Ethical Guidelines for Intervention Studies

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Foreword

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

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

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

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

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

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

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

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

Note

If you wish to comment on your experience with using the *Guidelines*, please contact the National Ethics Advisory Committee:

email: neac@moh.govt.nz (with 'Intervention Studies' in the subject line)

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

Contents

1. Introduction

1.1 These *Ethical Guidelines for Intervention Studies* (the *Guidelines)* are issued in accordance with the statutory function of the National Advisory Committee on Health and Disability Support Services Ethics (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 2008: 39–40).

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

1.4 An intervention study may be a 'clinical trial' for the purposes of the 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 2008)*, the International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS 2002) *and the ICH Harmonised Tripartite Guideline: Guideline for good clinical practice* (ICH 1996).

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

1.9 Detailed matters concerning ethics committee review of intervention studies are addressed in the terms of reference for the individual health and disability ethics committees (Minister of Health 2008) 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 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
- Care of Children Act 2004
- New Zealand Bill of Rights Act 1990
- Protection of Personal and Property Rights Act 1988

- Health and Disability Commissioner Act 1994
- Code of Health and Disability Services Consumers' Rights 1996 (the Code of Rights)
- Privacy Act 1993
- Health Information Privacy Code 1994.

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

2. Definitions and scope of the *Guidelines*

2.1 The *Guidelines* are intended primarily to guide investigators conducting intervention studies, and to assist them to conduct high-quality studies.

2.2 Scientific matters that raise specific ethical issues are discussed in the *Guidelines*, but they do not contain a complete description of all the scientific issues relating to intervention studies.

2.3 The *Guidelines* are designed for intervention studies in health or disability settings, but they may also be relevant to similar studies (eg, some studies of interventions in educational, sociological or psychological settings).

Definition of 'intervention study'

Intervention study

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

Intervention

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

- preventive, diagnostic or therapeutic
- a new intervention (including medication, psychological treatment, health education, radiation therapy, a vaccine, a surgical device, or a surgical or other technique)
- an intervention established in practice but not adequately substantiated by scientific evidence
- an established intervention being used for a new purpose
- the withholding or altered administration of an established intervention
- a change in the method of delivering care designed to add to knowledge of the health effects of the change (eg, the use of directly observed therapy for the treatment of tuberculosis as opposed to patient-administered medication, a new model of care, use of guidelines or protocols, use of different information formats, or care undertaken by a different group of professionals)
- a study that has no therapeutic value to the subject, conducted with healthy volunteers, giving them an intervention previously untested in humans to evaluate its safety.

2.6 The common types of intervention studies are explained in the Glossary. There are also emerging trial designs, not listed there, for which specific ethical issues may arise.

Features of intervention studies

Participants

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

Study groups

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

Allocation

2.9 Assignment of participants to study groups may be:

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

Allocation concealment

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

Blinding

2.11 Blinding is valuable in studies where there is subjectivity in assessing an outcome (eg, reduction in pain). Blinding prevents people involved in the study from knowing which intervention a participant has been allocated to. It is used in some intervention studies to minimise bias and maximise the reliability of study findings. In a single-blind study one group is blinded. Usually this group is the participants 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 or those writing the study report.

Scope of the *Guidelines*

2.12 The *Guidelines* apply to intervention studies in New Zealand health and disability settings. Intervention studies differ from observational studies because, in the latter, the study investigator has no control over the study conditions and merely collects data. For guidance on observational studies, see the *Ethical Guidelines for Observational Studies* (NEAC 2006).

2.13 The *Guidelines* do not normally concern interventions in observational studies (eg, biopsies), where such interventions are carried out to obtain information rather than to study the effect of the intervention.

2.14 Intervention studies may involve the collection and use of human tissue. Specific guidance on the collection and use of human materials can be found in *Guidelines on Ethics in Health Research* (HRC 2005b).

2.15 All clinical research involving the manipulation of human genetic material must be approved by the Health Research Council's Gene Technology Advisory Committee before approval by a health and disability ethics committee. See also:

- 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)
- Human Tissue Act 2008.

2.16 Some studies to evaluate health products are not intervention studies because their primary purpose is to study intervention presentation or marketing development rather than health or disability outcomes.

2.17 There is an overlap between intervention studies and innovative practice. Innovative practice is practice that is a planned deviation from currently accepted practice (Ministry of Health 2006b).

2.18 The scope of these *Guidelines* includes innovative practice in the context of an intervention study.

2.19 When intending to use an innovative practice, health practitioners have an obligation to objectively evaluate its efficacy and safety (Ministry of Health 2006b). This is best done with an intervention study.

3. Ethics of intervention studies

3.1 This section concerns the worth of intervention studies, and the 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 way of evaluating the worth of a treatment or a preventive intervention such as health promotion, screening or immunisation. They are valuable for this purpose. Without 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 addressed.

3.3 The potential benefits of intervention studies include:

- providing objective results that establish the safety, efficacy, effectiveness or cost-effectiveness of new and established interventions
- developing the 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 are entitled to health and disability support services that are safe and effective. Organisations that provide health care and disability support should foster high-quality intervention studies, because these contribute both directly and indirectly to service safety and quality.

Benefits to participants

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

Risk in intervention studies

3.7 In general, close ethical scrutiny is appropriate for intervention studies because the potential harms are generally greater than with other types of study due to the intervention itself. In addition, intervention studies may involve conducting research in the context of clinical care, and this creates the potential for conflict between the roles of investigator and clinician.

3.8 The level of risk that is acceptable is primarily a matter for the potential participants to decide. For this reason, informed consent is a central concept (see also ‘Free and informed consent’, paragraphs 6.6–6.23).

3.9 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. At a community level, potential harms may involve an inequitable burden without commensurate benefit to the community. Sometimes the benefits and harms may accrue to different individuals in an intervention study (eg, in randomised controlled trials of screening).

3.10 The risks must be proportional to the potential benefits.

Ethical review of intervention studies

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

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

3.13 All intervention studies require review by an ethics committee. The ethics committee should assess whether the investigator has ensured the study will meet established ethical standards.

4. Underlying ethical considerations

4.1 The ethical considerations stated in this section are important to the design and conduct of intervention studies. The application and weighting of these considerations will vary depending on the nature and circumstances of the intervention study in question.

4.2 Investigators should consider the features of a proposed study in light of the ethical considerations, and should then satisfactorily resolve any ethical issues raised by the study. Not all ethical considerations weigh equally.

