MEDSAFE

NEW ZEALAND MEDICINES
AND MEDICAL DEVICES
SAFETY AUTHORITY

A BUSINESS UNIT OF
THE MINISTRY OF HEALTH

Guideline on the Regulation of Therapeutic Products in New Zealand

Part 11:

Clinical trials – regulatory approval and good clinical practice requirements

MINISTRY OF HEALTH
MANATU HAUORA

Edition 2.0

November 2018

Contents

Section 1: Legislation

Section summary

This section identifies the legislation and other guidelines to be read in conjunction with Part 11 of the regulatory guideline.

1.1 Legislation relating to clinical trials

The following legislation should be read in conjunction with this part of the guideline:

- Medicines Act 1981 – "Medicines Act"; "the Act"

Section 2	Interpretation - meaning of 'medical device'
Section 3	Meaning of 'medicine', 'new medicine', 'prescription medicine' and 'restricted medicine'
Section 4	Meaning of 'therapeutic purpose'
Section 17	Manufacturers, wholesalers, packers of medicines, and operators of pharmacies to be licensed
Section 18	Sale of medicines by retail
Section 20	Restrictions on sale or supply of new medicines
Section 30	Exemption for clinical trial
Section 47	Storage and delivery of medicines
Section 88	Refusal of licensing authority to grant licence
Part IV	Medical advertisements

- Medicines Regulations 1984 – "Medicines Regulations"; "the Regulations"

Regulation 39	Conditions under which authorised prescribers and veterinarians may prescribe medicines
Part V	Manufacture, packing, storage and handling

- Misuse of Drugs Act 1975

Section 6	Dealing with controlled drugs (including import, supply, administration)
Schedules	Classes of Controlled Drugs

- Misuse of Drugs Regulations 1977

Regulation 31	Restrictions on supply on prescription

- Public Records Act 2005
  - Section 18 Disposal of public records and protected records
- Privacy Act 1993
- New Zealand Public Health and Disability Act 2000
- Accident Compensation Act 2001
- Hazardous Substances and New Organisms Act 1996
- Health and Disability Commissioner Act 1994
- Health Practitioners Competence Assurance Act 2003
- Health (Retention of Health Information) Regulations 1996
- Health Information Privacy Code 1994
- Injury Prevention, Rehabilitation and Compensation (Code of ACC Claimants' Rights) Notice 2002

1.2 Additional guidance material relating to clinical trials

In addition to the legislation listed above, the following guidance documents should also be read:

- Guideline for Good Clinical Practice E6(R2) (EMA/CHMP/ICH/135/1995)
- Guideline on Strategies to Identify and Mitigate Risks for First-In-Human Clinical Trials with Investigational Medicinal Products (EMEA/CHMP/SWP/28367/07 Rev.1)
- Medicines New Zealand Guidelines on Clinical Trials Compensation for Injury Resulting from Participation in an Industry-sponsored Clinical Trial
- Standard Operating Procedures for Health and Disability Ethics Committees
- National Ethics Advisory Committee Ethical Guidelines for Intervention Studies
- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH Harmonised Tripartite Guideline E2A)
- Health Research Council Guidelines on Ethics in Health Research
- Health Research Council of New Zealand. HRC Research Ethics Guidelines (Guidelines) September 2017
- Online Forms User Manual

Section 2: Overview of Regulation of Clinical Trials in New Zealand

Section summary

Under section 30 of the Medicines Act, approval from the Director-General of Health is required before a clinical trial using a new medicine may commence in New Zealand.

The approval process for clinical trials is administered by Medsafe.

The Health and Disability Ethics Committees administer the ethics approval system, which applies to all clinical trials conducted in New Zealand.

Approvals under other legislation may be required for clinical trials using certain types of medicines.

All clinical trials in New Zealand are expected to be conducted in accordance with internationally accepted Good Clinical Practice standards, even those that do not require approval under section 30.

2.1 Requirement for approval of a clinical trial under Section 30 of the Medicines Act 1981

Section 30 of the Medicines Act requires that clinical trials involving new medicines must be approved by the Director-General of Health. This requirement applies to all types of clinical trials of new medicines, including pharmacokinetic, bioequivalence and *first-in-human* studies.

The application and approval process for clinical trials is administered by Medsafe (the medicines and medical devices regulatory authority for New Zealand). The application and approval procedure is described in Section 3 of this guideline, and summarised here.

1. An application is received at Medsafe, which forwards the application to the Health Research Council of New Zealand (HRC).
2. A committee of the HRC considers the application.
3. The HRC makes a recommendation to the Director-General on the clinical trial application.
4. The applicant is issued approval, provisional approval or a decline letter by Medsafe based on the HRC recommendation, under authority delegated from the Director-General of Health.

