part B): 'Non-consensual studies' (paragraphs 6.24–6.31); and general aspects of the 'Best intervention standard' (paragraphs 5.9–5.13) and 'Equipoise standard' (paragraphs 5.14–5.17).

Some groups do not have the capacity to make their own informed decisions about study participation. These groups include unconscious people, young children, and those with severe intellectual disability or dementia.

Outline of the main issues

It is desirable to have well-designed therapeutic studies (those that offer direct diagnostic, therapeutic or preventive benefit for the individual participant) about the health of these groups, given that they aim to improve treatments for these groups by adding to knowledge. These studies often require the participation of those affected; without such participation, individual participants and the groups they represent would be denied the benefits of such studies. At the same time, the vulnerability of participants in such studies needs to be recognised and their interests robustly protected.

An example illustrates the above points. For many years it was standard practice to use corticosteroids in the treatment of significant head injuries, but this practice had never been adequately tested through clinical trials. A well-designed randomised controlled trial (the CRASH trial) was conducted to evaluate this practice. At the time of treatment and study enrolment, many patients were incapable of making their own decisions and therefore the participation of many in the study was non-consensual. The CRASH trial included New Zealand participants. It showed that the still widespread practice of using corticosteroids after head injury in fact significantly **increased** mortality and severe disability. If the study had not been performed, thousands more patients may have died, as the inadequately assessed standard practice might well have continued (Roberts et al 2004; Sauerland and Maegele 2004; Edwards et al 2005).

In sum, the CRASH trial was very beneficial to some participants and was equivalent to receiving standard care for the remainder. It benefited thousands of future patients, and it required the non-consensual participation of many patients.

Existing New Zealand guidance

This subsection outlines aspects of New Zealand law that are especially relevant to non-consensual studies. It then outlines the established ethical standards that are especially relevant.

New Zealand law relevant to non-consensual studies

In certain situations, specified people can legally consent on behalf of others ('legal proxies'). These people are: a parent or guardian (for children), a welfare guardian, or a person with enduring power of attorney. There is no legal provision for the 'next of kin' to consent to treatment or research on behalf of incompetent adults.

The New Zealand Bill of Rights Act 1990 states:

> Section 10: Every person has the right not to be subjected to medical or scientific experimentation without that person's consent.
>
> Section 11: Everyone has the right to refuse to undergo any medical treatment.

These rights are not absolute. They are subject to section 4 of the New Zealand Bill of Rights Act 1990, concerning enactments that are inconsistent with either right, and to section 5, which permits 'such reasonable limits prescribed by law as can be demonstrably justified in a free and democratic society'. A further issue is whether 'Every person' in section 10, and 'Everyone' in section 11, would be interpreted narrowly to apply to competent people only, or broadly to apply also to incompetent people.

Section 10(1) of the Protection of Personal and Property Rights Act 1988 (PPPR Act) states:

> On an application for the exercise of a Court's jurisdiction under this Part of this Act in respect of any person, the Court may, subject to subsection (2) of this section, make any one or more of the following orders:
>
> ...
>
> (f) An order that the person be provided with medical advice or treatment of a kind specified in the order.

This section establishes a power of the Court to make an order that a person in relation to whom it has jurisdiction under the Act be provided with medical advice or treatment.

Section 18(1) states:

> No court shall empower a welfare guardian, and no welfare guardian shall have power, –
>
> ...
>
> (f) To consent to that person's taking part in any medical experiment other than one to be conducted for the purpose of saving that person's life or of preventing serious damage to that person's health.

Where a person wholly or partly lacks capacity, therefore, this section limits the power of a welfare guardian to provide consent for that person to take part in a medical experiment to those experiments conducted for the purpose of saving the person's life or preventing serious damage to their health.

Thus, as outlined above, the court has limited power to order that a person be provided with treatment and a welfare guardian has limited power to consent to a person's taking part in any medical experiment. A further significant issue is whether the PPPR Act also limits the power of health practitioners to offer treatment in the context of research. This publication does not take any position on that further issue.

Right 7(4) of the Code of Health and Disability Services Consumers' Rights 1996 states:

> Where a consumer is not competent to make an informed choice and give informed consent, and no person entitled to consent on behalf of the consumer is available, the provider may provide services where –
>
> (a) it is in the best interests of the consumer; and
>
> (b) reasonable steps have been taken to ascertain the views of the consumer; and
>
> (c) either, –
>
> (i) if the consumer's views have been ascertained, and having regard to those views, the provider believes, on reasonable grounds, that the provision of the services is consistent with the informed choice the consumer would make if he or she were competent; or
>
> (ii) if the consumer's views have not been ascertained, the provider takes into account the views of other suitable persons who are interested in the welfare of the consumer and available to advise the provider.

Right 7(4) establishes a (limited) power of the provider to provide services where a consumer is not competent to make an informed choice and give informed consent. 'Services' in this context includes services provided in the context of research, since Right 9 states that the rights in the Code 'extend to those occasions when a consumer is participating in, or it is proposed that a consumer will participate in, teaching or research'. Right 7(4) is not absolute, as the Code provides in clause 3 that a provider is not in breach of the Code if the provider has taken reasonable actions in the circumstances to give effect to the rights and comply with the duties in the Code.

One issue is whether there is any conflict between the provisions of the Protection of Personal and Property Rights Act 1988 (PPPR Act), as outlined above, and Right 7(4) of the Code. The PPPR Act provisions primarily concern the powers of a court or a welfare guardian. If there is conflict, an Act of Parliament such as the PPPR Act normally prevails over a statutory regulation such as the Code. Clause 5 of the Code also states: 'Nothing in the Code requires a provider to act in breach of any duty or obligation imposed by any enactment or prevents a provider doing an act authorised by any enactment'.

For further discussion on matters of treatment without consent (including treatment in the context of research), see, for example, Dawson and Peart (2003) and Skegg and Paterson (2006).

Established ethical guidance relevant to non-consensual studies

The *Operational Standard* recognises the significant uncertainty that surrounds the legality of non-consensual studies. The *Operational Standard* states that:

> 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 ... (Ministry of Health 2006b: paragraph 306).

The *Operational Standard* also recommends that ethics committees:

> ... require researchers to 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 (Ministry of Health 2006b: paragraph 311).

Paragraph 311 of the *Operational Standard* establishes an ethical standard for ethics committees and indirectly also for researchers.

Issues with existing New Zealand guidance

There is an overwhelming consensus (of legal writers, practising lawyers, judges, and others) that health practitioners are frequently justified in proceeding to provide treatment without consent, when consent cannot be obtained (and has not previously been refused). In any week, there will be hundreds of thousands of instances in the common law world where treatment is provided on that basis (Skegg and Paterson 2006: 242).

In general, treatment offered in the context of a well-designed therapeutic intervention study also offers more protection to patients than is offered by treatment outside the research setting. This greater protection is due to various factors associated with treatment in the context of research, including more rigorous adherence to protocols, and additional levels of external scrutiny (Lantos 1999). This point applies also to well-designed non-consensual studies.

On the other hand, as outlined in 'Existing New Zealand guidance' above, New Zealand law substantially limits the powers of health practitioners to offer treatment to patients in the context of research. These limitations present challenges to the lawful conduct of studies of treatments to benefit people who are not capable of consenting to participating in a study.

In situations where it is possible to obtain consent before the person becomes incompetent, such as for procedures in intensive care following elective surgery, this should be done. It is recognised internationally, however, that obtaining this kind of prior consent is not always possible, and that well-designed non-consensual studies are also needed for the benefit of groups that cannot make their own decisions.

Many international guidelines state circumstances in which it is acceptable to conduct a study where it is not possible to obtain informed consent from individual participants. These international guidelines usually require that the research question is important, that it relates to this population specifically, and that there is no other way of obtaining consent.

The *Declaration of Helsinki* states:

> Research on individuals for whom it is not possible to obtain consent, including proxy or advanced consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population ... The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorised surrogate (WMA 2004: paragraph 26).

The CIOMS *Guidelines* outline some relevant requirements, including that:

> ... when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement will be supplemented by the permission of their legal guardians or other appropriate representatives (CIOMS 2002: Commentary on Guideline 13).

For studies in New Zealand that aim to identify beneficial treatments for patients who are not capable of giving consent, it would benefit potential study participants and researchers if lawful and practicable pathways were to be more clearly determined (for example, through legislative amendment or declarative judgement of the appropriate court). A review of the Code of Health and Disability Services Consumers' Rights (the Code) in 2004 highlighted this as an area that warrants further attention. The Health and Disability Commissioner acknowledged that, for much research in incompetent adults, there is no legal representative, or advance directive authorising research not known to be contrary to their best interests, and as a consequence consumers are deprived of the potential benefits of such research. The Commissioner recommended that:

> ... Right 7(4)(a) be amended to read: "It is in the best interests of the consumer or, in the case of research, is not known to be contrary to the best interests of the consumer and has received the approval of an ethics committee" (Health and Disability Commissioner 2004: 39).

However, further exploration of the options above is beyond the scope of this publication.

How the draft *Guidelines* address the issues

The draft *Guidelines* state ethical standards for the conduct of non-consensual intervention studies. These standards do not permit such conduct for studies that are non-therapeutic (that is, that do not offer benefit to participants). The draft *Guidelines* note that New Zealand law substantially limits the powers of health practitioners to offer treatment in the context of research; of particular relevance here are the New Zealand Bill of Rights Act 1990, the Protection of Personal and Property Rights Act 1988, and the Code of Health and Disability Services Consumers' Rights 1996. The draft *Guidelines* also state that it is the investigator's responsibility to ensure that all legal standards are met; and they emphasise that the ethical standards they state for non-consensual studies are applicable only to lawful studies.

The draft *Guidelines* propose that the legal standard for treatment without consent that is stated in Right 7(4) of the Code (quoted in 'Existing New Zealand guidance' above) is also the appropriate ethical standard for treatment without consent in therapeutic intervention studies. Consequently, the draft *Guidelines'* statement of this ethical standard closely parallels Right 7(4) of the Code. Central to this approach is a more general 'best interests' standard for study participation, which contains the following features.

1. The standard requires that, so far as can be known at the time treatment is offered in the study, each person will benefit as much from participating in the study as from not participating. This requirement will mean that study participation and non-participation are each in the 'best equal' interests of the participant. The draft *Guidelines* state this expectation about study participation in the 'best intervention' standard (paragraphs 5.9–5.13 of Part B: 'Comparison groups – Best intervention standard').
2. The standard does not require that research participation will benefit each participant more than non-participation. Such a demand would be inconsistent with clinical realities, which normally cannot provide such guarantees about treatment outcome. It would also be inconsistent with ethical best practice for intervention studies. The first reason for this inconsistency is that the purpose of such studies is often to find out which intervention is superior and therefore in participants' best interests. Secondly, such a condition would require, contrary to the 'best intervention' standard, that participants are to be offered treatment that is known to be better than the best that is available outside the study.
3. The standard requires that, so far as can be known at the time treatment is offered in the study, each study participant will benefit as much by allocation to one study group and intervention as by allocation to another. This requirement will mean that each intervention to which the participant might be allocated is in that person's 'best equal' interests. The draft Guidelines state this expectation about study participants in the equipoise standard (paragraphs 5.14–5.17 of Part B).

(See paragraphs 6.24–6.31 of the draft *Guidelines* (Part B) on non-consensual studies in particular, and paragraphs 5.9–5.17 for more general aspects of the 'best interests' standard.)