Respect for persons

4.3 Every person has the right to be treated with respect. (See also the Code of Rights, Right 1[1].)

4.4 Respect for people, and for their rights, incorporates at least two fundamental principles.

(a) Respect for autonomy requires that those who are capable of deliberation about their personal goals should be treated with respect for their capacity for self-determination. This may apply on an individual or collective basis.

(b) Protection of people, particularly those with impaired or diminished autonomy, requires that those who are dependent or vulnerable be afforded security against harm. (See also the Code of Rights, Right 7[2] and [3]; and 'Vulnerable people', paragraphs 5.27–5.33.)

Justice

4.5 Justice requires that, within a population, there is a fair distribution of the benefits and burdens of participation in a study and, for any participant, a balance of burdens and benefits. Accordingly, investigators must:

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

(b) design studies so that the inclusion and exclusion conditions for participants are fair. (See also the criteria in 'Inclusion and exclusion of participants', paragraphs 5.25–5.26.)

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

4.7 The Treaty of Waitangi is the founding document of New Zealand. The principles of partnership and sharing that are implicit in the Treaty should be respected by all researchers and, where applicable, should be incorporated into all health research proposals (HRC 2005b).

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

4.9 Any potential cultural and ethical issues pertaining to Māori must be addressed through appropriate engagement with Māori, which may include discussions with appropriate representatives of specific whānau, hapū and iwi as determined by the scope and method of the study.

4.10 Comprehensive, high-quality Māori health research and information can inform both the Government and iwi on the matter of health priorities and can assist whānau, hapū and iwi to be involved in meeting these priorities.

Beneficence and non-maleficence

4.11 The principle of beneficence refers to a moral obligation to act in a way that will benefit others. Non-maleficence refers to an obligation not to inflict harm on others (Beauchamp and Childress 2001).

4.12 In an intervention study the risks of the study should be reasonable in light of the expected benefits. The greatest risk is the potential for harm to study participants. This is particularly significant given that benefits often accrue to society but only in some cases to study participants. The greater the risk of harm from the study, the greater should be the care in addressing the ethical issues raised.

4.13 A study is within the range of minimal risk if potential participants can reasonably be expected to regard the probability and magnitude of possible harms from participation in the study as no greater than those encountered in everyday life (eg, where the only foreseeable risk is discomfort).

4.14 A study warrants greater provision for the protection of participants if they are to be exposed to more than minimal risk.

Integrity

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

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

Diversity

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

Addressing conflict of interest

4.18 Conflict of interest occurs when professional judgement concerning a primary interest, such as a patient's welfare or the validity of a study, tends to be influenced by a secondary interest, such as financial gain, special loyalties or protection of career advancement opportunities.

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

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

- is remunerated for participant recruitment (eg, with per capita payments)
- has a commercial interest in the intervention or financial links to the study sponsor
- will benefit in professional or academic terms from involvement in the study.

4.21 The investigator should disclose to relevant other parties (including the ethics committee, funder, employer, sponsor and study participants) any perceived potential or actual conflict of interest she or he has in relation to any others involved with the study. As appropriate to the circumstances, any conflict of interest should be avoided. Where this is not practicable, conflicts should be minimised and managed, using strategies such as oversight and disclosure.

4.22 Conflict of interest may also arise when the investigator is the participant's usual health or disability service provider. This may sometimes cause a conflict between the investigator role and the clinician role. In some circumstances this dual role will be appropriate. However, this possible conflict should always be disclosed and discussed with any potential participants.

4.23 Other members of the study team, such as research nurses, may also be placed in positions of conflict of interest if their employment prospects, job continuation or remuneration depend directly on their recruiting participants into studies.

5. Study and protocol design

Study question

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

5.2 Investigators should have a clear study question that identifies the participant population, the intervention and the main outcome of interest. Normally the outcome(s) to be studied should be clinically significant.

5.3 Every study question should be based on a thorough review of the relevant literature.

Study design

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

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

5.6 The intended number of participants in an intervention study should be sufficient to generate reliable study findings, and the consequent recruitment targets should be realistic. Statistical issues relating to trial design, sample size and analysis can be complex, and expert advice is usually required.

5.7 The study protocol should contain an overview of the planned statistical analyses, and these planned analyses should be adhered to in conducting the study.

5.8 Assignment of participants to study groups is best done by randomisation. This process tends to make study groups reliably comparable and minimises biases, especially uncontrolled confounding. Quasi-randomised or non-random methods are generally less reliable in this regard because of their potential to allow other factors to influence the assignment of participants to study groups. Allocation concealment also improves study validity and design through preventing selection bias (see also 'Features of intervention studies', paragraphs 2.7–2.11).

5.9 Use of blinding is desirable in an intervention study design when it can be shown that it has methodological advantages and minimal risks (see also 'Blinding', paragraph 2.11).

5.10 Every effort should be made to ensure complete follow-up of all study participants. Incomplete follow-up means there is data missing from the study. This will be for non-random reasons, and has the potential to compromise the reliability of the study findings (see also paragraph 6.20).

5.11 Peer review of the scientific validity of a study's protocols is beneficial and is advised for all but the least risky studies.

Comparison groups

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

Best intervention standard

5.13 An intervention study meets the best intervention standard if the intervention(s) in the study are tested against the best proven intervention(s) available outside the study. In many settings there might be more than one intervention that is equivalent to the best, according to the current evidence.

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

5.15 Withholding a proven intervention for a short time, whether or not it is replaced by a placebo, can sometimes be ethically justified to validate a measurement technique or to confirm the sensitivity of a therapeutic study design. An investigator who proposes any such approach should justify this to an ethics committee and explain how it can be undertaken without significant risk of harm to participants.

5.16 In some cases, one or more interventions provided in an intervention study are equivalent to the best proven intervention available locally outside a study but are known to be inferior to the best proven intervention available internationally. In such cases, the study can be justified only if the world-best intervention is unlikely to be available locally for the duration of the study and if the study can be justified in terms of its potential benefit to the community from which the participants are drawn. The same considerations apply to New Zealand-sponsored studies conducted in countries with less access to health interventions than New Zealand.

5.17 Investigators should ensure that participants understand that their participation in an intervention study is not designed to benefit them more than the benefit they would gain if they were instead receiving the best proven intervention available outside the study. (See also 'Equipoise standard', paragraphs 5.18–5.21.)