Medsafe also administers a notification scheme for clinical trial sites that have patients in residence, and maintains a list of sites for which it has received notification of compliance with Good Clinical Practice requirements. See Section 4 of this guideline for further details.

Ethics approval of a clinical trial by a Health and Disability Ethics Committee is also required. It is a separate process that is not administered by Medsafe. Further detail is provided in Section 2.6 of this guideline.

2.2 Good Clinical Practice requirements

All clinical trials are expected to be conducted in accordance with the internationally accepted standards set out in the CHMP guidance document EMA/CHMP/ICH/135/95 Guideline for Good Clinical Practice E6(R2) published by the European Medicines Agency (EMA) (the CHMP GCP guideline).

Where there is a conflict between the CHMP GCP guideline and specific requirements relating to clinical trials that are set out in section 30 of the Medicines Act, the Act takes precedence and modified CHMP requirements (in particular the reporting requirements) apply in New Zealand. These modifications are described in Sections 5 and 6 of this guideline.

2.3 What is a clinical trial?

The term 'clinical trial' is not defined in the Medicines Act. While there is no single internationally accepted definition, for the purpose of regulating clinical trials conducted in New Zealand, the definition in the CHMP GCP guidance document EMA/CHMP/ICH/135/95 Guideline for Good Clinical Practice E6(R2) applies. This defines a clinical trial as:

> *Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy.*

In this guideline, the terms 'clinical trial' and 'clinical study' are used interchangeably, as are the terms 'investigational medicine' and 'investigational product'.

2.4 Determining whether a clinical trial requires approval under the Medicines Act

Under section 20 of the Medicines Act, the consent of the Minister of Health is required before a new medicine can be distributed. Section 30 of the Act provides for an exemption from the requirement for Ministerial consent, if the new medicine is to be distributed solely for the purpose of using it in a clinical trial. A clinical trial must not commence before the Director-General of Health has given approval for the trial.

The provision for exemption under section 30 only applies to new medicines, and only applies when they are to be used solely in clinical trials. It does not apply to medicines that have already been granted consent for distribution.

The terms *medicine* and *new medicine* are defined in section 3 of the Act. Part 2 of the Guideline on the Regulation of Therapeutic Products in New Zealand provides additional guidance. The terms 'unapproved medicine' and 'lapsed approval' are synonymous with 'new medicine'.

'Unapproved medicines' include new chemical or biological entities and new dosage forms and new strengths of approved medicines, and a different, unapproved formulation of an approved medicine.

The following points will help applicants determine whether a clinical trial involves use of a new medicine and therefore requires approval under section 30 of the Act.

Situations not requiring clinical trial approval:

- Approval under section 30 is not required for a clinical trial that uses only medicines for which Ministerial consent for distribution in New Zealand has been granted (ie, approved medicines). This applies even if the trial is investigating a new indication. However, the medicine used in the trial must be the actual medicine formulation for which consent for distribution in New Zealand has been granted.

- If an approved medicine is repacked for use in a clinical trial, this does not make it a new medicine and the trial does not require approval.

- Placebos used in clinical trials are not considered to be new medicines. Therefore, a clinical trial involving only approved medicines and placebos does not require approval.

- A "laboratory observational" type extension to a clinical trial, where medication is not given to the subjects, does not require approval.

- Medical devices are specifically excluded from the definition of the term *medicine*. There is no provision under the current Medicines legislation to require approval of clinical trials involving medical devices under the Medicines Act. It should be noted, however, that Health and Disability Ethics Committee approval should be obtained for clinical trials of medical devices. Medsafe would like to be informed by email of any clinical trials of medical devices (via devices@moh.govt.nz).

- A clinical trial involving a xenotransplantation procedure is not a clinical trial that is regulated under section 30 of the Act. Xenotransplantation is regulated as a *specified biotechnical procedure* requiring the approval of the Minister of Health. See Medicines Act 1981 Part 7A for details. However, any trial involving xenotransplantation is expected to be carried out in accordance with Good Clinical Practice standards (see Section 5 of this guideline for further details).

Situations requiring clinical trial approval:

- Approval is required for a clinical trial of an unapproved (ie, different) formulation of an approved medicine. This includes the use of an unapproved dose form of an approved medicine.

- Approval is required for a clinical trial of a medicine for which consent to distribute was previously granted, but has lapsed. It does not matter if the indication being investigated has previously been approved. The approval status of medicines that have been previously considered by Medsafe can be viewed using the Product/Application Search facility on Medsafe's website.

- A clinical trial involving both a new medicine and an approved medicine, for example, as a comparator, requires approval.