NEAC recognises that conduct of non-consensual studies presents serious challenges, both ethically and legally. The Committee welcomes comment on its proposed approach to these issues, including any criticisms or suggested improvements. NEAC will also seek further legal advice on these issues.

2.9 Data monitoring

See draft *Guidelines* (Part B): 'Study monitoring and adverse events' which includes 'Processes and responsibilities' (paragraphs 6.40–6.49).

It is important to monitor study data to assess safety and to see if there is early evidence of beneficial effects in the treatment(s) being studied. Data monitoring can involve interim analyses of data to assess whether one intervention is superior to another, or to assess whether serious adverse events are occurring with an intervention in an unexpected way. It can also involve receiving and assessing adverse event reports, including aggregated reports of such events in unblinded form.

Outline of the main issues

While a study is being conducted, study data are often monitored by a data monitoring committee. The principal functions of the data monitoring committee are to monitor study data and to advise the principal investigator on issues related to this activity. It is generally accepted that the data monitoring committee should have sole access to aggregated unblinded data. This access should apply to all data on significant outcomes concerning risk or benefit, not only on adverse events.

Data monitoring committees also monitor reports from the study statistician of the aggregated data emerging from the study, and make recommendations to the trial management committee (see the Glossary) about continuing or halting the study and about other issues of study conduct.

Studies may be stopped if the intervention(s) in one arm of the study are found to be significantly better or significantly worse than in the other arm(s). To assist with this process, some studies have 'stopping rules', which are a predetermined list of conditions under which a study is to be stopped. Predetermined stopping rules ensure that a study is terminated early only when warranted by the results of emerging data. For example, initial data may clearly show that one treatment has detrimental effects compared with the other, taking into account the statistical limitations of such data.

Issues in this area relate to when data monitoring is required, in what form, and who is responsible for monitoring, reporting and follow-up.

Existing New Zealand guidance

The *Operational Standard* (Ministry of Health 2006b) states the following.

192. In general, researchers should be required to immediately report all serious or unanticipated adverse events to the committee. Committees should determine the exact requirements for reporting adverse events on a case-by-case basis taking into account the expected severity of anticipated adverse effects and the nature of a particular proposal.

193. Researchers should also be required to advise participants if new information relating to the safety of the study becomes available.

194. Reporting requirements should include instruction regarding the timeframe in which adverse events should be reported.

Ethical approval may be withdrawn:

iii. where new information becomes available that indicates that the safety of participants may be compromised

iv. where an applicant has not reported adverse outcomes to the committee (Ministry of Health 2006b: paragraph 213).

The HRC *Guidelines* recommend that:

> Research protocols should include stopping rules. Premature termination of the trial should take place if one treatment has been demonstrated to be superior, or if serious adverse effects occur (HRC 2005a: 16–17).

The Health Research Council's Data and Safety Monitoring Board (DSMB) establishes data monitoring committees for trials where such monitoring is appropriate. The DSMB's purpose is to provide objective, independent monitoring of clinical trials in New Zealand (see also HRC 2005b).

Primarily the DSMB is involved in large-scale public-good clinical trials initiated by New Zealand researchers in the setting of life-threatening diseases or diseases that cause irreversible morbidity. The DSMB may also be asked to participate in monitoring studies in other settings; for example, where there are special concerns regarding patient safety, where the study investigators are inexperienced, or where study integrity could be enhanced by the independence of a data monitoring committee. It is not anticipated that the DSMB would monitor small intervention studies with a short timeframe.

Where trials have New Zealand participants but are initiated in another country, the data monitoring committee is normally based in that other country.

Issues with existing New Zealand guidance

For those intervention studies with no data monitoring committee, there is a less independent form of data monitoring: health and disability ethics committees receive reports of adverse events from, for example, a study investigator. It is not clear, however, that ethics committees have the resources to assess whether there has been an appropriate response to reported adverse events. For studies with a data monitoring committee, it may be appropriate for this committee to make this assessment.

There is a need to ensure that a system of reporting adverse events is outlined in the study protocol, with details about how and in what timeframe any adverse events will be dealt with. Although there is a plurality of responsibilities, it is ultimately the trial management committee's responsibility to ensure that there is a plan for reporting and responding to adverse events. In situations where there is no trial management committee, this responsibility falls to the principal investigator.

The World Health Organization's *Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards* (WHO *Operational Guidelines*) lists the following kinds of studies where a data monitoring committee may be relevant:

- Controlled studies with mortality and/or severe morbidity as a primary or secondary end-point.
- Randomised controlled studies focused on evaluating clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality.
- Early studies of a high-risk intervention (risk of non-preventable, potentially life-threatening, complications; or risk of common, preventable adverse events of interest [especially type A drug reactions]), whether or not randomised.
- Studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes.
- Studies where the design or expected data accrual is complex, or where there may be ongoing questions with regard to the impact of accrued data on the study design and participants' safety, particularly in studies with a long duration.
- Studies where the data justify its early termination, such as the case of an intervention intended to reduce severe morbidity or mortality, which might turn out to have adverse effects or lack of effect, resulting in increased morbidity or mortality.
- Studies carried out in emergency situations.
- Studies which involve vulnerable populations (TDR 2004: paragraphs 2.1–2.8).

How the draft *Guidelines* address the issues

The draft *Guidelines* endorse independent monitoring of data, to protect participant safety. One application of the principle of proportionate review (the principle that the level of ethics review should be proportionate to the risk to subjects) is that the higher the potential risk to the study participants, the more likely it is that a data monitoring committee should be used, and the more important it is that the data monitoring committee is independent of the trial management committee.

Study protocols should include a plan for data monitoring, outlining how adverse events will be identified, timeframes for monitoring and reporting, and who is responsible for what aspects of these processes. Study protocols should also outline who will perform interim data analyses (if any), and what the criteria are for stopping a trial early. Copies of data monitoring committee recommendations to the trial management committee should routinely be copied to the health and disability ethics committee responsible for approving the research and to the study sponsor. Copies of trial management committee responses to these recommendations should likewise be distributed to these parties.

Data monitoring committees must have formally documented policies and procedures to function effectively. In general, they should be independent of those undertaking the study and should make recommendations to the trial management committee. Where study participation has the potential to increase the risk of (serious) harm to participants, the data monitoring committee should include an independent medical practitioner. However, in some relatively low-risk cases, the data monitoring committee may be constituted from the trial management committee. The data monitoring committee should then also include at least one independent advisor.

For certain types of intervention study there are good reasons to use an independent data monitoring committee. An example of such studies are those that meet the conditions set out in the WHO *Operational Guidelines* (see 'Issues with existing New Zealand guidance' above) and that are examining a novel treatment, or those with a serious study outcome, or research in vulnerable populations such as children. In multi-country studies with an overseas data monitoring committee, a clear policy of reporting should be presented to the ethics committee at the time of applying for its approval.

(See paragraphs 6.40–6.49 of the draft *Guidelines* (Part B): 'Study monitoring and adverse events', which includes 'Processes and responsibilities'.)

2.10 Monitoring study conduct

See draft *Guidelines* (Part B): 'Study monitoring and adverse events – processes and responsibilities' (paragraphs 6.41–6.43); 'Study monitoring and adverse events – responsibilities for monitoring adverse events' (paragraph 6.50).

Outline of the main issues

Monitoring study conduct involves monitoring the investigator's adherence to study protocols. It also involves ensuring that the investigator responds appropriately to any issues that emerge during the study, which might go beyond what is in the study protocol.

Existing New Zealand guidance

The *Operational Standard* (Ministry of Health 2006b) states:

> 191. Committees should require researchers to submit progress reports as a condition of ethical approval. Reports are required at least yearly, but may, depending on the nature of the proposal, be required more frequently.
>
> 192. In general, researchers should be required to immediately report all serious or unanticipated adverse events to the committee. Committees should determine the exact requirements for reporting adverse events on a case-by-case basis taking into account the expected severity of anticipated adverse effects and the nature of a particular proposal.
>
> 194. Reporting requirements should include instruction regarding the timeframe in which adverse events should be reported.

The *Operational Standard* also states that ethical approval may be withdrawn if there is deviation from the approved protocol, where an applicant has failed to report adverse outcomes to the ethics committee, or where an applicant has not met one or more of the conditions placed on them when ethical approval was given (Ministry of Health 2006b: paragraph 213). There is no guidance that outlines who is responsible for ensuring compliance or how compliance is to be monitored.

The HRC *Guidelines* state that:

> Individual host institutions should ensure that there are appropriate guidelines for the conduct of research and procedures for dealing with allegations of misconduct in research (HRC 2005a: 31).

Issues with existing New Zealand guidance

Although national guidance about what should be reported has been established, there is little information on whose responsibility it is to detect non-compliance or what procedures are needed to monitor investigator compliance throughout the duration of the study.

The *Declaration of Helsinki* acknowledges that the ethics committee has the right to monitor ongoing trials. However, the onus is on the researcher to provide monitoring information to the ethics committee (WMA 2004: paragraph 13).

How the draft *Guidelines* address the issues

The draft *Guidelines* state that study conduct and adherence to the protocol should generally be monitored by a person or group independent of the conduct of the study. The duration and frequency of monitoring should be in proportion to the level of potential risk to participants. The sponsor should take ultimate responsibility for ensuring that the study protocol is adhered to.

(See paragraph 6.41–6.43 and 6.50 of the draft *Guidelines* (Part B): 'Study monitoring and adverse events – processes and responsibilities' and 'responsibilities for monitoring adverse events'.)

2.11 Post-study access to interventions

See draft *Guidelines* (Part B): 'Care of participants' (paragraph 6.59).

Outline of the main issues

Some interventions being studied may not be available for general use by the wider population at the time the study is conducted. It is important that, where and when appropriate, study participants and the wider population are able to benefit from the study by having access to the intervention at the appropriate point after completion of the study.

The previous Minister of Health, the Hon Annette King, asked NEAC to provide guidance on this issue (Hon A King 2004, personal communication).

Existing New Zealand guidance

The Operational Standard states:

> Where research will lead to the development of a new medical device or drug, the proposal should describe the potential availability and affordability of such devices and drugs to the research participants and to the wider public (Ministry of Health 2006b: paragraph 84).

The *Interim Good Clinical Research Practice Guideline* recommends that ethics committees be advised of whether the product will be made available to participants when the study ends and, if so, whether continuing treatment will involve any cost to the participant (Medsafe 1998: 7).

Issues with existing New Zealand guidance

Internationally it is generally recommended that participants should have access to interventions that were studied at the completion of the trial, if a new trial intervention was found to be superior to current therapy.

The *Declaration of Helsinki* states:

> At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study (WMA 2004: paragraph 30).

The following note of clarification was added to paragraph 30 in October 2004 after substantial debate about the practicality and/or necessity of including this ethical principle:

> The World Medical Association hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review (WMA 2004: note of clarification on paragraph 30).

Ambiguity remains about:

- whether the requirement is purely procedural (that is, the conditions for post-trial access must simply be specified) or also substantive (that is, there must also be post-study access to the best intervention)
- the nature of access (for example, is it provision at reduced cost, or only some lesser form of access that is required?)
- access for interventions that are awaiting regulatory approval.

In New Zealand, some therapies that are licensed for use are not publicly funded. This status can, in effect, make them unobtainable for some study participants.

How the draft *Guidelines* address the issues

The draft *Guidelines* state that the ideal is for every participant to have access to the best proven intervention. The wider requirement is that it should be reasonably likely that the participants' communities will benefit from the study through access to any proven beneficial intervention.