Equipoise standard

5.18 An intervention study meets the equipoise standard if the evidence is 'equally poised' as to the overall balance of risks and benefits of each of the interventions offered in the study, so that it cannot be determined in advance which of the groups in a proposed study will be better off.

5.19 Any intervention study to compare two or more interventions should be designed to meet the equipoise standard. For example, study participants may not be assigned to different interventions when the available evidence demonstrates that one intervention has a better expected overall balance of benefits over risks than the other(s).

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

5.21 In addition to equipoise of evidence, the preferences of individual participants are important here. For example, a potential participant might have a strong preference for the less radical of two alternative interventions that are in equipoise. If a potential participant has a strong preference for one of the options over the other(s), they may wish to decline to participate once given full information about the study.

Use of a placebo

5.22 Use of a placebo or no intervention as a control may be ethically acceptable in an intervention study when:

- there is no proven effective intervention, or
- withholding a proven intervention would not expose the participant to any additional risk of serious or irreversible harm but, at most, would expose them only to temporary discomfort or delay in relief of symptoms, or
- there are compelling methodological reasons to believe that using an established effective intervention as comparator would not yield reliable findings on safety or efficacy, and use of a placebo would not add any risk of serious or irreversible harm to participants.

5.23 In some intervention studies all participants receive the best proven current intervention, and are given either a placebo or the study intervention as well. This approach does not raise any particular ethical issues, because the best proven current intervention is still given to all participants. A similar situation may also arise with other study designs.

5.24 When a placebo control is used, the investigator should ensure that each participant is fully informed about:

- any intervention that will be withdrawn or withheld for the purposes of the study
- the consequences that can reasonably be expected from not having this intervention
- the scientific justification for proceeding with a placebo-controlled study.

Such a study should also meet other ethical requirements, such as the best intervention standard (see 'Best intervention standard', paragraphs 5.13–5.17).

Inclusion and exclusion of participants

5.25 Inclusion of participants in intervention studies must be equitable. Investigators may not exclude participants on the basis of sex, ethnicity, national origin, religion, education or socioeconomic status, except where such exclusion or inclusion is essential to the purposes of the study.

5.26 Inclusion and exclusion of participants affect the extent to which study findings can be generalised. To contribute to an equitable distribution of study benefits and burdens, investigators should, when practicable, consider including all those who may benefit from the study findings.

Vulnerable people

5.27 Vulnerable people include those who have restricted capability to make independent decisions about their participation in the study. Restricted capability does not apply to all individuals in these groups and may only apply intermittently. Examples of potentially vulnerable people include:

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

5.28 Vulnerable people should have the opportunity to be included in high-quality studies on questions that might affect their health.

- The study should ask questions that matter to the participant's community, and the answers should benefit the community.
- Studies should not be performed with vulnerable groups if they can be adequately performed with other groups.
- Where a study with a vulnerable group is conducted, it should involve the least vulnerable people in that group (eg, older rather than younger children).

- Intervention studies should be conducted only if the risk to vulnerable people is at an acceptable minimum. (See also the guidance contained in the *Operational Standard* [Ministry of Health 2006b] and referred to in paragraph 5.33 below.)
- Study participation should be a matter of free and informed decision-making by study participants wherever possible. (See also the Code of Rights, Rights 7[2] and [3]; and the guidance referred to in paragraph 5.33 below.)

5.29 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 any of the interventions being studied are invasive.

5.30 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 the 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.

5.31 Even when a vulnerable person is competent to decide her or his own study participation, it is often appropriate to notify and seek advice from a person or persons with knowledge of, or responsibilities for, that vulnerable person. (See also 'Non-consensual studies', paragraphs 6.24–6.29.)

5.32 If the competence of a vulnerable person to decide her or his own study participation is unclear, it may be appropriate for the investigator to seek both the informed consent of that person and the informed agreement of another person who is interested in, or has responsibilities for, that person's welfare. (See also paragraph 6.29.)

5.33 Further guidance on research with particular vulnerable populations is contained in appendices to the *Operational Standard for Ethics Committees*, including guidelines for research on children, research involving people with intellectual disabilities, research involving unconscious people, research involving consumers with a terminal illness, and research involving older persons (Ministry of Health 2006b).

Skills and resources

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

5.35 Necessary skills include competence in:

- the field of study, demonstrated by knowledge and experience
- administering study interventions
- monitoring the health of participants throughout and after the study
- identifying and applying relevant study methods, with the ability to take full responsibility for proper study design, conduct and analysis
- ethical conduct of research, with the ability to take full responsibility for ethical considerations.

5.36 An investigator should proceed with a study only when the locality (eg, staff, facilities and equipment) is known to be adequate. This includes the capability to provide emergency medical care of an acceptable standard, if required. An acceptable standard is to be determined having regard to the anticipated risk of the study to participants and is the standard reasonably to be expected of the facility in which the study is undertaken, or at least the standard expected of a competent general practitioner working in her or his surgery (see also 'Study locality', paragraph 5.44).

5.37 All those responsible for study conduct must be provided with enough information to ensure the safety of participants.

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

Study protocol

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

Registering studies

5.40 The purposes of study registration are to avoid duplication of studies and to foster the publication of key study outcomes. All clinical trials (this includes Phase I to Phase IV trials) should be registered with a World Health Organization-approved register. Such registers include, but are not limited to, the Australian and New Zealand Clinical Trials Registry (ANZCTR) and the International Standard Randomised Controlled Trial Number (ISRCTN) Register.

5.41 The registered trial details should include the data items identified by the WHO Trial Registration Data Set, including:

- public and scientific titles
- sponsor(s)
- the study intervention(s)
- the primary and secondary outcomes
- target sample size.

5.42 New Zealand-based clinical trials can be registered without charge on the Australian and 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 made indicating that the trial is currently being registered and giving the name of the registry.

5.43 International trials that have a New Zealand arm should likewise be registered with an appropriate register.

Study locality

5.44 The appropriateness of the study locality should be considered in terms of the following factors.

- The facility must be of an adequate standard to ensure safe and appropriate conduct of the study. Meeting this standard requires appropriate expertise of staff to conduct the study and manage any adverse events that may result.
- The facility must be of an adequate standard to implement the study without any adverse effect on access to treatment at that facility.
- For information on locality assessment, see the New Zealand Health and Disability Ethics Committees website (http://www.ethicscommittees.health.govt.nz). Early engagement in the locality assessment process is desirable.