- In some circumstances, a substance that is commonly used as an ingredient in a

food, dietary supplement or cosmetic is used in a clinical trial. That substance, when administered to human beings for a therapeutic purpose as part of a clinical trial, is considered to be a new medicine and approval for the trial is required.

- Clinical trials involving products that are not medicines in other jurisdictions, but are considered to be new medicines under New Zealand legislation, require approval before they can proceed. Any queries regarding the categorisation of a product to be used in a clinical trial should be directed to Medsafe.

- A clinical trial involving human tissues or cells (eg stem cells, blood products) requires approval under section 30 of the Act, and may also have to comply with the Human Tissues Act 2008 before proceeding.

- Any subsequent amendment of a trial protocol must also be approved by the Director-General of Health.

- An extension to a clinical trial, where an intervention is involved, requires approval.

If there is to be an open extension phase of a clinical trial, the protocol for the open extension phase should ideally be submitted as part of the original clinical trial application.

A subsequent application may be made for approval of an open extension phase provided it can be shown that extension of the study will yield scientifically valid results. Extension trials using safety endpoints are considered to be scientifically valid.

If a rescue medication to be used in a clinical trial is a different formulation, presentation (including packaging and labelling), strength, dose form, indications, product name, manufactured by a different manufacturer or obtained from a different sponsor or imported from overseas, to that approved in New Zealand, the rescue medication is an unapproved medicine, and is considered to be a trial medicine also, for the purposes of the trial.

2.5 Other legislative requirements relating to clinical trials

A clinical trial involving a *new organism* or *genetically modified organism* requires compliance with the Hazardous Substances and New Organisms Act 1996. This is independent of the process for approval for a clinical trial under section 30 of the Medicines Act.

Applicants should contact the Environmental Protection Authority about their obligations:

Email: info@epa.govt.nz

A clinical trial involving the use of a *Controlled Drug*, requires compliance with the Misuse of Drugs Act 1975 and associated regulations. These set out licensing requirements for importation, possession and supply of controlled drugs, as well as storage and prescribing requirements.

For further information, contact Medicines Control at:

Email: medicinescontrol@moh.govt.nz

Clinical trials should also comply with the requirements of the Privacy Act 1993.

It is the applicant's responsibility to ensure that all other legislative obligations are met and the applicant has all the necessary approvals issued before they proceed with starting the trial or importing the investigational product. For example, for a trial involving a new organism as the investigational medicine, the applicant should also have an approval from the Environmental Protection Authority to import or use the new organism. For a trial involving a new controlled drug, a Licence to Deal in a Controlled Drug from Medicines Control is required. The timeline for obtaining approval for each aspect may differ significantly from Medsafe's.

2.6 Health and Disability Ethics Committees approval

All clinical trials must comply with the Health and Disability Ethics Committees' (HDEC) requirements, regardless of whether they are trials that require approval under section 30 of the Medicines Act.

Ethics Committees approval is a separate process from clinical trial approval under section 30 of the Medicines Act and is **not** administered by Medsafe.

For all trials, the application for Ethics Committees approval may be made at any time before, during or after consideration of the application for clinical trial approval under section 30.

For particulars about Ethics Committees approval, applicants should contact the Health and Disability Ethics Committees at:

Email: hdecs@moh.govt.nz

Applicants are advised to contact the Health and Disability Ethics Committees regarding their reporting requirements.

2.7 Advocacy Services

The Health and Disability Services Commissioners Code of Rights requires that patients have access to services such as Advocacy Services when they are enrolled in a clinical study. It is desirable but not essential to appoint a patient advocate to a study. If no advocacy service is appointed the sponsor must tell patients how and where they can obtain such services if they require them.

Section 3: Application for Approval of a Clinical Trial under Section 30 of the Medicines Act

Section summary

This section describes the application and approval procedure administered by Medsafe for the approval of clinical trials under Section 30 of the Medicines Act 1981.

3.1 Role of Medsafe in the clinical trial approval procedure

Medsafe administers the application and approval process for clinical trials under an authority delegated from the Director-General of Health. Medsafe receives and processes applications, liaises with the relevant Health Research Council committee (see Section 3.2) and the applicant, and issues approval letters. All communication regarding an application for approval of a clinical trial must be addressed to the Clinical Trial Co-ordinator at Medsafe.

The email address is: clinicaltrials@medsafe.govt.nz

3.2 Role of the Health Research Council in the clinical trial approval procedure

Section 30 of the Medicines Act authorises the Director-General of Health to approve a clinical trial on the recommendation of the Health Research Council of New Zealand.