Given these parameters, the minimum requirement for investigators is to inform study participants of the post-study access arrangements. As part of this process, they should acknowledge any sources of uncertainty, such as licensing and public funding issues, including the potential for restrictions on conditions of access (for example, limitations on stage(s) of disease or duration of therapy for which public funding might be made available, or any costs to those being treated).

(See paragraph 6.59 of the draft *Guidelines* (Part B): 'Care of participants'.)

2.12 Ancillary care responsibilities

See draft *Guidelines* (Part B): 'Care of participants – clinical responsibilities' (paragraphs 6.61–6.63).

Ancillary care is health care provided to participants that is not necessarily directly related to the study itself, but that may be identified in the course of conducting the study as being needed for one or more participants.

Outline of the main issues

It is generally agreed that researchers have responsibilities in relation to ancillary care. However, there is debate about the scope and nature of these responsibilities.

Existing New Zealand guidance

This area is not addressed in the *Operational Standard*. The *Interim Good Clinical Research Practice Guideline* states that:

> It is the responsibility of the investigator to ensure that participants are provided with high quality medical care during and after the study, including care to the participants should they suffer an adverse event and be withdrawn from the study (Medsafe 1998: 15).

The *Interim Good Clinical Research Practice Guideline* also recommends following up all clinically significant laboratory results or clinical observations that developed during the course of the study. The sponsor should be provided with a report detailing the follow-up actions taken after completion of the study and the outcomes of these actions (Medsafe 1998: 19).

Issues with existing New Zealand guidance

There is little international guidance relating to ancillary care. The CIOMS *Guidelines* state:

> When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care (CIOMS 2002: Commentary on Guideline 21).

Belsky and Richardson (2004) argue that study sponsors often have a duty to go beyond this and provide health care for participants, particularly if their condition was detected as a result of an examination or investigation that was performed as part of the study. However, there is a risk that their recommended approach might discourage studies with populations that have multiple health issues, because investigators' ancillary care responsibilities would be especially heavy in such settings. The need to do research with patient groups that stand to benefit should therefore be balanced with ancillary care responsibilities.

How the draft *Guidelines* address the issues

It is important to take care of participants while still allowing research to be undertaken in populations with significant health needs. The draft *Guidelines* aim to recognise both of these considerations by stating that study sponsors and investigators have a responsibility to take all reasonable steps to ensure that appropriate care is provided to study participants.

(See paragraphs 6.61–6.63 of the draft *Guidelines* (Part B): 'Care of participants – clinical responsibilities'.)

2.13 Publishing study results

See draft *Guidelines* (Part B): 'Disclosure of information obtained by intervention studies' (paragraphs 7.3–7.10, especially paragraph 7.7); 'Publishing study results' (paragraphs 7.11–7.15); 'Study protocol – registering trial protocols' (paragraphs 5.33–5.36).

Outline of the main issues

When study results are published, the knowledge gained from individual studies can be used in wider clinical practice. Published study results can both inform practice and shape the overall body of evidence. If findings are not published, the information that is publicly available can be misleading, and this can adversely affect patient care.

The published literature can become biased if only studies with certain outcomes – for example, only those that show a new intervention is better than the standard treatment – are published. The amount of publication bias of this nature is unknown. In some instances it is unclear whether the results published were the primary end-points that were identified in the study protocol, or other end-points or outcomes (Chan et al 2004). Publishing outcomes other than the primary end-points can result in biased estimates of treatment effects (see also Section 2.5 above (Part A): 'Registering trial protocols').

Existing New Zealand guidance

NEAC's Ethical Guidelines for Observational Studies state:

> The publication of both positive and negative study results is important (for example, that no link was found between a particular study variable and disease) since it helps to prevent publication bias and allows for additional information to be gleaned through meta-analyses (NEAC 2006: paragraph 10.6).

The *Operational Standard* states that if the results of completed research are not intended to be publicly available or published, there must be adequate justification for not doing so; and also that the results of research or innovative practice should be available to consumers or research participants (Ministry of Health 2006b: paragraph 62). Although the *Interim Good Clinical Research Practice Guideline* comments that the results of all studies should be published, it also states that there should be clarification about whether the sponsor will place any restrictions on the publication of results (Medsafe 1998: 19).

Issues with existing New Zealand guidance

Non-publication of study results has serious scientific and ethical implications. If results are not published:

- data are not available to inform clinical care and to contribute to systematic reviews and meta-analyses
- the study exposes participants to risk and inconvenience, without adding to knowledge.

It is desirable for study results to be published and in a timely manner. It is important that negative as well as positive results are published. In addition, investigators should publish on all and only the predetermined end-points, unless exceptions can be explicitly justified in a particular case.

The *Declaration of Helsinki* states:

> In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available ... Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication (WMA 2004: paragraph 27).

How the draft *Guidelines* address the issues

The draft *Guidelines* recommend the publication of study results to ensure that information gained from studies is disseminated. This dissemination should reduce duplication of studies and reduce the amount of publication bias.

(See paragraphs 7.7 and 7.11–7.15 of the draft *Guidelines* (Part B): 'Disclosure of information obtained by intervention studies' and 'Publishing study results'.)

The registration of trial protocols is a tool to assist in this area.

(See paragraphs 5.33–5.36 of the draft *Guidelines* (Part B): 'Study protocol – registering trial protocols'.)

Research funders may also be able to take initiatives to assist the publication of study results. For example, it may be possible to give more specific scrutiny to applications for research funding, by focusing on the applicant's history of producing timely publications from any studies that the funding body in question might have funded previously.

2.14 Compensation for injury

See draft *Guidelines* (Part B): 'Compensation for injury' (paragraphs 8.1–8.6).

Outline of the main issues

There is potential for participants to suffer injury while participating in an intervention study. In New Zealand, participants' entitlements to be compensated for such injuries vary.

The previous Minister of Health, the Hon Pete Hodgson requested that NEAC provide advice on this subject (Hon P Hodgson, personal communication, 19 July 2007).

Existing New Zealand guidance

Compensation arrangements for participants injured in clinical trials in New Zealand are complex. Compensation arrangements for injuries that arise during the course of an intervention study raise significant issues. It cannot always be assumed that participants will be covered by the Accident Compensation Corporation (ACC), for reasons outlined in this subsection.

Current compensation arrangements are referred to in:

- the Injury Prevention, Rehabilitation, and Compensation Act 2001 (IPRC Act)
- *Compensation for Injuries Caused as a Result of Participation in a Clinical Trial and the Role of Ethics Committees: Guidelines*, Ministry of Health and ACC (Ministry of Health – ACC *Guidelines*) (Ministry of Health and ACC 1993)
- *Guidelines on Clinical Trials: Compensation for Injury Resulting from Participation in an Industry-sponsored Clinical Trial*, Researched Medicines Industry Association of New Zealand (RMI *Guidelines*) (RMI 1997).

Participants in clinical trials may obtain compensation through ACC as a 'treatment injury', or through the sponsor of the trial. Both of these options are subject to restrictions.

The Injury Prevention, Rehabilitation, and Compensation Act 2001 (IPRC Act) (section 32) **does** provide for compensation and rehabilitation through ACC for claimants after personal injury resulting from participation in a clinical trial when:

- an approved ethics committee approved the trial

  and
- the ethics committee was satisfied that the trial **was not** to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled.

Trials in this category are called 'A trials'. Participants are also covered if they did not agree, in writing, to participate in the trial.

Participants in clinical trials are **excluded** from ACC cover under the general provisions of the IPRC Act if:

- an approved ethics committee approved the trial

  and

- the ethics committee 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.

Trials in this category are called 'B trials'.

The IPRC Act does not define 'clinical trial' for purposes of the above restrictions of study participants' entitlements, and there is no other authoritative definition. In practice, however, most intervention studies and many other sorts of studies are considered to be 'clinical trials', and consequently fall within the scope of these restrictions of study participant entitlement. They are included because Ministry of Health – ACC *Guidelines* define clinical trials very broadly, as:

> Any research on human subjects conducted to gain new knowledge into mental and physical health and disease. It would exclude research based on the analysis of secondary sources of health information. Clinical trials involve a wide range of health professionals with different qualifications, skills and expertise and would usually be conducted in hospitals, other health care settings, the community and academic host institutions (Ministry of Health and ACC 1993).

In practice, only studies that are confirmed to be clinical trials through the ethics committee approval process are subject to the above restrictions on study participants' entitlements. In addition, as part of the application for ethics committee approval (NAF-2005-v1), for trials that the ethics committee considers to be B trials, applicants are required to provide information relating to compensation for injury to trial participants. The compensation arrangements are to be in accordance with the Researched Medicines Industry Association of New Zealand's *Guidelines* (RMI 1997). In various respects, however, as discussed further below, sponsor adherence to the RMI *Guidelines* does not assure study participants of access to at least ACC-equivalent compensation cover.

Issues with existing New Zealand guidance

Current cover arrangements mean that study participants' entitlement to compensation for injury is based on who the principal beneficiary of the trial is, and what phase trial they participate in. Several issues arise about the cover arrangements, as follows.

1. The RMI *Guidelines* are written principally for medicines, not medical devices. Cover arrangements for participants injured in B trials of medical devices are unclear.

2. The RMI *Guidelines* relate only to phase II and III trials and consequently appear not to cover phase 1 trials. (For definitions, see paragraph 2.4 of the draft *Guidelines* (Part B): 'Types of intervention studies'.) This exclusion has the potential to leave participants in phase I B trials with neither ACC-equivalent nor RMI-equivalent cover.

3. The RMI *Guidelines* do not recommend the same level of cover that would be offered by ACC. The amount of compensation suggested by the RMI *Guidelines* is determined by the nature, severity and persistence of the injury. Compensation may be abated or excluded if the disease is not considered 'serious', if there was a high probability of adverse reactions occurring or if the participant was warned that adverse events might occur. These conditions leave participants vulnerable to receiving less than ACC-equivalent cover.

4. It is not clear what injuries are to be compensated. The *Operational Standard* states:

> Compensation will generally not cover expected or foreseen adverse effects from investigational therapies or other procedures performed to diagnose or prevent disease, because such outcomes could equally occur in medical practice (Ministry of Health 2006b: paragraph 95).

   Nevertheless, in clinical practice these outcomes might well be covered by ACC. Overall, the effect is to make participants somewhat uncertain about which injuries they can expect cover for.

5. There are a number of situations in which participants may not be entitled to any compensation for injury, such as where there is:
   - medical negligence in B trials
   - 'significant' departure from the study protocol by either the investigator or the participant in B trials.

   In these situations the participant's only method of receiving compensation may be through pursuit of a tort law action.

   An additional area of uncertainty is whether ACC covers injuries sustained in a trial that was not approved by an approved ethics committee.

In 2005 the ACC legislation was amended. Under the previous system, for a participant to be covered by ACC for an injury or adverse consequence arising from a clinical trial, the injury or adverse consequence had to be either:

1. the result of a health practitioner's negligence ('medical error') or
2. severe, with a low likelihood of occurring. This condition specifically excluded a person from compensation if the person had been advised beforehand of the risk of the injury ('medical mishap').

The Ministry of Health – ACC *Guidelines* and the RMI *Guidelines* have not yet been updated to reflect this change in legislation.

How the draft *Guidelines* address the issues

The draft *Guidelines* state the principle that study participants should be treated fairly relative to similarly placed non-participants. In the present setting, this principle means they should be provided with at least ACC-equivalent compensation for injury. Provisions that are directed toward this goal are covered in paragraphs 8.1–8.6 of the draft *Guidelines* (Part B). Note, however, that it is a challenge to achieve this goal within present policy settings.

In addition, parties other than NEAC may wish to consider the following as possible ways for addressing these issues.