Studies with distinctive features

Non-therapeutic studies

5.45 Therapeutic intervention studies examine interventions or procedures that hold the prospect of direct diagnostic, therapeutic or preventive benefit for the individual participant. Non-therapeutic studies examine interventions that do not hold the prospect of direct diagnostic, therapeutic or preventive benefit to individual participants. Types of non-therapeutic studies include some phase I studies (see also 'Phase I studies', paragraphs 5.47–5.48), bioequivalence studies and bioavailability studies (see Glossary).

5.46 A non-therapeutic intervention study is justified only when the importance of the objective outweighs the inherent risks and burdens to the participant, and participants are well informed of the possible risks (see also 'Non-consensual studies', paragraph 6.28).

Phase I studies

5.47 Phase I studies test interventions in human populations, often for the first time (see Glossary). These interventions may already have established risk profiles from other studies in humans (eg, a new combination of two established agents where the potential interaction between them is in question rather than the tolerability of either used on its own). Some phase I studies are 'first-in-human' studies, where subjects are administered an intervention that has not previously been given to humans. In these circumstances the investigators are relying on pre-clinical data and, where available, previous human experience with similar interventions. Some first-in-human studies therefore may be of significantly higher risk to subjects.

5.48 Following a first-in-human phase I study in the United Kingdom where six volunteers required intensive care support due to severe adverse reactions, an independent report on these events was commissioned (Expert Scientific Group on Phase I Clinical Trials 2006). The report focused on the study of higher risk compounds such as those that may have a novel mechanism of action, a highly species-specific action, or that were directed towards immune system targets. Although risk assessment of individual phase I studies in New Zealand is the role of regulatory bodies such as the Standing Committee on Therapeutic Trials (SCOTT), phase I study investigators should be familiar with the 22 recommendations made in this report (pp. 6–11) in order to evaluate their capability to conduct the study in an ethically acceptable manner. These recommendations cover:

- pre-clinical and early clinical development
- the process of preparation and review of clinical trial applications, and early access to advice for both regulators and sponsors
- determining and administering the initial doses in humans
- the clinical environment for first-in-human studies
- developing the skills and training to meet future needs.

Community intervention studies

5.49 In a community intervention study, interventions are allocated primarily to whole communities or groups (see Glossary). Before undertaking a community intervention study the investigator must make every effort to ensure that:

- the study is responsive to the health needs and priorities of the population
- any intervention or product developed will be made reasonably available for the benefit of that population or community.

5.50 Individual consent to participate in a community intervention study should not be required if gaining that consent is impracticable, and if the benefits from the study are sufficient and the potential harms are minimal. An example of such a study might be one examining the effects of a media campaign to reduce adolescent tobacco use.

5.51 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.

5.52 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 (eg, through submissions or public meetings).

Collective consultation

5.53 When an intervention study focuses on an intervention for a whole community, rather than for individuals, it is normally appropriate for the community as a whole, rather than individuals, to be consulted about participation in the study.

5.54 Some intervention studies are conducted within identifiable communities but with the intervention(s) targeted at individuals. For example, a primary care study may allocate schools or hapū to study groups, while individual members of those groups receive the intervention(s). In such cases, investigators should consult with the community about conducting the study, and obtain informed consent from individuals to receive the intervention.

5.55 In consulting a community or group about participation in a study, the investigator should approach its representative(s) in accordance with the group's practices and shared values. Agreement given by a community representative should be consistent with general ethical principles. In general, investigators should consider collective entitlements and protection as they would individual entitlements and protection.

5.56 In studies with Māori 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 protocol that group agreement for individuals to be approached to participate was obtained from the representatives/participants at a hui.

5.57 In studies with Māori where no investigator is a member of the whānau, hapū or iwi to be studied, a system of investigator accountability to the whānau, hapū or iwi concerned should be instituted after full discussion and agreement between the participants and investigators.

6. Study processes

Recruitment of participants

6.1 Adequate recruitment is important to ensure that the number of participants is sufficient to reliably answer the study question(s).

6.2 The investigator should choose a method of approaching participants that meets applicable ethical and scientific standards. Depending on the study question and design, the approach may be made directly to the potential participant (eg, by advertisement, telephone or letter), or indirectly (eg, by the participant's own doctor or relevant health practitioner).

6.3 In some circumstances the investigator may also be a potential participant's own doctor or other relevant health practitioner. In this circumstance it is important for the investigator to recognise the potential for conflict of interest this creates and to remove any element of coercion into, or inappropriate discouragement from, participation in the study (see also 'Addressing conflict of interest', paragraphs 4.18–4.23). On the other hand, the regular practitioner may be the best person to approach their patient (eg, because of patient preference, ability to reduce poorly judged approaches, or the need to maintain continuity of care) rather than transferring this task and the patient's management to a second practitioner.

6.4 If a patient (or her or his family or friends) approaches her or his health practitioner or an investigator about study participation, this needs to be managed using the same principles outlined in paragraph 6.3 above.

6.5 Where intervention studies are designed as non-therapeutic, group-based or community-based studies (with the exception of phase I studies), the prospective involvement of the participant's regular doctor is not mandatory, although subsequent communication about participation is desirable if the participant agrees to this. (See also 'Clinical responsibilities', paragraph 6.66.)

Free and informed consent

General principles

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

6.7 Informed consent has two basic components.

(a) The decision is informed by adequate understanding of any information that is relevant to that decision.

(b) The decision is voluntary, and is therefore free from undue influence such as manipulation or coercion.

6.8 People are entitled to make free and informed decisions about their participation in a study. The purposes of this are to ensure that such decisions express the will of potential and actual participants and to protect them from coercion, manipulation and other undue influence.

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

6.10 Verbal information provided should be tailored to the individual, taking into account the participants' level of knowledge, understanding and the amount of detail they desire. Written information provided should be tailored to the study population, and should have a reading age appropriate to that population.

6.11 Consent provisions should include establishing access to an ongoing dialogue about the study and giving opportunity throughout the duration of the study for any

questions to be asked and answered. Providing such ongoing access to information is often a better way to communicate than providing a lot of extra written material.

6.12 Investigators should effectively communicate to participants the purpose and practical implications of all key study features, including any randomisation, placebo control or blinding (see also 'Features of intervention studies', paragraphs 2.7–2.11).