The HRC maintains two standing committees to consider clinical trial applications and make recommendations to the Director-General. The Standing Committee on Therapeutic Trials (SCOTT) considers applications for pharmaceutical-type medicines. The Gene Technology Advisory Committee (GTAC) considers applications for trials involving gene and other biotechnology therapies.

The Terms of Reference for these standing committees are published on the Health Research Council website. The sponsor of a clinical trial should read these documents before submitting an application, as they provide guidance on the committee standing processes and the data requirements for applications to be considered by each standing committee.

3.3 Submitting an application for approval of a clinical trial

An application for approval of a clinical trial is made by the person responsible for the trial in New Zealand. This person is referred to in the Medicines Act as 'the applicant'.

The applicant must be the person in New Zealand who takes legal responsibility for the conduct of the trial in New Zealand. For more information on the responsibilities of the applicant, see Section 4.3, Section 5.2.1 and Section 6.

Applications for approval of clinical trials must be made using the online system. Paper-based/emailed applications will not be accepted.

Any paper or email based applications received will be disposed of.

3.3.1 Making an online application for a clinical trial

An online application for a clinical trial approval is made using the NZ Online Forms at:

https://nz.ethicsform.org/signin.aspx

The applicant must first create an account to get access to SCOTT / GTAC and HDEC application forms. Instructions for creating an account and how to prepare and submit applications electronically are on this website.

The Online Forms User Manual provides guidance on this process.

The applicant should use the SCOTT Online Form for applications to either SCOTT or GTAC. Applicants should note that an application to the Health and Disability Ethics Committees for ethics approval should be made on the separate HDEC Online Form.

Delivery site addresses for the trial medicines should be clearly stated on the application form. These delivery site addresses will be included on the approval letter issued by Medsafe if the trial is approved. Applicants should be aware that Customs will not clear delivery of any investigational medicine to unapproved sites or investigators if these are not on the approval letter.

3.4 Administrative processing of clinical trial applications

On receipt of the online application, Medsafe will send an acknowledgement letter and an invoice to the applicant within 7 days.

Payment of the invoice should be made within 7 days. If the recommendation is for approval, the clinical trial approval will not be issued until payment has been received.

Applicants must ensure that all communication regarding the application is sent to Medsafe at clinicaltrials@medsafe.govt.nz.

3.5 Clinical trial application fee and fee waiver

The fee for an application for approval of a clinical trial under section 30 is set out in regulation 61 of the Medicines Regulations 1984. See the Medsafe Fee Schedule for current fee details. The Director-General of Health may, under regulation 61A, grant a waiver of the fee in certain circumstances.

Applications for fee waiver will only be considered when they are submitted with the initial application. Applications will be considered on a case-by-case basis.

3.5.1 Criteria for fee waiver

A waiver may be considered for a clinical trial conducted for the public good, or for specific types of bioequivalence studies utilising new generic medicines. Applications should include the reasons for requesting a waiver.

The criteria taken into consideration for granting a fee waiver are as follows.

- The time reasonably required to consider any application made or notice given under the Medicines Act 1981.
- The degree of complexity involved in considering any such application or notice.
- The interests of public health in New Zealand.
- Any funding that the trial receives.

3.6 Consideration of applications for approval of clinical trials

Applications are considered by the relevant standing committee of the Health Research Council (SCOTT or GTAC). Following its consideration of an application, the standing committee conveys its recommendation to Medsafe. The standing committee may:

- Recommend that the clinical trial is approved
- Recommend that the clinical trial is approved subject to certain conditions
- Request more information in relation to the application
- Recommend that the clinical trial is not approved.

Within 45 calendar days of receiving the application, Medsafe will notify the applicant of the outcome of the Director-General's consideration of the HRC's recommendation, and will then liaise with the applicant regarding any proposed conditions of approval (such as amendment to the trial protocol) or requests for further information. All correspondence relating to the application must be addressed to Medsafe.

Following the resolution of any issues relating to the application, if the Director-General's decision is to approve the trial, Medsafe will issue an approval letter. If the decision is to decline an application, the reasons for this decision will be provided to the applicant. The applicant then has 28 days in which to lodge an appeal with the Medicines Review Committee.

The appeal provisions are set out in Section 88 of the Medicines Act 1981.

3.7 Abbreviated clinical trial approval process for bioequivalence studies

Medsafe operates an abbreviated approval process for eligible clinical trial applications. This abbreviated approval process applies only to bioequivalence studies and **does not apply to bio-similar products**.

- The clinical trial is a bioequivalence study that utilises an investigational product that contains the same active pharmaceutical ingredient included in a medicine that is approved for distribution in New Zealand; and
- The proposed route of administration for the investigational product is the same as that for the approved medicine; and
- The proposed dosage for the investigational product is within the recommended dosage range for the approved medicine.