1. The present legislative exclusion of some participants in clinical trials from ACC cover could be removed. This approach would establish equality of access to such cover for all participants in clinical trials, and would be a different means of ensuring that industry meets the cost of compensation for injury in trials that it sponsors. Given that this measure would require legislative amendment, it is beyond the scope of this NEAC project on intervention studies.
2. The ethics committee review system could be developed further to assist committees to apply a standard that, where participants of intervention studies are not covered by ACC, sponsors of those studies must ensure that participants have access to at least ACC-equivalent cover. Study sponsors might then be required to outline these provisions to the ethics committee as part of the process of applying for its approval.
3. RMI could revise its *Guidelines* to more closely align the provisions with current ACC provisions. This revision work would reflect the changes in ACC legislation that have occurred since the RMI *Guidelines* were established.

(See paragraphs 8.1–8.6 of the draft *Guidelines* (Part B): 'Compensation for injury'.)

Part B

Draft Ethical Guidelines for Intervention Studies

1 Introduction

1.1 These *Ethical Guidelines for Intervention Studies* (*Guidelines*) are issued in accordance with the statutory function of the National Advisory Committee on Health and Disability Support Services Ethics (National Ethics Advisory Committee – Kāhui Matatika o te Motu, or NEAC), under section 16 of the New Zealand Public Health and Disability Act 2000 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 2007: 29).

1.3 In general, the *Guidelines* constitute ethical standards for intervention studies, for the purposes of the Code of Health and Disability Services Consumers' Rights 1996 (the Code), Right 4(2).

1.4 An intervention study may be a 'clinical trial', for the purposes of the Injury Prevention, Rehabilitation, and 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 2004), 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).

1.8 The *Guidelines* are written primarily for investigators conducting intervention studies. They are structured around the process of designing and conducting a study, from the beginning stages of consideration of the underlying ethical issues, through to the communication of study results and post-study access to interventions.

1.9 Detailed matters concerning ethics committee review of intervention studies are addressed in the Terms of Reference for the individual health and disability ethics committees (Minister of Health 2004) established under section 11 of the New Zealand Public Health and Disability Act 2000 and in the *Operational Standard for Ethics Committees* (the *Operational Standard*) (Ministry of Health 2006b). The *Guidelines* have precedence over the *Operational Standard* on any point of conflict but in all other respects the *Operational Standard* applies to intervention studies.

1.10 Many of the ethical considerations stated in NEAC's *Ethical Guidelines for Observational Studies* (NEAC 2006) are also applicable to intervention studies.

1.11 The *Guidelines* include references to legislation. It is the investigator's responsibility to comply with all relevant legal requirements, including those set out in: the Injury Prevention, Rehabilitation, and Compensation Act 2001; the New Zealand Bill of Rights Act 1990; the Health and Disability Commissioner Act 1994; the Code of Health and Disability Services Consumers' Rights 1996; the Privacy Act 1993; and the Health Information Privacy Code 1994.

1.12 The Code of Health and Disability Services Consumers' Rights 1996 (the Code) is a regulation issued under the Health and Disability Commissioner Act 1994, section 74. The Code sets out 10 rights that are applicable to all health and disability services consumers, including those involved in research. Investigators conducting intervention studies should be familiar with their responsibilities under the Code, and should consider their study in light of the rights of (proposed) participants. The Code is available at the Health and Disability Commissioner's website (http://www.hdc.org.nz). Particular Code rights are referenced at relevant points throughout the *Guidelines*.

2 Definitions and scope of the *Guidelines*

2.1 This guidance is intended primarily to guide investigators conducting intervention studies, and assist them to conduct high quality studies.

Definition of 'intervention study'

2.2 In an **intervention study**, 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.

2.3 In an intervention study, an intervention may be, for example:

- preventive, diagnostic, prophylactic or therapeutic
- a new intervention (including a medication, radiation therapy, vaccine, surgical device, or surgical or other technique)
- an intervention established in practice but unproven as a matter of 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 (for example, the use of directly observed therapy (DOT) for the treatment of tuberculosis as opposed to patient-administered medication)
- a specific intervention for an identified group, or a whole intervention service or design.

Types of intervention studies

2.4 Intervention studies are studies in health or disability settings where a new intervention is compared with current or previous practice. The *Guidelines* may also be relevant to similar studies; for example, some studies of interventions in educational, sociological or psychological settings. The common types of intervention studies are listed in the box below.

A **clinical trial** is a study in which an intervention intended to improve a health outcome is allocated in advance to humans to evaluate its safety and/or its efficacy. Especially in studies of medicines, clinical trials are divided into four phases. Three of these phases are now outlined. See also phase IV trial in paragraph 2.5 below.

A *Phase I clinical trial (safety and pharmacologic profiles)* is a study in which an intervention (for example, a medicine or vaccine) is first introduced into a human population (usually of healthy volunteers) to determine its safety and mode of action. Normally, these studies are conducted with a small number of closely monitored participants.

A *Phase II clinical trial (pilot efficacy study)* is a study in which the efficacy of an intervention is first examined in humans. With medicines, the focus is on safety and efficacy in comparison with existing interventions; with vaccines, the focus is on immune response.

A *Phase III clinical trial (extensive clinical trial)* is a study intended for complete or definitive assessment of safety and efficacy of an intervention. It involves larger numbers of participants, usually with random allocation to study and control groups, as in a randomised controlled trial.

A **randomised controlled trial (RCT)** is 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. The study findings are assessed by comparing rates of disease, death, recovery or other appropriate end-points in the intervention and control groups.

A **pilot or feasibility study** is a preliminary study of an intervention that may use only intermediate end-points and may have no control group. For example, the study may instead make comparisons with international standards.

A **community intervention study** is a study in which interventions are allocated primarily to whole communities or to groups (such as schools or households) with other communities serving as comparison. For example, it 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.

2.5 A **phase IV trial** is a study conducted after approval or registration of an intervention, and is designed to assess the effectiveness and potential adverse effects of the intervention in 'field conditions'. Such studies may determine the effects of long-term use, or the effects in populations not included in earlier phases (for example, those with multiple health problems), or they may identify interactions among interventions and monitor changes in administration of interventions. In general, phase IV trials are observational studies rather than intervention studies, because the investigator observes health outcomes but does not control study variables or the intervention being studied. See also *Ethical Guidelines for Observational Studies* (NEAC 2006).

Features of intervention studies

2.6 **Participants:** The primary participants in most intervention studies are individuals. In some studies, the primary participants are grouped in communities (for example, geographical communities or organisations such as schools).

2.7 **Study groups:** 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 or a placebo or no intervention. The 'intervention' group receives the intervention that is primarily being studied.

2.8 **Randomisation:** Assignment of participants to study groups may be:

- randomised, by a method (for example, a random numbers table or computer-generated random sequence) that uses chance to assign participants with equal probability to each study group
- quasi-randomised (for example, through assignment by date of birth, day of the week, medical record number, or order of recruitment to the study)
- non-random.

2.9 **Allocation concealment:** Allocation concealment entails 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 ensure that the assignment of participants to study groups is truly random.

2.10 **Blinding:** 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 and they 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, and neither group knows which intervention the participants have been allocated to. Other groups that may be blinded include the outcome assessors, the data analysts and those writing the study report.

2.11 **Placebo:** A placebo is 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 of which group each participant has been allocated to.

2.12 **Investigator:** An investigator is any qualified individual who conducts all or part of an investigation. The **principal investigator** is the qualified health professional and/or qualified researcher with primary responsibility for the design and conduct of a particular investigation.

2.13 **Sponsor:** A sponsor is an individual, company, institution or organisation that is responsible for the initiation, management, and/or financing of a clinical trial. The sponsor can be a pharmaceutical or therapeutic device company, a funding organisation, such as the Health Research Council (HRC), or a contract research organisation (Ministry of Health 2006b: 105).

2.14 **Approved ethics committee:** An approved ethics committee is the Health Research Council Ethics Committee (HRCEC) or any ethics committee in New Zealand approved by the HRCEC, in accordance with the Health Research Council Act 1990, section 25. The standards established in these *Guidelines* may also be of assistance to other ethics committees.

2.15 **Data monitoring committee:** A data monitoring committee is an independent advisory body responsible for assessing data during the course of a study in a manner that contributes to the scientific and ethical integrity of the study (TDR 2005: 23).

Scope of these *Guidelines*

2.16 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 study variables and merely observes outcomes. For example, a study of the natural history of a disease is an observational study.

2.17 In general, these *Guidelines* do not concern interventions in observational studies (for example, biopsies) because such interventions are carried out to obtain information, rather than to study the effect of the intervention.

2.18 A small number of intervention studies include activities – such as specimen collection, storage and use, and genetic testing – that are not addressed in these *Guidelines*. Investigators should refer to relevant international and national guidance regarding research involving the use of human tissue.

Information on the collection and use of human materials can be found in *Guidelines on Ethics in Health Research* (HRC 2005).

All clinical research involving the manipulation of human genetic material must be approved by the Health Research Council's Gene Technology Advisory Committee as well as by a health and disability ethics committee. See also: the Medicines Act 1981, section 30; *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); and the Human Tissue Act 2008.

2.19 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.

2.20 There is a potential overlap between intervention studies and **innovative practice**. Innovative practice is practice that differs from established practice to an extent greater than mere routine variation. Some innovative practice is the subject of intervention studies, while other innovative practice occurs outside the setting of any study. These *Guidelines* relate to innovative practice only as it occurs in the context of an intervention study.

2.21 A study of change in a method of delivering care, undertaken by those making the change, is an intervention study rather than innovative practice if it is designed to add to knowledge of the health effects of the change.

2.22 A study of a change in a method of delivering care is an observational study rather than an intervention study if the study is performed separately from (for example, later than) the change that is made to the method of delivering care.

3 Ethics of intervention studies

3.1 This section concerns the worth of intervention studies, and responsibilities for their ethical review, including ethics committee review.

Worth of intervention studies

3.2 Intervention studies, especially randomised controlled trials, are often the best methods 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 such 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 dealt with.

3.3 Potential benefits of intervention studies include:

- providing objective results that establish the safety and efficacy of new and established interventions
- developing skills of practitioners in critical thinking, innovation and evidence-based practice.

3.4 To make an optimal contribution, intervention studies must be of high scientific quality and their ethical issues must be well understood and addressed.

3.5 The public is 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 as these contribute both directly and indirectly to service safety and quality.

Benefit to participants

3.6 There is a range of motives for participating in intervention studies. These motives can include gaining benefit for oneself and/or for others, and helping to contribute to knowledge.

Risk in intervention studies

3.7 In general, close ethical scrutiny is appropriate for intervention studies. The potential harms are generally greater than with other types of study, because of the intervention itself. Additionally, participants are more likely to be dependent on the investigator, and there is potential for conflict between the roles of investigator and clinician.

3.8 Potential harms to participants in intervention studies can include physical harms such as adverse events or lack of efficacy from the intervention. The potential for harm is particularly important in non-therapeutic studies, where there is no expected compensatory benefit from the intervention provided.

3.9 The greater the potential harm from a study, the closer the scrutiny that is required of the ethical issues raised.

Ethical review of intervention studies

3.10 Investigators are responsible for identifying and satisfactorily addressing the ethical issues in their studies (see Section 4: 'Underlying ethical considerations'). Where there is more than one investigator, the principal investigator has overall responsibility for the ethics of the study.

3.11 All intervention studies require review by an ethics committee. There should be just one such New Zealand review. The ethics committee should establish that the investigator has ensured that the study will meet established ethical standards.