6.13 Investigators are responsible for designing and conducting studies to maximise the validity and quality of participants' informed consent. Ethics committees are responsible for checking that proposed study information sheets and consent forms enhance informed consent of this nature.

6.14 Providing information that is too detailed or complex can frustrate rather than assist free and informed consent. If a consent form or information sheet for a study is very long and complex, participants may be overwhelmed by the information and may not be able to process the critical information. Further detail about informed consent for specific groups is located in the appendices of the *Operational Standard* (Ministry of Health 2006b).

6.15 It is preferable that participants provide in writing their consent to participate in an intervention study. There may be some situations where this is not possible; for example, due to a participant's illiteracy or physical inability. The principles of justice and non-exclusion imply that prospective participants should not be excluded from research purely on the basis of illiteracy or physical inability. However, any exceptions to obtaining written informed consent should be justified to an ethics committee. In all cases where consent is not provided in writing, the procedures used to seek free and informed verbal consent, and the fact that consent was given, should be documented. (See also the Code of Rights, Right 7[6].)

6.16 The purposes of consent are normally best served by decision-making that occurs prior to a participant's inclusion in a study. Any exception requires justification to an ethics committee on grounds that prior consent is one or both of the following:

- impracticable (eg, for studies in emergency care, community intervention studies)
- undesirable (eg, when any delay of the intervention[s] to be studied would harm the person). (See also 'Non-consensual studies', paragraphs 6.24–6.29.)

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

6.18 During the initial consent discussion about the study, due regard should be paid to the circumstances of the potential participant. If a potential participant is in pain or under stress, a short discussion may suffice. This brief dialogue should be followed up with more detailed information about the study once the participant is more comfortable.

6.19 People are entitled to refuse to participate in intervention studies and to withdraw their consent to participate. They may make either of these decisions whenever practicable and without experiencing any disadvantage. (See also the Code of Rights, Right 7[7].)

6.20 Those who ask to withdraw from a study may wish only to withdraw from any interventions they are yet to receive rather than from all aspects of the study. Normally, those who withdraw should be asked whether they are willing for their data to remain in the study, and if they are willing to have further data recorded, particularly data on study end-points (see the Glossary). Any new data or data that have already been collected could provide beneficial information for the study. (See also paragraph 5.10.)

6.21 If a study is amended significantly, or if new information becomes available after informed consent has been obtained, participants must be notified. It may also be appropriate to seek their consent to continue to participate. The ethics committee should review any proposal to make significant amendments to the study protocol.

Features of informed consent

6.22 Informed consent is essentially a matter of good communication between people. Information should be provided to potential participants in a form and in a way that assists their informed decision-making. For example, the information should as far as possible be provided in lay terms. In general, such information should:

- explain the study, including:
  - the purpose of the study, including its expected contribution to knowledge and its benefits to communities
  - 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 and sources of funding of the study, the institutional affiliations of the investigator(s), and who can be contacted to answer questions and how to contact them
  - the study's status, with a current approval from an ethics committee
- describe what the study involves, including:
  - what will be done in the study, including how participation in it will differ from not being in the study
  - the time involved in participation (eg, the number and duration of any visits to the research centre, and the expected finishing date of the study)
  - the purpose and expected number of any extra tests to be performed during the study
- outline potential benefits, risks and compensation, covering:
  - foreseeable risks, side-effects, discomforts and possible direct benefits of study participation, including any risks or benefits to the health of a participant's family 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 to participants during the study
- explain the rights of participants, covering:
  - the voluntary nature of participation, including that they are free to decline to participate, or to withdraw from the research at any practicable time, without experiencing any disadvantage
  - 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 study that becomes available during the study that may have an impact on their health
  - what provision will be made for the privacy and confidentiality of individuals
- describe what will happen after the study, covering:
  - whether any study intervention will be available to participants after the study and, if so, under what conditions (including any cost to them)
  - how study data will be stored and for how long, whether the data will be retained for possible future use, who will be responsible for their secure storage and how they will be destroyed
  - whether any biological specimens collected during the research will be destroyed at its conclusion and, if not, details of their storage and possible future use
  - how the study findings will be communicated on completion of the study, including to participants, and in what expected timeframe.

6.23 Paragraph 6.22 is subject to the principles stated in 'Free and informed consent – General principles', paragraphs 6.6–6.21). For a pro forma of a consent form, see the *Guidelines for the Completion of the National Application Form for Ethical Approval of a Research Project* (Ministry of Health 2005). For an example of an information sheet, see the WHO consent form templates (http://www.who.int/rpc/ research_ethics/informed_consent/en/).

Non-consensual studies

6.24 Some people who have diminished competence or no competence at the time a study is conducted (eg, potential participants in a study of the care provided in an intensive care unit after major elective procedures) may be competent to make decisions about study participation at an earlier time. In such cases investigators should make all reasonable efforts to obtain prior consent to participate by the person, and to identify any prior consent or refusal to participate by the person, and should give effect to any such prior decision. (See also the Code of Rights, Right 7[5] and clause 4; and the Health and Disability Commissioner Act 1994, section 2, definition of 'health care procedure'.)

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

6.26 In non-consensual studies it is the investigator's responsibility to ensure that all applicable legal standards are met. New Zealand law substantially limits the powers of health practitioners to offer treatment without consent in the context of research. It also substantially limits the powers of others to consent to such treatment on behalf of any person who is not competent. (See, in particular, the New Zealand Bill of Rights Act 1990, the Protection of Personal and Property Rights Act 1988, and the Code of Health and Disability Services Consumers' Rights 1996, particularly Right 7[4].)

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

6.28 Intervention studies with no therapeutic intent should be undertaken only with the prior informed consent of the competent individual, unless a legal proxy can consent for an incompetent individual. (See also 'Studies with distinctive features – Non-therapeutic studies', paragraphs 5.45–5.46.)

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

- meet appropriate ethical standards, which include the best intervention standard (see 'Best intervention standard', paragraphs 5.13–5.17) and the equipoise standard (see 'Equipoise standard', paragraphs 5.18–5.21)
- be consistent with the views of other suitable people who are interested in the person's welfare and available to advise on this
- be in accordance with a study protocol approved by an ethics committee.