A reduced fee applies to clinical trial applications meeting these criteria, and a response will be issued within five working days. See the Medsafe Fee Schedule for current fee details.

Section 4: Notification of Clinical Trial Sites

Section summary

Medsafe administers a *Clinical Trial Site Notification* scheme covering sites which have study participants in residence while the clinical trial medicines are administered. The notification is site-specific and confirms the site's procedures for dealing with any emergencies arising from a clinical trial. It is completed by the person responsible for the site and should be updated whenever the information in the original notification form is changed.

4.1 Clinical Trial Sites requiring notification under the scheme

Section 30 of the Act sets out the information that must be provided in an application for approval of a clinical trial. Section 30(3)(g) specifies that the application must include information about the site(s) at which the trial is to be conducted, and the facilities available at those sites. This information is taken into consideration in deciding whether to grant approval for the trial.

If study participants are staying overnight or longer for monitoring purposes as a result of receiving a study medication, information about the facilities and procedures in place to deal with possible emergencies (Critical Incidents) arising from the study medication must be provided. A Critical Incident is described as a life-threatening or disabling event arising from the study medication.

Medsafe administers a *Clinical Trial Site Notification* scheme to facilitate the collection and processing of this information for both the regulator and for applicants.

4.2 Operation of the Clinical Trial Site Notification scheme

Under this scheme, the person who manages the site (where study participants stay overnight) completes a **Clinical Trial Site Notification** form (see CTSN Form), and notifies that the site has adequate emergency procedures in place. In most instances, the site manager will be a site staff member in charge of the site, who has the responsibility for managing the site, its staff and its procedures.

The notification can be made at any time and does not need to coincide with submission of an application for approval of a particular clinical trial.

On receipt of a completed notification, Medsafe will add the site to a list of *Notified Clinical Trial Sites* on the Medsafe website (http://www.medsafe.govt.nz/regulatory/CSSites.htm).

Re-notification of a clinical trial site is required if there is a change to any of the information in the original notification form.

4.3 Applicant responsibilities relating to trials being conducted at notified clinical trial sites

Applicants requesting approval of a clinical trial where subjects are kept overnight for monitoring purposes as a result of receiving the study medications need to check that the proposed clinical trial site has been notified. This can be done by checking Medsafe's Notified Clinical Trial Sites webpage. If the site has not been notified, the applicant should contact the manager of the site to submit a notification.

Applicants should not commence a clinical trial that requires trial subjects to stay at a site overnight (or longer), unless the site has been notified.

Section 5: Good Clinical Practice Requirements

Section summary

This section establishes the requirement for clinical trials to be conducted in accordance with the CHMP Guideline for Good Clinical Practice and explains the modifications to the CHMP GCP guideline that are needed to achieve alignment with New Zealand regulatory requirements.

5.1 Compliance with Good Clinical Practice

All clinical trials are expected to be conducted in accordance with the Guideline for Good Clinical Practice E6(R2) (EMA/CHMP/ICH/135/1995) – the CHMP GCP guideline, even those that do not require approval from Medsafe (eg, a clinical trial involving an approved medicine).

In some cases, requirements set out in the CHMP GCP guideline do not cover, or are in conflict with, particular provisions in the Medicines Act 1981 or in other relevant New Zealand legislation (eg, legislation relating to reporting requirements or the retention of records). For this reason, some of the requirements specified in the CHMP guideline must be modified in order to achieve compliance with New Zealand law.

Modifications are required in respect of:

- the definitions and obligations of particular persons (see Section 5.2)
- the manufacture, labelling and dispensing of investigational products (see Section 5.3)
- the retention of records (see Section 6)
- adverse event reporting (see Section 6.2)
- clinical trial reporting requirements (see Section 6.6).

5.2 Responsibilities of the applicant, sponsor, investigator and monitor

Sections 1, 4 and 5 of the CHMP GCP guideline set out the obligations of the applicant, sponsor, investigator and monitor in clinical trials. In contrast, the Medicines Act uses the terms applicant and investigator, but does not refer to a sponsor or monitor. The responsibilities of those involved in conducting clinical trials in New Zealand are outlined below.

5.2.1 Applicant and New Zealand sponsor

The CHMP GCP guideline defines *sponsor* as an individual, company, institution or organisation which takes responsibility for the initiation, management and/or financing of a clinical trial.

The Medicines Act does not use the term *sponsor* but refers to an *applicant*. The applicant is the person who imports or manufactures or commissions the manufacture of a new medicine for use in a clinical trial. The responsibilities of the *applicant* under New Zealand legislation are defined in section 30 of the Medicines Act 1981 and parallel those of the *sponsor* in the CHMP guideline (except for the reference to financing the trial).