4 Underlying ethical considerations

4.1 The following ethical considerations 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 the light of ethical considerations and should then satisfactorily resolve 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, 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.

(b) **Protection of people**, particularly those with impaired or diminished autonomy, requires that those who are dependent or vulnerable be afforded security against harm.

4.5 The Government has stated a commitment to fulfilling the special relationship between iwi and the Crown under the Treaty of Waitangi (Minister of Health and Associate Minister of Health 2002).

4.6 There should be due recognition of Māori as the tāngata whenua and indigenous people of Aotearoa New Zealand.

4.7 Issues relating to Māori cultural and ethical values should be addressed in discussion with Māori. This discussion may involve appropriate whānau, hapū or iwi representatives.

4.8 The Government has recognised the need for comprehensive, high quality Māori health research and information as it can inform the Government and assist whānau, hapū and iwi to determine and provide for their own health priorities (Minister of Health and Associate Minister of Health 2002).

Justice

4.9 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 achieve both of the following.

(a) They must avoid imposing on particular groups an unfair burden of participation in intervention studies. For example, vulnerable members of communities should not bear disproportionate burdens of studies from which other members of the community are intended to benefit.

(b) They must design studies so that the inclusion and exclusion conditions for participants are fair. (See criteria in paragraphs 5.21–5.22: 'Comparison groups – Inclusion and exclusion of participants'.)

4.10 Justice involves reducing inequalities. Decision-making about the study question should include consideration of the potential to reduce health inequalities.

Beneficence and non-maleficence

4.11 The risks of the study should be reasonable in light of the expected benefits. In particular, there is potential for risk of harm to study participants. Benefits accrue to society and 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.

- 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 (for example, where the only foreseeable risk is discomfort).
- A study warrants greater provision for the protection of participants if they are to be exposed to more than minimal risk.

Integrity

4.12 The investigator's commitment to the advancement of knowledge implies a duty to conduct honest and thoughtful inquiry and rigorous analysis, and to accept responsibility for her or his activities.

4.13 In intervention studies there is the potential for bias in the analysis and presentation of results. All investigators need to be aware of this potential and take steps to eliminate any bias and conduct studies with integrity.

Diversity

4.14 As they conduct intervention studies, investigators should understand, respect and make due allowance for diversity among participants and their communities. See also the Code:

> Every consumer has the right to be provided with services that take into account the needs, values, and beliefs of different cultural, religious, social, and ethnic groups, including the needs, values, and beliefs of Māori (Right 1(3)).

Addressing conflict of interest

4.15 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.

4.16 If an investigator has a conflict of interest, it can compromise study design or conduct, or reliability of study findings. It can also expose study participants to risk or inconvenience.

4.17 In intervention studies, potential for conflict of interest may arise when the investigator:

- is remunerated for participant recruitment (for example, with per capita payments)
- has a commercial interest in the intervention or financial links to the study sponsor
- is the participant's usual health or disability practitioner, therefore facing a potential conflict between the investigator role and the clinician role.

4.18 The investigator should disclose to relevant others (including 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 minimised.

5 Study and protocol design

Study question

5.1 Investigators should undertake studies that address important health and disability problems.

5.2 Every study question should be based on a thorough systematic review of relevant literature.

Study design

5.3 The study design should be the one best suited to answer the study question, while also minimising harm, maximising benefit and meeting other ethical standards.

5.4 Scientific soundness is ethically important. Projects without scientific merit can waste resources and can needlessly expose participants to risk and misuse their time.

5.5 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. Meeting this standard requires carefully determining the minimum clinically important difference and not overestimating the potential benefit of interventions. These statistical issues can be complex and individual assessment of each study is required.

5.6 Assignment of participants to study groups is generally best done by randomisation. This process tends to make study groups reliably comparable and minimises biases, especially uncontrolled confounding (see definitions below). Quasi-randomised or non-random methods are generally less reliable in this regard because of their potential to allow other factors to influence assignment of participants to study groups. Allocation concealment also improves study validity and design through preventing selection and confounding biases. Bias and confounding are defined as follows:

> Bias refers to the tendency of a measurement or a statistic to deviate from the true value of the measure or statistic (Brownson and Petitti 1998: 50).
>
> Confounding is a distortion of the estimated effect of an exposure on an outcome, caused by the presence of an extraneous factor associated with both the exposure and the outcome (Last 2001). For example, smoking is a risk factor for ischaemic heart disease, so confounding can occur in a study of an anti-angina medicine if the control group contains more smokers than the intervention group.

5.7 Use of blinding (see paragraph 2.10 on blinding in 'Features of intervention studies') is desirable in an intervention study design when it can be shown that it has methodological advantages and minimal risks.

Comparison groups

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

'Best intervention' standard

5.9 The 'best intervention' standard is met by an intervention study if the risks and benefits of the intervention(s) in the study are tested against those of 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.

5.10 All intervention studies should meet the 'best intervention' standard, unless there are only temporary and minimal departures from the 'best intervention', and a justification for any such departures is provided to an approved ethics committee.

5.11 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 confirm the sensitivity of a therapeutic study design. An investigator who proposes any such approach should justify this to an approved ethics committee and explain how it can be undertaken without significant harm to participants.

5.12 In some cases, one or more interventions provided in an intervention study are equivalent to the best proven intervention available locally outside a study but are known to be inferior to the best proven intervention available worldwide. In such cases, the study can be justified only if the world-best intervention is unlikely to be available locally for the foreseeable future 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.

5.13 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 paragraphs 5.14–5.16 below: 'Equipoise standard').

Equipoise standard

5.14 An intervention study meets the equipoise standard if the evidence is 'equally poised' as to the comparative overall risk–benefit of each of the interventions offered in the study.

5.15 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 available evidence demonstrates that one intervention has better expected overall risk–benefit than the other(s).

5.16 Equipoise is a matter of the evidence that should inform the decisions of study designers and potential study investigators. For some proposed studies, there may be reasonable professional debate about whether or not the evidence is in equipoise. However, certainty or uncertainty alone, however genuinely felt, is not enough to demonstrate the presence or absence of equipoise.

5.17 In addition to equipoise, the values and circumstances of individual participants are relevant to the design of the study. For example, a potential participant might have a general preference for the less radical of two alternative interventions that are in equipoise or might have a known adverse response to one of the interventions. Investigators should take account of such individual characteristics when designing each study and when considering the particular circumstances of each potential study participant.

Use of a placebo

5.18 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 using an established effective intervention as comparator would not yield reliable findings on safety or efficacy and use of placebo would not add any risk of serious or irreversible harm to participants.

5.19 In some intervention studies, all participants receive the best proven current intervention, with placebo versus another intervention as additional interventions. This approach does not raise any particular ethical issues, because the best proven current intervention is not withheld in such cases.

5.20 When a placebo control is used, the investigator should ensure, and the approved ethics committee should check, that each participant or individual legally entitled to decide on that participant's behalf has consented, after being 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.

Such a study should also meet other ethical requirements, such as the 'best intervention' standard (see paragraphs 5.9–5.13 above: '"Best intervention" standard').

Inclusion and exclusion of participants

5.21 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 without good reason. (An example of an acceptable reason might be that the study question and future use of the intervention under study concern a specific population group; it would therefore be necessary to exclude people outside this group.)

5.22 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 inclusion of all those who may benefit from the study findings.

Vulnerable people

5.23 Vulnerable people include those who have restricted capability to make independent decisions about their study participation, and those whose participation may have direct implications for others. Examples of potentially vulnerable people include:

- children
- people with mental illness
- people with serious intellectual disability
- members of communities unfamiliar with medical or research concepts
- people with English as a second language and/or a different cultural background to the investigators (for studies whose details are primarily, or are only, stated in English)
- people whose freedom to make independent choices is restricted (for example, prisoners, employees of a sponsoring company or medical students)
- unemployed people, or people of low socioeconomic status
- people with a serious illness for which the study treatment is either the only treatment available, or offers benefits that substantially exceed those of any other available treatment.

5.24 Vulnerable people should have the opportunity to be included in high quality studies on questions that matter to their health.

- Research should only be performed in vulnerable groups if it cannot be adequately performed in other groups.
- The study should ask questions that matter to the participants' communities; the answers should benefit the communities.

- Where research in a vulnerable group is conducted, it should involve the least vulnerable people in that group (for example, older rather than younger children).
- Intervention studies should be conducted only if the risk to participants is at an acceptable minimum.
- Study participation is a matter of free and informed decision-making by study participants wherever possible.

5.25 The interests of vulnerable individuals must be protected and these individuals must not be exploited for the advancement of knowledge. Adhering to this principle is especially important if one or more of the interventions being studied is invasive.

5.26 When a vulnerable person is competent to decide her or his own study participation, this person's decision should be respected. For example, if such a person consents to participate in a study, it is inappropriate to seek consent of a legal proxy in addition or instead. If a person declines to participate, this decision should not be overruled by the decision of a legal proxy. (See also paragraphs 6.24–6.31 below: 'Non-consensual studies'.)

5.27 Further guidance on research with particular vulnerable populations is contained in appendices to the *Operational Standard for Ethics Committees* (Ministry of Health 2006b).

Skills and resources

5.28 Studies should be conducted and supervised only by investigators with the necessary skills and resources to do so. These skills and resources include those needed to deal well with any contingencies that may affect participants.

5.29 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 conduct.

5.30 An investigator should not proceed with a study when the resources, staff, facilities or equipment available to complete it are known to be inadequate.

5.31 Investigators must operate under professional standards or employment requirements that oblige them to maintain the confidentiality of patient data.

Study protocol

5.32 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 proportional to the level of risk the study presents to participants.

Registering trial protocols

5.33 All intervention studies should have a protocol registered with an approved register. The purposes of this measure are to avoid duplication of trials and to foster publication of key study outcomes.

5.34 The registered protocol should include the data items identified by international guidelines, including:

- public and scientific titles
- sponsor(s) and principal investigator
- the study objectives
- the primary and secondary outcomes
- target sample size and statistics.

5.35 New Zealand-based clinical trials can be registered without charge on the Australian New Zealand Clinical Trials Registry (http://www.anzctr.org.au). Evidence of registration should be provided when submitting an application for ethics committee approval. Alternatively, a statement should be given that the register in question, which should be named, requires studies to have ethics committee approval prior to registration.

5.36 International trials that have a New Zealand arm should be registered with an appropriate register. The relevant registration identification should be given when submitting an application for ethics committee approval.

Study locality

5.37 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. Achieving this level of expertise may necessitate training for those undertaking the study.
- The facility must be of an adequate standard to implement the study without any adverse effect on the access to treatment of others at that facility.

For information on locality assessment, see the New Zealand Health and Disability Ethics Committees website (http://www.ethicscommittees.health.govt.nz).

Studies with distinctive features

Non-therapeutic trials

5.38 Therapeutic intervention trials examine interventions or procedures that hold the prospect of direct diagnostic, therapeutic or preventive benefit for the individual participant. Non-therapeutic trials examine interventions that do not hold the prospect of direct diagnostic, therapeutic or preventive benefit to individual participants. Types of non-therapeutic trials include phase I trials (see paragraphs 5.40–5.42 below: 'Phase I trials'), bioequivalence studies and bioavailability studies (see the Glossary).

5.39 A non-therapeutic intervention study is justified only when the importance of the objective outweighs the inherent risks and burdens to the subject and, wherever feasible, participants are well informed of the risks.