Study conduct

Deception and concealment

6.30 To maintain study validity, it may sometimes be appropriate to withhold information from participants until after study completion, or to conceal certain aspects of study design. Some examples of these circumstances are where:

- participants are not told the purpose of tests performed to monitor their adherence to the study protocol

- prospective participants are asked to consent to remain uninformed of the purpose of some procedures until the study is completed
- participants are not told that some information has been withheld until the study has been completed, because their knowledge of this aspect of the study would jeopardise its validity.

6.31 When the investigator believes deception or concealment is scientifically justified, the following criteria apply.

- There are no suitable alternative methods.
- Participants are not exposed to increased risk of harm.
- The extent of deception or concealment is defined in the study protocol.
- Adequate and prompt disclosure is made, and debriefing is provided, as soon as is appropriate and practicable.
- Participants are entitled to require the withdrawal of study data that were obtained from them without their knowledge or consent.
- The deception or concealment will not compromise the relationship between the community and the investigators or research.
- The investigator justifies the deception or concealment to an ethics committee.

Inducements for participants

6.32 Inducement for study participants can normally be ethically acceptable only if the study would be ethically acceptable in the absence of the inducement. Investigators may seek to create legitimate motivation for participation in studies but may not exert undue influence by offering inappropriate inducements.

6.33 Inducement can take many forms. For example, it can occur directly or indirectly through financial or other recognition, or offers of treatment that would otherwise not be available. Inducement can be in the form of the influence and status of the health professional or investigator. As a result there is potential for inducement to exploit the vulnerability of individuals and to be inappropriate.

6.34 Appropriate inducement may include:

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

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

6.35 Payments or free health services should not be of such value that they induce prospective participants to consent against their better judgement. Risks involved in participation should be acceptable to participants even in the absence of any inducement.

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

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

Study monitoring and adverse event reporting

6.38 Every intervention study should have appropriate oversight of the conduct of the study to ensure the safety of the participants and the integrity and validity of the study data (National Institutes of Health 1998).

6.39 Every intervention study should include documentation of the planned monitoring arrangements (a 'monitoring plan') for the study.

6.40 The overall goals of study monitoring are to ensure that:

- the rights and wellbeing of human subjects are protected
- the reported study data are accurate, complete and verifiable from source documents
- the conduct of the study adheres to the study protocol, and is consistent with appropriate good clinical practice guidelines.

6.41 The nature and extent of monitoring should depend on the level of study risk, and should be based on considerations such as the study objectives, design (including patient population, intervention and study outcome measures), complexity, size and duration, and the experience of the investigators.

Monitoring arrangements

6.42 The mechanisms for meeting the monitoring goals outlined in paragraph 6.40 range from committees with responsibility for oversight, to day-to-day monitoring of data on site. The study's monitoring plan should state all appropriate monitoring arrangements. These will depend on the nature of the study.

6.43 Study monitoring arrangements may include one or more of the following.

Trial oversight committees

These may include one or more of:

- a trial steering committee (TSC), whose role is to provide overall supervision of the trial and to ensure that it is being conducted in accordance with the principles of good clinical practice, and which may have members who are independent of the study investigators
- a trial management group (TMG) – every trial should have a TMG (although in small, simple studies it may comprise just the principal investigator), which is responsible for the day-to-day management of the trial, and often also includes the statistician, the trial co-ordinator, the data manager and research nurse(s)
- a data monitoring committee (DMC), whose purpose is to protect the safety of the study participants, the credibility of the study and the validity of the study results (Ellenberg et al 2003: 1), and which is generally an independent body, although in some circumstances it may be internal to the study, including representation from the TSC and/or study sponsor (factors determining the need for an independent DMC are outlined in 6.52–6.55 below).

Co-ordinating centre/database monitoring

- The trial co-ordinating centre monitors data as it goes onto the database during the course of the trial. This monitoring includes: checking the data against the protocol and for internal logic; and checking eligibility, recruitment rates, withdrawals, missing data, and loss to follow-up. This monitoring should be done for all trials to ensure integrity of study data.

On-site monitoring

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

Data monitoring committee

6.44 A data monitoring committee (DMC) is an advisory body responsible for monitoring emerging safety and efficacy data, reviewing trial conduct and making recommendations to the trial steering committee and study sponsor(s). Normally, the DMC should have sole access to the data emerging in the study. The DMC makes recommendations on early termination of the study if there is convincing evidence of benefit, unfavourable results ruling out benefit, safety concerns, or a low probability of the trial achieving its objectives. (For an example of DMC operating guidelines, see http://www.hrc.govt.nz/root/pages_ regulatory/Data_Monitoring_Core_Committee.html)

6.45 The primary responsibilities of a DMC are to:

- safeguard the interests of the study participants
- preserve the integrity and credibility of the study so that future patients may be treated optimally
- ensure definitive and reliable results are available in a timely way to the health care community.

6.46 Where the risks of a study are low, it may be appropriate for there not to be a DMC.

6.47 Where a DMC is appropriate, the following criteria apply.

- The DMC's monitoring plan should specify the DMC membership, with a brief indication of the expertise of the members, both in the study area and on DMCs.
- The DMC should have operating guidelines, including statements as to the data to be reviewed, the timing and form of meetings, and reporting policy (HRC 2005a).
- Plans for any interim analysis of both efficacy and safety data and criteria for early termination should be specified in the study protocol, and agreed between the study sponsor, the trial steering committee and the DMC. These plans should be appropriate to the setting. They should indicate the statistical approach for preserving overall error rates when multiple analyses are carried out, and should give appropriate recognition to the unreliability of early results due to random fluctuations.

The independence of the data monitoring committee

6.48 All intervention studies need monitoring but not all studies need an independent DMC (Ellenberg et al 2003: 153–6).

6.49 An independent DMC is independent of those conducting the study the DMC is monitoring. It has a multidisciplinary membership, including physicians from relevant medical specialties and biostatisticians. In many cases its membership also includes others with relevant expertise, including ethicists, epidemiologists and basic scientists. At least some members, especially the chair and the biostatistician, should have prior DMC experience.

6.50 An independent DMC should have its membership limited to individuals free of any significant conflict of interest in relation to the study being monitored, whether this is financial, intellectual, professional or regulatory in nature.

6.51 For studies with an independent DMC, that DMC should ideally be the only party to whom the data analysis centre provides interim results on the relative efficacy and

safety of the study interventions. This protects the study from inappropriate early termination, which can be caused by premature judgement based on potentially misleading early results.

6.52 An independent DMC is most needed for an intervention study that aims to provide definitive data on treatments intended to save lives or prevent serious disease (Ellenberg et al 2003: 153–6).