In New Zealand, the term ***applicant*** is used when referring to the person who makes the application for approval of the trial.

Once the trial is approved, the applicant becomes the ***sponsor***, assuming responsibility (including legal liability) for the trial in New Zealand. The *sponsor*, who must be a person in New Zealand, is responsible for:

- the preservation of records
- reporting adverse events (see Section 6.2 of the guideline)
- notifying and seeking approval for any changes in the clinical trial protocol (see Section 6.6.1) to the Director-General of Health (through Medsafe, and for ethics approval through HDEC)
- informing the Director-General of Health of the identifying name or mark by which the trial medicine may be recognised before the trial medicine is distributed (section 30(7)(a) of the Act).

While the supporting documentation required to be submitted with an application may be prepared by the overseas sponsor of the trial, it is the person responsible for the trial in New Zealand (the applicant) who must make the application to the Director-General for approval of the trial.

When the application is approved the applicant becomes the 'sponsor' and is responsible for ensuring that the trial is conducted in accordance with both New Zealand law and Good Clinical Practice standards.

In the case of a multi-centre trial that is being conducted and administered by a research body outside New Zealand, it is common for the principal investigator in New Zealand (or a local person or company, such as a clinical research organisation acting in that capacity) to undertake the role of applicant (and subsequently, the sponsor).

5.2.2 Investigators

The ***principal investigator*** is the person with overall responsibility for the conduct of the clinical trial in New Zealand. There is only one principal investigator for a trial, regardless of the number of trial sites involved.

The principal investigator must be resident in New Zealand, have competence and experience in a relevant field of study, and hold appropriate qualifications that are recognised within New Zealand. Where the principal investigator is not medically qualified, the trial protocol must identify the clinician responsible for medical supervision of the trial and oversight of the medical care of the participants in the trial.

A ***lead investigator*** is the person responsible for the conduct of a trial at a particular trial site. For a multi-centre trial, there will be a lead investigator for each trial site. Where a trial is conducted by a team of investigators at a particular site, the lead investigator is the

responsible leader of the team. The principal investigator for the trial may also be the lead investigator at a particular trial site.

An *investigator* is an individual who is designated to conduct clinical trial procedures at a particular trial site. All investigators must have New Zealand-recognised qualifications and experience appropriate to their particular role in the conduct of the trial.

5.2.3 Monitor

The *monitor* (or clinical research associate) is an individual appointed by the sponsor and is responsible for carrying out monitoring activities in accordance with the sponsor's requirements to ensure that the trial is conducted and documented properly. The monitor should be independent of the clinical trial site, be qualified by scientific and/or clinical knowledge and have appropriate training and experience.

5.3 Investigational products

The CHMP GCP guideline discusses investigational products in points 4.6, 5.12, 5.13 and 5.14. Investigational products, including active comparators and placebos, are expected to be manufactured in accordance with applicable GMP.

In New Zealand, investigational products are expected to be manufactured in accordance with the New Zealand Code of Good Manufacturing Practice for Manufacture and Distribution of Therapeutic Goods found at:

http://www.medsafe.govt.nz/regulatory/Guideline/NZRGMPart1.asp

Annex 13 of the Code provides additional guidelines for investigational medicinal products. The Medicines Act also places a number of conditions on the distribution of a medicine under section 30 of the Act.

Where the investigational medicine is manufactured in New Zealand, the manufacturer must hold a file that describes the specification of the investigational medicine manufactured for the clinical trial, and an outline of the manufacturing process.

The specification file must be consistent with the approved clinical trial documents (for example, specifications of the investigational product in the Investigators Brochure, etc.). The manufacturer must issue a Certificate of Analysis for the medicine to the sponsor of the trial.

The *sponsor* of the trial should verify that the investigational medicine meets the approved specifications and is suitable for use before it is released for the trial.

5.3.1 Labelling of investigational medicines

Section 30(7)(b) requires that every label on every package of a medicine used in a clinical trial must have the words "***To be used by qualified investigators only***". It is Medsafe's practice to accept these words or words of similar meaning.

The investigational product should be labelled according to Annex 13 of the Code, which requires the name, address and telephone number of the sponsor, contract research

organisation or investigator (the main contact for information on the product, clinical trial and emergency unblinding). The New Zealand contact details must be used, in the event that an emergency occurs, and the sponsor or Principal Investigator has to be contacted.

The address and telephone number of the main contact for information on the product, clinical trial and for emergency unblinding need not appear on the label if the subject has been given a leaflet or card which provides these details, and has been instructed to keep this in their possession at all times.