Phase I trials

5.40 Phase I trials test interventions in human populations for the first time (see paragraph 2.4 above: 'Types of intervention studies'). Due to their potential to cause serious adverse reactions, special care should be taken when testing interventions that can stimulate an immune response. Examples of interventions in this category are use of T cells and biologic agents with a high affinity to the target organ, such as antibodies.

5.41 Early clinical studies of novel biologic or chemical agents with potential to cause harm should be conducted only under the following conditions.

- '[T]he importance of the objectives outweighs the inherent risks and burdens to the subject' (WMA 2004: paragraph 18).
- The study is conducted in a research facility that is on or adjacent to the site of a hospital with intensive care facilities and is covered by the hospital resuscitation team.
- Only one subject receives the active agent on the first day ('staggered dosing').
- Investigators have appropriate training or significant experience in phase 1 (first-in-human) trials, with close involvement of a medical monitor.

5.42 Protocols for phase I trials should be reviewed internally and externally by groups with appropriate technical, scientific and medical experience.

Community intervention studies

5.43 In a community intervention study, interventions are allocated primarily to whole communities or groups (see paragraph 2.4 above: 'Types of intervention studies'). 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.

5.44 Individual consent to participate in a community intervention study should not be required if gaining that consent is impracticable, if the benefits from the research are sufficient and if the potential harms are minimal.

5.45 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.

5.46 To the extent possible and whenever appropriate, investigators should involve community representatives in the planning and conduct of the study and give community members the opportunity to contribute, for example, through submissions or public meetings.

Collective consultation

5.47 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 study participation.

5.48 Some intervention studies are conducted within identifiable communities, or with the whole community as the unit to which the intervention is allocated, 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 studies, investigators should consult with the community and seek the agreement to participate from individuals.

5.49 In consulting a community or group regarding participation in a study, the investigator should approach its representative(s) in accordance with its 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.

5.50 The remaining provisions in this subsection provide more detail on collective consultation for studies in Māori settings.

5.51 Where the investigators include one or more members from a whānau, hapū or iwi to be studied, it may be preferable to have a statement in the study proposal that group agreement for individuals to be approached to participate was obtained from the representatives/participants in hui. This statement may be provided via a kaumātua or other person of authority in the group.

5.52 Where the investigators do not include any member from 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 with and agreement by 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 ethical and scientific standards. The approach may be made direct, or indirect (for example, by the participant's own doctor or relevant health practitioner). If the approach is not to be made through the participant's health practitioner, the reasons for an alternative approach should be presented to the ethics committee. In such cases, either prior agreement from the participant's health practitioner should be sought to invite the individual to take part, or the participant's health practitioner should be informed that the individual will be invited to take part. In the latter circumstance, the participant should be informed of the name of the person who agreed that he or she could be approached. Where approaches to participants identified through health records involve visiting or telephoning them at their home, giving some advance notice (for example, through a letter) is generally desirable.

6.3 Further guidance on access to health records is available in NEAC's *Ethical Guidelines for Observational Studies*, 'Section 6: Collection of health information' (NEAC 2006).

6.4 In general, ethics committee approval is required to access health records (including disease registries) for the purpose of identifying and approaching potential participants for intervention studies.

Free and informed consent

General principles

6.5 Informed consent is best understood in terms of decision-making that is based on good communication between people, rather than simply as transfer of information from one person to another (Manson and O'Neill 2007).

6.6 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. It is therefore free from undue influence such as manipulation or coercion.

6.7 People are entitled to make free and informed decisions about their study participation. The purposes of this principle are to ensure that such decisions express the will of the decision-makers and to protect them from coercion, manipulation and other undue influence.

6.8 The person making the decision must have sufficient competence to make that decision, in terms of their ability to understand and weigh the information.

6.9 Information provided should be tailored to the individual, taking into account participants' level of knowledge, understanding, and the amount of detail they desire.

6.10 Consent provisions should include establishing access to a potentially ongoing dialogue about the study and giving opportunity throughout the duration of the study for any questions to be answered. Providing this kind of ongoing access to information is often a better way to communicate than providing a lot of extra written material.

6.11 Investigators should effectively communicate to participants the purpose and practical implications of all key study features, including any randomisation, placebo control, or blinding.

6.12 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 studies would secure informed consent of this nature.

6.13 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. One option is to limit the consent form and information sheet to the essentials, and cross-reference these to an attached appendix that contains further details for those who might be interested.

6.14 Multi-country studies with consent forms and information sheets that diverge from the above guidelines could provide a summary sheet to give to New Zealand participants in addition to the other study forms.

6.15 It is preferable that the participants record in writing their consent to participate in an intervention study. There may be some situations where this is not possible or desirable, for example due to a participant's illiteracy or physical inability or for cultural reasons. The principles of justice and non-exclusion dictate that prospective participants should not be excluded from research purely on the basis of illiteracy, physical inability or for cultural reasons. However, any exceptions to obtaining written informed consent should be justified to an approved ethics committee. In all cases where consent is not recorded in writing, the procedures used to seek free and informed verbal consent should be documented. (See also the Code, 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 approved ethics committee, on grounds that prior consent is one or more of the following:

- unnecessary (for example, where the intervention(s) to be studied are very minor and consent during or after intervention may suffice)
- impracticable (for example, for studies in emergency care)
- undesirable (for example, when any delay of the intervention(s) to be studied would harm the person).

6.17 People are ethically entitled to be informed about their study participation, whether their participation is 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 approved ethics committee, on grounds that informing participants is unnecessary and/or impracticable and/or undesirable (see paragraph 6.16 above).

6.18 Due regard should be paid to the circumstances of the person during the initial consent discussion. 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, Right 7(7).)

6.20 Those who ask to withdraw from a study may wish only to withdraw from the intervention they are receiving rather than from the study itself. In general, those who withdraw should be asked whether they are willing for their data to remain in the study, or if they are willing to have further data recorded, particularly study end-points. Any new data or data that have already been collected could provide beneficial information for the study.

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. For any study that requires ethics committee review, the ethics committee should review any proposal to make significant amendment to the study protocol.

Features of informed consent

6.22 Informed consent is essentially a matter of good communication between people. Information should consequently be provided to potential participants in a form and 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**, covering:
  - the purpose of the study, including its expected contribution to knowledge and its benefits to communities
  - the reason that potential participants have been asked to participate

  - the voluntary nature of the participation, including potential participants' entitlement not to participate or to withdraw from participation at any stage
  - an explanation of how the study meets the 'best intervention' and equipoise standards
  - an explanation of the purpose and practical significance of the use of randomisation, blinding or placebo
  - the nature, sponsors and 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
  - an explanation of data monitoring throughout the trial, including who will be undertaking this.
- Describe **what the study involves**, covering:
  - 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 (for example, 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 member(s)
  - arrangements for personal compensation for injury, including whether the study is covered by the Injury Prevention, Rehabilitation and Compensation Act 2001
  - what payments or other forms of reimbursement, if any, will be provided in recognition of participation
  - the extent of the investigator's responsibility to ensure that care is provided for participants during the study.
- Explain **the rights of participants**, covering:
  - that they are free to refuse to participate, or to withdraw from the research at any practicable time, without experiencing any disadvantage
  - that they have the right to access information about them collected as part of the study
  - that they will be told of any new information about adverse or beneficial effects related to the trial that becomes available during the study that may 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, 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 paragraphs 6.5–6.21 above ('Free and informed consent – General principles'). To improve participant understanding, one option is to limit the consent form and information sheet to a minimum summary of the relevant information, and cross-reference this to an attached appendix that contains further details for those who might be interested.

Non-consensual studies

6.24 Some people who have diminished competence or no competence at the time the study is conducted may be competent to make decisions about study participation at an earlier time (for example, potential participants in a study of Intensive Care Unit care after major elective procedures). Investigators should make all reasonable efforts to identify any prior consent or refusal to participate by the person, and should give effect to any such prior decision.

6.25 People who have diminished competence to make decisions about their study participation are entitled to make informed decisions to the extent appropriate to their level of competence. (See also the Code, Right 7(3).)

6.26 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 Health and Disability Services Consumers' Rights 1996. In non-consensual studies, it is the investigator's responsibility to ensure that all applicable legal standards are met.

6.27 The ethical standards for non-consensual studies that are stated in these *Guidelines* are applicable only to those studies that are lawful.

6.28 The ethical standards for non-consensual studies that are stated in these *Guidelines* apply only to therapeutic intervention studies. Non-therapeutic studies should be undertaken only with the prior informed consent of the competent individual. (See paragraphs 5.38–5.39 above: 'Studies with distinctive features – Non-therapeutic trials'.)

6.29 If any person is included in a study without her or his consent, this must only be if it is impracticable for them to give their consent. For situations in which a legal proxy can give consent, this consent should be obtained. Where such consent is not possible, in addition to adhering to paragraphs 6.24 – 6.28 above, and as soon as practicable, the investigator must seek the participant's informed consent to continue participating in the study. (For example, a person's informed consent to continue her or his participation in an emergency care study should be sought as soon as practicable after he or she has recovered sufficient competence to decide the matter.)

6.30 If a person is not competent to make an informed decision about participating in a study, then the decision may be made by an individual who is legally entitled to decide on behalf of the person. If no such individual is available, and the investigator can legally undertake the study, then study participation must be:

- in the best interests of the person, and
- in accordance with a study protocol approved by an ethics committee, and
- underpinned by either:
  - the investigator's belief, on reasonable grounds, that the decision is consistent with the informed choice that the person would have made if he or she were competent, or
  - if it cannot be ascertained what decision the person would have made, the investigator's consideration of the views of other suitable people who are interested in the person's welfare and available to advise the investigator.

Note that this standard draws substantially on the Code, Right 7(4).

6.31 For the purposes of paragraph 6.30, study participation is in the best interests of a person only if the study meets appropriate ethical standards. These standards include the 'best intervention' standard (see paragraphs 5.9–5.13 above: 'Comparison groups – Best intervention standard') and the equipoise standard (see paragraphs 5.14–5.17 above: 'Comparison groups – Equipoise standard').

Study conduct

Deception and concealment

6.32 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.

6.33 When the investigator believes deception or concealment is scientifically justified, the following requirements 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 provided as soon as is appropriate and practicable.
- Participants are entitled to withdraw 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 investigators or research.
- The investigator justifies the deception or concealment to an approved ethics committee.

Inducements for participants

6.34 Inducement for study participants can 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.

6.35 Inducement can take many forms, some of which are inappropriate. For example, it can occur directly or indirectly through financial or other recognition (such as promises of treatment), it can exploit the vulnerability of individuals, or it can use the influence and status of the health professional or investigator.

6.36 Appropriate inducement may include:

- reimbursement of incurred expenses of participants (for example, 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 (but it is generally not appropriate to discuss koha prior to agreement to participate).

  Traditionally, koha is an acknowledgement of the knowledge and/or hospitality extended by tāngata whenua to manuhiri. Koha is presented as part of the pōwhiri onto a marae or other venue of the tāngata whenua. However, the definition of koha should not be restricted by reference to its traditional roots; contemporary meanings include the giving of koha in a different manner during research (NEAC 2006: paragraph 6.23).

6.37 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.

6.38 All inducement payments, reimbursements and health services provided to study participants must be approved by an ethics committee.

6.39 When payments are used, it should be stated at the outset of the study if withdrawal either due to health grounds or any other reason or wilful non-adherence will affect any payments and, if so, what this effect will be.