6.53 An independent DMC should also be considered in early phase studies, whether or not randomised, of a high-risk intervention; for example:

- where there is risk of non-preventable, potentially life-threatening complications
- where the intervention is novel and there is very limited information on clinical safety, or where prior information raises concern regarding potential serious adverse events
- where professional or financial goals may be perceived to unduly influence the sponsor and/or investigators
- studies in which interim analyses of efficacy (allowing planning for the possibility of early study termination) and safety are considered essential to ensure patients' safety
- studies in vulnerable populations, such as children or people with mental illness
- studies with the potential for a large public health impact
- studies carried out in emergency settings (Ellenberg et al 2003: 153–6).

6.54 In settings other than those stated in 6.52–6.53, some aspects of the oversight provided by a DMC may still be valuable and could be carried out by a group that is not fully independent of the study, sometimes termed an 'internal' DMC (Ellenberg et al 2003: 157–8). An internal DMC can significantly improve patient safety and trial integrity through regular meetings to review data on study conduct and relative efficacy and safety. Its membership should be multidisciplinary, and may include the principal (clinical) investigator for the study and the study statistician.

6.55 The table below gives an indication of the most appropriate form of DMC monitoring for an intervention study (Ellenberg et al 2003: 160).

Appropriate form of DMC monitoring

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

1 Setting 1 includes: life-threatening diseases (treatment, palliation and prevention); diseases causing irreversible serious morbidity (treatment, palliation and prevention); novel treatments for life-threatening diseases (treatment, palliation and prevention) with potential for significant adverse events; and vulnerable populations. Setting 2 includes trials not included in setting 1.

2 An internal DMC would be advised if an independent DMC is not established.

3 Integrity/credibility issues could motivate use of an independent DMC; for example, if a trial in this setting were to impose interim monitoring of comparative data.

Adverse event monitoring

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

Term	Definition
Adverse event (AE)	Any untoward medical occurrence in a patient administered a study product and which does not necessarily have to have a causal relationship with this product.
Adverse drug reaction (ADR)	Any untoward and unintended response in a subject to an intervention which is related to any dose administered to that subject.
Unexpected adverse reaction	An adverse reaction, the nature and severity of which is not consistent with information about the intervention in the investigator's brochure (or, for a product with marketing authorisation, in the summary of product characteristics for that product).
Serious adverse event, serious adverse drug reaction or unexpected serious adverse reaction	An adverse event, adverse drug reaction, or unexpected adverse reaction, that: • results in death, or • is life-threatening, or • requires inpatient hospitalisation or results in prolongation of existing hospitalisation, or • results in persistent or significant disability or incapacity, or • consists of a congenital anomaly or birth defect, or • is a medically important event or reaction.
Suspected unexpected serious adverse reaction (SUSAR)	Any unexpected serious adverse reaction which is suspected to be related to the intervention under study.

Source: MHRA 2009

Responsibilities for monitoring adverse events

6.57 The protocol and/or monitoring plan of any intervention study should state the processes and responsibilities for identifying, coding, analysing and reporting adverse events. Reliable interpretation of AEs requires coding according to body system and severity (eg, *Medical Dictionary for Regulatory Activities* [MedDRA 2009], or *Common Terminology Criteria for Adverse Events* [CTEP 2009]) and comparison of grouped data across intervention arms (with consideration of the benefit and risk profile). An independent DMC is the group best placed to reliably interpret such safety data.

6.58 Prompt reporting of serious adverse events is especially important for suspected unexpected serious adverse reactions (SUSARs) (see paragraph 6.56).

6.59 A mechanism should be in place for responding to any potential safety concerns. In general, reliable interpretation of the safety signals would require an interim report on safety and efficacy, in a form unblinded by intervention arm.

6.60 In studies with an independent DMC, the responsibility for monitoring safety data, including monitoring appropriate responses to the prompt reports of SUSARs, could be delegated by the ethics committee to the DMC.

Terminating a study

6.61 There are some circumstances (eg, a major deviation from study protocol) that may make it appropriate to terminate an intervention study early.

6.62 For any study with a DMC, any issues about early termination of the study should be addressed in the study's monitoring plan (see also paragraph 6.47), and any early termination of the study should be in accordance with the study's monitoring plan and under the advice of the DMC. For any study without a DMC, the study's monitoring plan should include comment on whether (and if so under what conditions) early termination of the study would be considered.

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

Care of participants

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

6.65 Ideally, phase III intervention studies should be designed to assure that every participant has post-study access to the best-proven intervention. The minimum requirement is that investigators make clear to all participants the post-study access arrangements, including any uncertainties in this regard. The sponsor and investigator should also pursue matters of access to effective interventions for study and target populations with relevant authorities. In most intervention studies it cannot be known which intervention is best until after the study has been completed.

Clinical responsibilities

6.66 Responsibilities to inform other health professionals of a participant's study involvement depend on the nature of the study. For some studies the investigator should inform professionals responsible for the health care of participants of their participation in a study, usually at the time of enrolment in the study, and provide information about the possible health implications of this involvement. For other studies, informing other health professionals is desirable, with the participant's consent. There are also some studies (eg, where risk is minimal – see paragraph 4.13) for which it is not necessary to inform any other professional of the participant's study participation. (See also paragraphs 6.5 and 7.8–7.10.)

6.67 Participants (and their main care provider) must be informed of any clinically significant abnormal laboratory results or clinical observations that develop or are detected during the course of a study. Appropriate follow-up must be arranged.

6.68 Where participants are found through the conduct of a study to have a previously undetected health care need that is not directly related to the study, arrangements should be made for them to receive that care. Investigators and study sponsors have a responsibility to take all reasonable steps to ensure that appropriate care is provided.

6.69 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.

7.2 Investigators should make arrangements for protecting the confidentiality of study data.

7.3 Investigators must ensure the adequate physical and electronic security of data.

7.4 For studies involving the collection of information about illegal activities (eg, the use of illegal substances), potential participants should be made aware whether investigators can or cannot ensure confidentiality.

7.5 In the unusual event that individual or group confidentiality cannot be maintained or is violated, investigators should take all reasonable steps to maintain or restore the good name and status of the individual(s) or group.