5.3.2 Distribution and supply of investigational medicines

Section 30(7)(c) requires that every person to whom the trial medicine is distributed must be approved to conduct the trial (ie, be an approved investigator), and the medicine must be used solely by that person or under his/her direction for the purposes of the trial.

Supplying clinical trial medicines to trial participants is not considered to be prescribing or *dispensing* and the requirements set out in Part 7 of the Medicines Regulations 1984 do not apply. However, where clinical trial medicines are required to be repacked ready for supply to trial participants, this must be undertaken by a person who is the holder of a packing licence or is otherwise authorised to pack medicines (see section 17 of the Medicines Act 1981).

Clinical trial medicines may be supplied to trial participants by an investigator, pharmacist, nurse or other suitably qualified member of the clinical trial team. The arrangements for supply to patients should be specified in the clinical trial protocol at the time the application for approval of the trial is made. The investigator may subsequently submit a protocol amendment delegating responsibility for supply to another suitably qualified person.

The quantity of trial medicine to be supplied to trial participants at one time should be specified in the trial protocol. Where a clinical trial uses a product containing a substance listed in a schedule to the Misuse of Drugs Act 1975, the supply restrictions relevant to that class of controlled drug will apply. The restrictions are set out in the following table:

Controlled Drug class	Period of supply
Class A	1 month
Class B	1 month
Class C	3 months

The investigational medicine(s) should be stored as specified by the sponsor (see points 5.13.2 and 5.14.3 of the CHMP GCP guideline) and handled in accordance with section 47 of the Medicines Act (Storage and delivery of medicines), and Part 5 (regulations 26-37) of the Medicines Regulations 1984.

Section 6: Records and Reporting

Section summary

This section describes the records and reporting requirements for clinical trials.

6.1 Preservation of records

The preservation of records is detailed in points 4.9.4, 4.9.5, 5.14.4 and 5.15 of the CHMP GCP guideline. Advice on standards for electronic records, retention and disposal should be sought from Archives New Zealand.

In New Zealand the following points must also be taken into consideration:

- The applicant / sponsor is responsible for ensuring that a complete set of study records and data relating to New Zealand trial participants is retained.
- The applicant/sponsor must ensure compliance with New Zealand privacy legislation (Privacy Act 1993) and the Health (Retention of Health Information) Regulations 1996.
- The trial records may be held by the principal investigator or transferred to another responsible person. The applicant/sponsor must hold information on the location of the records, the name of the person responsible for their retention, and the means by which prompt access can be assured.
- For all trials, the records may be stored overseas provided they are stored in accordance with New Zealand privacy legislation and Health (Retention of Health Information) regulations, and are maintained in an accessible form until they are disposed of in accordance with New Zealand law.
- The timeframes for retention of records will depend on the nature and duration of the trial. Records must be kept for a minimum of 10 years from date the study ends.

6.2 Reporting adverse events

Adverse reactions to **unapproved** medicines being used in clinical trials are to be reported to Medsafe.

The reporting requirements for adverse events of unapproved medicines used in clinical trials are detailed in points 4.11 and 5.17 of the CHMP GCP guideline.

The reporting requirements in New Zealand differ from those set out in the CHMP GCP guideline in that only expedited reports of serious adverse events occurring in New Zealand trial participants must be sent to Medsafe.

In line with the CHMP GCP guideline, the investigator should report adverse events (as detailed in the protocol) to the sponsor.

6.3 Reporting other adverse events

The sponsor is required to hold reports of all (worldwide) SUSARs (suspected unexpected serious adverse reactions, as defined in ICH guideline E2A). These reports should not be routinely sent to Medsafe, but must be held in an accessible form and made available to Medsafe on request.

The adverse event reporting requirements of the Health and Disability Ethics Committees are outlined in their standard operating procedures.

All serious adverse reactions to **approved** medicines used in clinical trials should be reported to the Centre for Adverse Reactions Monitoring (CARM). Sponsors should follow the process for reporting adverse reactions in the Guideline on the Regulation of Therapeutic Products in New Zealand, Part 8: Pharmacovigilance.

6.4 Expedited reporting of suspected unexpected serious adverse reactions (SUSARs)

The sponsor is required to report all fatal or life-threatening suspected unexpected serious adverse reactions (SUSARs) occurring in New Zealand trial participants where the treatment is known.

Adverse reactions occurring in a clinical trial's participants are considered to be unexpected if they are not outlined in the protocol and investigator's brochure, and are not defined study end-points.

Within 7 days of the sponsor receiving an investigator's report of a fatal or life-threatening SUSAR, the sponsor must send the report to Medsafe. Follow-up reports are required only if there is significant new information.