Study monitoring and adverse events

6.40 Study monitoring and key terms relating to this activity are defined in the box below.

Definitions

Term	Definition
Adverse event	Any undesirable event occurring to a participant during an intervention study, whether or not related to the intervention.
Serious adverse event	An adverse event that is fatal or life-threatening, is disabling, requires or prolongs in-patient hospitalisation (except where death or hospitalisation is a defined end-point of the study), or is a congenital anomaly, malignancy or overdose (Medsafe 1998).
Monitoring	Monitoring activities include: • checking for the occurrence of adverse events • checking the conduct of the study including investigator adherence to the study protocol • monitoring and/or analysing emerging data from the study. Monitoring, for the purpose of this document, does not concern the in-trial, internal monitoring of the health of participants and adherence to treatment.
Data and Safety Monitoring Board (DSMB)	The Health Research Council has a DSMB that establishes data monitoring committees for trials it is asked to monitor. The DSMB's purpose is to provide objective, independent monitoring of clinical trials in New Zealand.
Data monitoring committee	A data monitoring committee is an independent body, advisory to the study team and study sponsor, and responsible for monitoring emerging data during the course of a study to ensure both safety of participants and high quality conduct of the study to generate reliable answers to its study question(s). The data monitoring committee is usually constituted by the study sponsor.

Processes and responsibilities

6.41 Monitoring of study conduct and adherence to study protocol should generally be undertaken by an independent person or group.

6.42 Data monitoring contributes to the safety of participants and should also generally be undertaken by an independent person or committee. The study protocol should include a monitoring plan, containing information on:

- how serious or unexpected adverse events will be identified and reported
- to whom and by whom serious or unexpected adverse events will be reported
- timeframes for reporting
- how often interim analyses (if these are to be performed) will be carried out
- the composition of any data monitoring committee (if applicable) and/or arrangements for internal monitoring
- under what circumstances a study would be stopped early (for example, in case of data on adverse events or from interim analyses).

6.43 In accordance with the principle of proportionate review, the frequency and type of monitoring of a study should reflect the degree of risk to participants.

6.44 Investigators and sponsors should consider an independent data monitoring committee for the following kinds of studies:

- randomised controlled trials with mortality and/or severe morbidity as a primary or secondary end-point
- randomised controlled trials to evaluate clinical efficacy and safety of a new intervention intended to reduce severe morbidity or mortality
- early phase studies, whether or not randomised, of a high-risk intervention (for example, risk of non-preventable, potentially life-threatening complications; or risk of common, preventable adverse events of interest, especially type A drug reactions)
- early phase studies of novel interventions where there is very limited information on clinical safety or where prior information raises concern regarding potential serious adverse outcomes
- studies where the design or expected data accrual is complex, or where there may be ongoing questions regarding the significance of accrued data for the study design and participants' safety, particularly in studies with a long duration
- studies in which the data could potentially justify early termination of the study (for example, where the intervention is intended to reduce severe morbidity or mortality, but there is also potential for adverse effects or lack of effect and consequent increase in morbidity or mortality)
- studies carried out in emergency situations, as recommended in the World Health Organization's *Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards* (TDR 2005). For New Zealand–led studies, see also the HRC's *Data Safety Monitoring Board Operating Guidelines* (HRC 2005b).

6.45 A data monitoring committee should be involved only if it is able to assist in practice with ensuring participant safety and study validity.

6.46 The data monitoring committee itself must have documented policies and procedures.

6.47 Where study participation can increase the risk of serious harm to participants, the data monitoring committee should include an independent medical practitioner.

6.48 In some relatively low-risk cases, the data monitoring committee may be constituted from the trial steering group or management committee. The data monitoring committee should then also include at least one independent advisor.

6.49 Any multi-centre study that has a data monitoring committee should have just one such committee. In any multi-country study with an overseas data monitoring committee, a clear policy of reporting should be presented to the ethics committee at the time of applying for ethical approval.

Responsibilities for monitoring adverse events

6.50 Responsibilities in regard to monitoring adverse events are outlined for key agents below.

Agent	Responsibilities
Investigator(s)	Take the lead monitoring role, being uniquely placed to observe the study process and any unexpected or adverse outcomes. Report promptly all serious or unanticipated adverse events to the relevant approved ethics committee. Ensure (eg, via the study statistician), if required, that such events are reported, in unblinded form, to the data monitoring committee Report to the ethics committee in a timely way any decisions made in response to any data monitoring committee recommendations. Submit regular (at least annual) reports to the sponsor and ethics committee.
Data monitoring committee	Monitoring may be undertaken by the Data and Safety Monitoring Board (DSMB) of the Health Research Council where: • large-scale clinical trials are initiated by New Zealand investigators in the setting of life-threatening diseases, or diseases that cause irreversible morbidity • there are special concerns regarding patient safety • the study investigators are inexperienced • the integrity of the study could be enhanced by the independence of the DSMB. Make timely recommendations to the investigator(s) and study sponsors, in light of its monitoring activities, and copy these recommendations to the ethics committee.
Sponsor	Take ultimate responsibility for ensuring the study protocol is adhered to and that quality monitoring takes place. Monitor the serious adverse event process. Respond appropriately (eg, reporting to regulatory bodies or ethics committees) to reports from the investigator(s), the data monitoring committee and others that indicate that participant safety may be compromised by the study.
Approving ethics committee	Review the safety monitoring plan and system of monitoring. Make timely decisions as to the continuation or withdrawal of its approval for studies.

Stopping a study

6.51 It is normally unethical for an investigator to continue a study if:

- the investigator has substantially deviated from the study protocol
- there are adverse events of unexpected type, severity or frequency
- during study conduct, one or more of the interventions being compared is demonstrated to be better or worse than the other(s) or than the best proven intervention available outside the study, such that continuation of the study would clearly disadvantage some or all participants.

6.52 The study protocol should include 'stopping rules' for early termination of the study to address potential situations such as the following.

- One intervention has been demonstrated conclusively to be superior to another or to be the best proven intervention available outside the study, in terms of either efficacy or safety. Early termination therefore minimises the use of an intervention known to be inferior.
- It becomes clear that the study can neither answer its study question nor generate sufficiently valuable data for meta-analyses. (For example, key study design flaws become evident; minimum recruitment rates cannot be achieved; or the required study resources or personnel cannot be maintained.)
- Unexpected, serious adverse events occur.

6.53 Where there is an internal monitoring process or an independent data monitoring committee, a study would normally be stopped early in light of advice from that body.

6.54 Study stopping rules should cover how it will be determined that one intervention is superior and who is responsible for reaching this conclusion.

6.55 Studies should not be terminated simply for reasons of commercial interest or public relations.

6.56 If significant new information about the intervention becomes available after the study begins, this information should be provided to the ethics committee and also to the participants. Investigators should explain to the ethics committee what significance they believe this new information has for continuation or termination of the study, or for modification to its design and/or communication with participants. See also Right 6(1) of the Code, which states:

> Every consumer has the right to the information that a reasonable consumer, in that consumer's circumstances, would expect to receive, including –
>
> ...
>
> (b) an explanation of the options available, including an assessment of the expected risks, side effects, benefits, and costs of each option.

6.57 In some studies, evidence may emerge, from the study or from other sources, demonstrating that the study no longer meets the 'best intervention' standard (see paragraphs 5.9–5.13 above: 'Comparison groups – "Best intervention" standard'). Investigators should design any intervention study so that, as soon as reasonably practicable after such evidence emerges, they can stop the study and make all reasonable efforts to ensure that participants are offered the newly proven best intervention, based on the overall balance of benefits and risks.

Care of participants

6.58 Investigators have obligations to ensure the availability of health care services that are essential to the safe conduct of a study and for participants who suffer injury as a consequence of study interventions.

6.59 Ideally, phase III intervention studies should be designed to assure every participant of 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 some intervention studies, it cannot be known which intervention is best until after the study has been completed.

Clinical responsibilities

6.60 An investigator must inform professionals who may be responsible for the health care of patients or healthy volunteers of the participation of these people in a trial. Following this guideline will almost always require the investigator to notify the general practitioner when the patient is enrolled in the study, and to provide accompanying information about the possible medical implications of this involvement.

6.61 Participants (and their primary 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.

6.62 Where participants are found through 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.

6.63 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. If study data are to be used for any purpose, or by any people, other than as specified in the approved protocol, investigators should submit a proposed revision of the study protocol for ethics committee review.

Confidentiality of data

7.2 For guidance on privacy and confidentiality, refer to NEAC's *Ethical Guidelines for Observational Studies*, 'Section 8: Confidentiality of data' (NEAC 2006).

Disclosure of information obtained by intervention studies

7.3 Where findings suggest serious disease, study participants who have not given permission for the transfer of the information to their medical advisor should be urged to seek further advice.

7.4 Care should be taken not to interfere with health professional–patient relationships. Investigators should usually refrain from giving an opinion about how a particular finding should be dealt with by a participant's doctor.

7.5 Individuals' privacy and confidentiality of information need to be protected unless there is an overriding concern (for example, 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 participants of the event and the reasons for it.

7.6 Investigators have an obligation to advocate the release of information that is in the public interest even when the data are retained by governmental, commercial or other sponsors.

7.7 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.

7.8 Investigators have an obligation to disclose to participants and their legal proxies, if they have any, 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. This participant right should be indicated in the informed consent process and in the data monitoring plan.

7.9 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. Restrictions on publication of study results or dissemination of findings are also inappropriate, so investigators should not normally enter into contracts that limit, or apply time restrictions to, publication.

7.10 Contracts between investigators and study sponsors should be submitted to an ethics committee as part of the study approval process. Any restrictions on investigator access to study data should also be justified to the ethics committee. (For example, where it is appropriate for a study to have a data monitoring committee, that committee should generally have sole unblinded access to emerging data.)

Publishing study results

7.11 Investigators have a responsibility to the study participants, future patients, and the wider scientific and general community to publish the results of their studies.

7.12 Full publication of study results also 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.

7.13 Study protocols should include 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 release of study results can be more harmful than beneficial to individuals and to society. It may be difficult 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. However, where the findings lead to immediate benefit to patients, it is the responsibility of the investigators to make these results available to the relevant parties in an expeditious manner.

7.14 Study results should be published in a form that gives due regard to cultural and other sensitivities. In general, this guideline implies that they should not be published in a form that permits identification of individual participants.

7.15 In the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*, the International Committee of Medical Journal Editors 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).

For any intervention study or part of such a study conducted in New Zealand, this reporting includes indicating whether the procedures of the study were followed in accordance with these *Guidelines*.

8 Compensation for injury

8.1 Investigators, study sponsors and ethics committees have responsibilities to ensure that compensation for injury is available to all participants in intervention studies, to at least the level of cover provided by the Accident Compensation Corporation (ACC) for those who have comparable injuries outside a clinical trial.

8.2 In general, the Injury Prevention, Rehabilitation, and Compensation Act 2001, section 32, provides for compensation and rehabilitation for claimants after personal injury resulting from participation in an intervention study.

8.3 Participants in intervention studies are excluded from cover under the general provisions of the Injury Prevention, Rehabilitation, and Compensation Act 2001 if all of the following conditions are met.

- The participant's personal injury results from medical treatment.
- This injury occurs during 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.
- The ethics committee 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.

If all these conditions are met, investigators, study sponsors and ethics committees have responsibilities to ensure alternative compensation cover for study participants, to at least ACC-equivalent standard.

8.4 In their consent process for participants, and in their application for ethics committee approval, investigators must explain how they will ensure provision of at least ACC-equivalent compensation cover for participants for accidental injury as a result of their study participation.

8.5 Neither the fact that any adverse reaction causing an injury was foreseeable or predictable, nor the fact that the participant has freely consented (whether in writing or otherwise) to participate in a study, should exclude the provision of compensation for injury. Moreover, these conditions should not reduce any entitlements to such compensation.