7.6 Note that 'privacy' is the status of information about aspects of a person's life over which she or he claims control and may wish to exclude others from knowing. Privacy is a relative status and claims to it must be negotiated against countering claims, such as the rights of others or collective societal goods. 'Confidentiality' is the respectful handling of information disclosed within relationships of trust, especially as regards further disclosure (Lowrance 2002).

7.7 See also the Health Information Privacy Code 1994, Rules 5 and 11, and the Privacy Act 1993, Principles 5 and 11.

Disclosure of information obtained by intervention studies

7.8 Where findings obtained by an intervention study 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.

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

7.10 Individuals' privacy and confidentiality of information need to be protected unless there is an overriding concern (eg, health or safety) justifying the release of such information. If privacy or confidentiality must be breached, the investigator should first make a reasonable attempt to inform participant(s) of the event and the reasons for it.

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

7.12 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.

7.13 Investigators have an obligation to disclose to participants and their legal proxies, where applicable, any unforeseen risks discovered during the course of a study, and any other new information that might reasonably affect their consent to participate or their future health and safety. This participant right should be indicated in the informed consent process and in the study's monitoring plan.

7.14 Investigators should not normally enter into contracts with clauses that restrict or prohibit disclosure of risks or lack of benefit of research products to participants, other members of the research group, ethics committees, regulatory agencies, or the scientific or general community.

7.15 Any contractual restrictions to investigator access to study data should be declared when applying for ethics committee approval. 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 normally have sole unblinded access to emerging data.)

Publishing study results

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

7.17 Investigators should not normally enter into contracts that limit, or apply unreasonable time restrictions to, the publication of study results.

7.18 Full publication of study results helps to prevent publication bias and allows for additional information to be gleaned through meta-analyses. All end-points stated in the study protocol – including positive, negative, significant and non-significant results – should be published. Results from all participants in the trial, including all arms of the trial, should be published. Where such a comprehensive approach is not practicable, the published report should acknowledge and explain any departures, including any omissions or additions, from the end-points specified in the study protocol.

7.19 It is normally not appropriate to publish incomplete results from intervention studies (eg, publication only of early results, results only of secondary end-points, or results from only some study centres), because incomplete results have the potential to be misleading.

7.20 Study protocols should include a provision for communicating results in a timely, understandable and responsible way by suitable means, so that the widest possible community stands to benefit. The optimal time at which to disseminate the results of intervention studies can be difficult to determine. Both premature release and unnecessary delay in the release of study results can be more harmful than beneficial to individuals and to society. It may be necessary to balance the need for cautious communication of results to other investigators with appropriate peer review and the need for expeditious communication of results to other interested parties. Where availability of the results would lead to immediate benefit to patients, investigators are responsible for making these results available to the relevant parties in an expeditious manner.

7.21 Study results should be published in a form that gives due regard to cultural and other sensitivities. This normally implies that they should not be published in a form that permits the identification of individual participants. (See also paragraph 7.5.)

7.22 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 Section 32 of the Injury Prevention, Rehabilitation, and Compensation Act 2001 (IPRC Act 2001) sets out the limited circumstances in which there will be cover for 'personal' (physical) injury suffered as a result of treatment provided as part of an intervention study. This cover is provided through the Accident Compensation Corporation (ACC).

8.2 Participants in clinical trials are excluded from cover under the general provisions of the IPRC Act 2001 if they agreed in writing to participate in the trial and an approved ethics committee did not approve the clinical trial. Participants are also excluded if *all* of the following conditions are met:

- the participant's personal injury results from medical treatment
- this injury occurs during or after his or her participation in a clinical trial
- the medical treatment is provided as part of the study
- the medical treatment is provided by a registered health practitioner
- the participant agreed, in writing, to participate in the study
- an approved ethics committee approved the trial, and was satisfied that the trial was to be conducted principally for the benefit of the manufacturer or distributor of the medicine or item being trialled.

8.3 Investigators and sponsors should ensure that the extent of each participant's compensation entitlements in the event of adverse consequences arising out of her or his participation in an intervention study are outlined clearly to her or him as part of the informed consent process. Where personal injury suffered as a result of treatment given as part of a clinical trial is covered under the accident compensation scheme, participants must be advised that compensation may not be available or may be modest.

8.4 If cover under the IPRC Act 2001 will be excluded for the intervention study, investigators and study sponsors have responsibilities to ensure alternative compensation cover for study participants to at least ACC-equivalent standard. This may include earnings-related compensation.

8.5 Ethics committees have a responsibility to check that at least ACC-equivalent compensation is available to participants in clinical trials that are not covered by the accident compensation scheme.

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 the two forms and attendant declarations for compensation in the following settings:

- Form A is for clinical trials for which ACC provides for compensation for injury
- Form B is for clinical trials for which the manufacturer provides for compensation for injury.

Glossary

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Innovative practice: a planned deviation from the currently accepted practice of a New Zealand body of health professionals involving an untested or unproven clinical intervention intended to be used on an ongoing basis (Ministry of Health 2006b: paragraph 121).

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

Intervention study: a study in which the investigator controls and studies 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.

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

IPRC Act 2001: the Injury Prevention, Rehabilitation, and Compensation Act 2001.

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

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

Operational Standard: the *Operational Standard for Ethics Committees* (Ministry of Health 2006b).

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

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

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

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

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

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

Principal investigator: the qualified health professional and/or qualified researcher with primary responsibility for the design and conduct of a particular investigation.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Appendix:
The National Ethics Advisory Committee

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

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

NEAC works in the context of the New Zealand Public Health and Disability Act 2000.

The members of NEAC, appointed by the Minister, bring expertise in ethics, health and disability research, health service provision and leadership, public health, epidemiology, law, Māori health and consumer advocacy.

Committee membership for this project

Andrew Moore, Chair

Allison Kirkman, Deputy Chair (to December 2007)

Geoffrey Fougere, Deputy Chair (from November 2008)

Michael Ardagh (to December 2007)

Dale Bramley (to December 2007)

Michael Findlay

Andrew Hall (from November 2008)

Elisabeth Harding (to December 2007)

John Hinchcliff (to June 2009)

Barbara Holland (to June 2009)

Te Kani Kingi (to June 2009)

Robert Logan (from November 2008)

Joanna Manning

Robin Olds (from November 2008)

Charlotte Paul

Ann Richardson (from November 2008)

Elizabeth Smales (from November 2008)

Martin Sullivan (to December 2007)

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 (2007–2009)

Vanessa Roberts, Analyst

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

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