Medsafe does not require all other SUSARs that are not fatal or life-threatening to be reported within 15 days. These reports should not be routinely sent to Medsafe, but must be held in an accessible form and made available to Medsafe on request.

6.5 Notifying Medsafe of actions relating to an investigational medicine

Medsafe must be informed within 7 calendar days of the sponsor becoming aware, of any of the following actions, occurring in relation to an investigational medicine being used in a clinical trial in New Zealand:

- withdrawal from continued development
- withdrawal from the market in another jurisdiction, for any reason
- termination of an overseas study or a study in New Zealand due to serious or unexpected adverse events. The reasons for halting the study and the arrangements for halting the New Zealand arm of the study are required to be included in the report
- temporary halt for safety reasons to an overseas study also being conducted in New Zealand.

6.6 Study reporting requirements

6.6.1 Amendments to the trial

Once the clinical trial has been approved, any changes to the trial protocol must be submitted and approved before they can be implemented. These include protocol amendments and changes to trial sites and/or investigators.

Changes to essential trial documents such as investigator brochures (see the CHMP GCP guideline for other examples) should be notified, together with the submission of the changed documents. However, these do not require prior approval. The changed documents should be submitted as soon as is practicable.

It is the applicant/sponsor's responsibility to keep the approval letter details up-to-date with regard to changes to sites and investigators. Applicants are reminded that Customs may not release investigational medicines to unapproved sites, or to investigators if they are not mentioned on the approval letter.

6.6.2 Study progress reports

Section 30(7)(d)(ii) of the Act requires the sponsor to submit routine progress reports to Medsafe. Reports should be submitted online.

The first report should be sent to Medsafe not more than 6 months after the date of approval of the trial, whether or not recruitment of New Zealand trial participants has commenced.

Subsequent reports should be submitted at 6 monthly intervals throughout the duration of the trial in the New Zealand.

Medsafe should be informed when the New Zealand trial, or the New Zealand arm of a multinational trial, is completed. There is no need to continue submitting 6 monthly progress reports once the New Zealand arm has been completed, even if the trial continues elsewhere.

6.6.3 Final report

Section 30(7)(d)(iii) requires a final report to be sent to Medsafe on termination of the clinical trial.

Prior to the End of Trial report being available, Medsafe should be sent a 'Notification of Conclusion of the Study' using a Post Approval Form (PAF) in Online Forms https://nz.ethicsform.org. This allows Medsafe to be informed the study has ended in New Zealand yet may be ongoing globally.

At the global End of Trial, a synopsis of the final report should be sent to Medsafe when available, using a Post Approval Form (PAF) in Online Forms https://nz.ethicsform.org.

The full report should not be routinely sent to Medsafe, but must be held in an accessible form and made available to Medsafe on request.

The reporting requirements of the Health and Disability Ethics Committees are outlined in their standard operating procedures.

6.7 How to submit changes to clinical trials, adverse reaction reports and study reports to Medsafe

All reports and applications related to clinical trials should be submitted using the online clinical trial application system at:

https://nz.ethicsform.org/signin.aspx

If you experience difficulties you may submit by email in order to meet deadlines.

Email: clinicaltrials@moh.govt.nz

and put in the subject line: **Attention**: Clinical Trial Co-ordinator.

Appendix 1 - Essential documents to be submitted with a Clinical Trial application and to support changes proposed to be made to the trial

A1.1 Documents which must be included with the initial application

- CV for Co-ordinating investigator
- CVs for other Investigators
- GMP certification for manufacturer
- GMP certification for packer
- Signed Investigator consent form / Signed protocol
- Investigator's Brochure
- Signed Protocol
- Sample labels

Applicants may submit any other documents which they consider are pertinent to the trial.

A1.2 A minimum list of documents which should be submitted after approval

- Adverse Event Reports as per Medsafe's guideline (see *Sections* 6.2, 6.3, *and* 6.4)
- CVs for new investigators
- Signed Investigator consent form / Signed protocol for new investigators
- Protocol Amendments including Note to Files and Protocol Clarification Letters
- Protocol deviations where they result in the suspension of a trial
- Six monthly progress reports
- Updated GMP certification for manufacturer
- Updated GMP certification for packer
- Updated Investigator's Brochure
- Updated labels

Applicants may submit any other documents which they consider are pertinent to the trial.

A1.3 A minimum list of documents which should be submitted

after the trial has completed in New Zealand

- Notification that the trial sites in New Zealand have been closed out and the trial is completed in New Zealand
- Synopsis of final clinical study report when this is available

Applicants may submit any other documents which they consider are pertinent to the trial.