8.6 The Ministry of Health's *Guidelines for the Completion of the National Application Form for Ethical Approval of a Research Project (NAF-2005 v1)* (Ministry of Health 2005) contain details of Form A (for clinical trials for which ACC provides for compensation for injury) and Form B (for clinical trials for which the manufacturer should ensure provision of compensation for injury) and the attendant declarations.

Questions for the draft *Guidelines*

- How useful would you find these *Guidelines* for assisting your work in intervention studies?
- Have the key issues been identified and well addressed?
- Are there any points made in the Discussion Document that should be better reflected in the finalised *Guidelines*?
- What other suggestions do you have for improving the draft *Guidelines*?

See also 'Questions for feedback' on page 90.

References

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

ABPI, BIA (Association of the British Pharmaceutical Industry, BioIndustry Association). 2006. *Early Stage Clinical Trial Taskforce: Joint ABPI/BIA Report*. Association of the British Pharmaceutical Industry and BioIndustry Association. Available from http://www.abpi.org.uk/information/pdfs/BIAABPI_taskforce2.pdf Accessed 1 November 2007.

Altman DG, Schultz KF, Moher D, et al for the CONSORT group. 2001. The revised CONSORT statement for reporting randomised controlled trials: explanation and elaboration. *Annals of Internal Medicine* 134: 663–94.

Bankert E, Amdur R. 2002. Informed consent feedback evaluation tool. In R Amdur, E Bankert (eds) *Institutional Review Board Structure and Function.* Massachusetts: Jones and Bartlett.

Belsky L, Richardson HS. 2004. Medical researchers' ancillary clinical care responsibilities. *British Medical Journal* 328: 1494–6.

Brownson RC, Petitti DB (eds). 1998. *Applied Epidemiology: Theory to Practice*. New York: Oxford University Press.

Chan A-W, Hŕobjartsson A, Haahr MT, et al. 2004. Empirical evidence for selective reporting of outcomes in randomized trials. *Journal of the American Medical Association* 291(20): 2457–65.

Chow S-C (ed). 2003. *Encyclopaedia of Biopharmaceutical Statistics*. 2nd edition. New York: Marcel Dekker Inc.

CIHR, NSERCC, SSHRCC (Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, Social Sciences and Humanities Research Council of Canada). 1998 (with 2000, 2002, 2005 amendments). *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans*. Available from http://www.pre.ethics.gc.ca. Accessed 23 April 2008.

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

Dawson J, Peart N (eds). 2003. *The Law of Research*. Dunedin: University of Otago Press.

De Angelis C, Drazen J, Frizelle F, et al. 2004. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. *The Lancet* 364: 911–12.

Edwards P, Arango M, Balica L, et al. 2005. Final results of MRC CRASH: A randomised placebo-controlled trial of intravenous corticosteroid in adults with head injury – outcomes at six months. *The Lancet* 365(9475): 1957–9.

Elliott C. 2008. Guinea-pigging. *The New Yorker*, 7 January.

Gamble VN. 1997. Under the shadow of Tuskegee: African Americans and health care. *American Journal of Public Health* 87(11): 1773–8.

Gammelgaard A. 2004. Informed consent in acute myocardial infarction research. *Journal of Medicine and Philosophy* 29(4): 417–34.

Glanz K, Rimer B, Lerman C. 1996. Ethical issues in the design and conduct of community-based intervention studies. In SS Coughlin, TL Beauchamp (eds) *Ethics and Epidemiology*. Oxford: Oxford University Press.

Health and Disability Commissioner. 2004. *A Review of the Health and Disability Commissioner Act 1994 and the Code of Health and Disability Consumers' Rights: Report to the Minister of Health 2004.* Wellington: Health and Disability Commissioner.

HRC (Health Research Council of New Zealand). 2005a. *Guidelines on Ethics in Health Research*. Available from http://www.hrc.govt.nz.

HRC (Health Research Council of New Zealand). 2005b. *Data Safety Monitoring Board Operating Guidelines*. Available from http://www.hrc.govt.nz/root/pages_regulatory/Data_Safety_Monitoring_Board.html. Accessed 23 April 2008.

ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use). 1996. *ICH Harmonised Tripartite Guideline: Guideline for Good Clinical Practice*. Available from http://www.ich.org.

ICMJE (International Committee of Medical Journal Editors). 2004. *Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication*. Philadelphia: International Committee of Medical Journal Editors. Available from http://www.icmje.org.

Joffe S, Cook E, Cleary P, et al. 2001. Quality of informed consent in cancer clinical trials: a cross-sectional survey. *The Lancet* 358: 1772–7.

Laine C, Horton R, DeAngelis CD, et al. 2007. Clinical trial registration: Looking back and moving ahead. *Journal of the American Medical Association*; doi: 10.1001/jama.298.1.jed70037.

Lantos JD. 1999. The 'inclusion benefit' in clinical trials. *Journal of Pediatrics* 134(2): 130–1.

Last JM (ed). 2001. *A Dictionary of Epidemiology*. 4th edition. New York: Oxford University Press.

Manson NC, O'Neill O. 2007. *Rethinking Informed Consent in Bioethics*. Cambridge: Cambridge University Press.

Medsafe (New Zealand Medicines and Medical Devices Safety Authority). 1998. *New Zealand Regulatory Guidelines for Medicines: Volume 3: Interim Good Clinical Research Practice Guideline*. Available from http://www.medsafe.govt.nz/Regulatory/Guideline/medicines.asp. Accessed 17 September 2007.

Minister of Health. 2004. *Terms of Reference for Health and Disability Ethics Committees.* Wellington: Ministry of Health. Available from http://www.ethicscommittees.health.govt.nz.

Minister of Health, Associate Minister of Health. 2002. *He Korowai Oranga: Māori Health Strategy*. Wellington: Ministry of Health. Available from http://www.moh.govt.nz.

Ministry of Health. 2005. *Guidelines for the Completion of the National Application Form for Ethical Approval of a Research Project (NAF-2005 v1)*. Available from http://www.ethicscommittees.health.govt.nz.

Ministry of Health. 2006a. *Guidelines for Using Cells from Established Human Embryonic Stem Cell Lines for Research.* Wellington: Ministry of Health.

Ministry of Health. 2006b. *Operational Standard for Ethics Committees: Updated edition*. Wellington: Ministry of Health.

Ministry of Health. 2007. *Guidelines for the Use of Human Tissue for Future Unspecified Research Purposes.* Wellington: Ministry of Health. Available from http://www.moh.govt.nz.

Ministry of Health, ACC (Accident Compensation Corporation). 1993. *Compensation for Injuries Caused as a Result of Participation in a Clinical Trial and the Role of Ethics Committees: Guidelines*. Wellington: Ministry of Health.

NEAC (National Ethics Advisory Committee). 2006. *Ethical Guidelines for Observational Studies: Observational Research, Audits and Related Activities.* Wellington: Ministry of Health. Available from http://www.neac.health.govt.nz.

NEAC (National Ethics Advisory Committee). 2007. *Fifth Annual Report to the Minister of Health: National Ethics Advisory Committee – Kāhui Matatika o te Motu 2006*. Wellington: Ministry of Health. Available from http://www.neac.health.govt.nz.

O'Neill O. 2002. *Autonomy and Trust in Bioethics*. Cambridge: Cambridge University Press.

RMI (Researched Medicines Industry Association of New Zealand). 1997. *Guidelines on Clinical Trials: Compensation for Injury Resulting from Participation in an Industry-sponsored Clinical Trial*. Wellington: Researched Medicines Industry Association of New Zealand. Available from http://www.rmianz.co.nz.

Roberts I, Yates D, Sandercock P, et al. 2004. Effect of intravenous corticosteroids on death within 14 days in 10 008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *The Lancet* 364(9442): 1321–8.

Sauerland S, Maegele M. 2004. A CRASH landing in severe head injury. *The Lancet* 364(9442): 1291–2.

Skegg PDG, Paterson R. 2006. *Medical Law in New Zealand*. Wellington: Thomas Brookers.

TDR (World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases). 2005. *Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards*. Geneva: World Health Organization.

WHO (World Health Organization). 1995. *Guideline for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products*. WHO Technical Report Series, No. 850, Annex 3. Available from http://homepage.vghtpe.gov.tw/~mre/goodexp/Fercap-Survey/WHO-GCP-1995.pdf Accessed 19 March 2008.

Wilets I, Schears RM, Gligorov N. 2005. Communicating with subjects: Special challenges for resuscitation research. *Academic Emergency Medicine* 12(11): 1060–3.

WMA (World Medical Association). 2004 (first adopted in 1964 and revised in 1975, 1983, 1989, 1996 and 2000 with notes of clarification added by the WMA General Assembly on Paragraph 29 in 2002 and Paragraph 30 in 2004). *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Available from http://www.wma.net/e/policy/b3.htm. Accessed 7 March 2006.

Appendix: The National Ethics Advisory Committee

About 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 within the context of the New Zealand Public Health and Disability Act 2000 and the key strategy statements for the health sector.

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 for this project

Andrew Moore – chair
Allison Kirkman – deputy chair
Michael Ardagh
Barbara Beckford
Dale Bramley
Michael Findlay
Elisabeth Harding
John Hinchcliff
Te Kani Kingi
Joanna Manning
Charlotte Paul
Martin Sullivan

Secretariat for this project

Annabel Begg – Public Health Medicine Registrar (2004–2005)
Barbara Burt – Senior Analyst
Fiona Imlach – Public Health Medicine Registrar (2006–2007)
Gabrielle McDonald – Public Health Medicine Registrar (2007 – present)
Vanessa Roberts – Analyst

Questions for feedback

Ethics of Intervention Studies

The National Ethics Advisory Committee – Kāhui Matatika o te Motu (NEAC) seeks your feedback on its publication *Ethics of Intervention Studies*.

NEAC is interested in your comments on any aspect of the Discussion Document (Part A) and draft *Guidelines* (Part B). In providing feedback, you may find the following questions helpful.

See also 'How to respond' on page v and the tear-out page on page 91.

Question for the Discussion Document

- Have the key issues been identified and well addressed?

Questions for the draft *Guidelines*

- How useful would you find these *Guidelines* for assisting your work in intervention studies?
- Have the key issues been identified and well addressed?
- Are there any points made in the Discussion Document that should be better reflected in the finalised *Guidelines*?
- What other suggestions do you have for improving the draft *Guidelines*?

Ethics of Intervention Studies: Discussion Document and draft *Guidelines*

How to respond

There are two ways you can respond to this publication. You may like to send us this page with your response.

1. Complete the questions as an electronic Word document and either email it, or print it out and send it by post, to NEAC at the relevant address below.
2. Write your comments as an email or as a letter that you can send to NEAC at the relevant address below.

Please respond by 23 July 2008.

Contact details

Postal address: NEAC – Intervention Studies
PO Box 5013
WELLINGTON

Email: neac@moh.govt.nz
(Please put 'Intervention Studies' in the subject line.)

This response was completed by:

Name: .....

Address: .....

.....

.....

Email: .....

Organisation (if applicable): .....

Position (if applicable): .....

Date: .....

Official Information Act 1982

Details of your response may be requested under the Official Information Act 1982. If this happens, your response will be released to the person who requested it. However, if you are an individual rather than an organisation, you can choose to have your personal details removed from your response by ticking the box below.

☐ I do not give permission for my personal details to be released to persons under the Official Information Act 1982.

Thank you for your feedback.

neac
National Ethics Advisory Committee
Kāhui Matatika o te Motu