MEDSAFE

New Zealand Medicines and Medical Devices Safety Authority

Proposed updates to the Guidelines on the Regulation of Therapeutic Products in New Zealand: Clinical Trials

Consultation outcome

Contents

Executive Summary

From August to November 2024 Medsafe consulted on proposed updates to the GRTPNZ Part 11: Clinical trials – Regulatory Approval and Good Clinical Practice requirements, Edition 2.0, November 2018.

We also consulted on two new secondary guidance documents (Considerations for First-in-Human [FIH] and Early Phase Clinical Trials and Clinical Trial Safety Monitoring and Reporting).

We received 23 submissions. This document provides an overview of the responses and comments received, and Medsafe's response to the points raised.

Background information

Medsafe is the New Zealand Medicines and Medical Devices Safety Authority and is responsible for the regulation of therapeutic products in New Zealand by administering the Medicines Act 1981 and Medicines Regulations 1984.

The requirements under the legislation are further outlined through the Guidelines on the Regulation of Therapeutic Products in New Zealand (GRTPNZ).

Consultation results

Thank you to everyone who responded to the consultation.

We have analysed and summarised the results below, in the order the questions were asked in the consultation.[1]

The results are divided into parts as follows:

- Overview of respondents
- Summary of responses for GRTPNZ: Clinical trials – Regulatory Approval and Good Clinical Practice Requirements (GRTPNZ: Clinical Trials)
    - Definitions
    - Section 1: Legislation
    - Section 2: Overview of the Regulation of Clinical Trials in New Zealand
    - Section 3: Application for Approval of a Clinical Trial Under Section 30 of the Medicines Act
    - Section 4: Notification of Clinical Trial Sites
    - Section 5: Good Clinical Practice Requirements
    - Section 6: Records and Reporting
    - Section 7: Medical Device Trials
    - Section 8: Further comments
- Summary of responses for secondary GRTPNZ documents
    - Section 9: Considerations for First-in-Human (FIH) and Early Phase Clinical Trials
    - Section 10: Clinical Trial Safety Monitoring and Reporting.

The number of participants who agreed or disagreed with proposed changes are shown for each question (where relevant), along with the number of respondents who provided comments. Where possible, the comments have been summarised into common themes rather than listing each individual comment. For brevity, where comments have already been addressed in earlier questions they are generally not repeated. Minor editorial suggestions are not included in this document.

[1] Questions 1-7 included mainly administrative information and are not discussed in detail in this document.

Overview of respondents

We received 23 submissions via the consultation tool. Information about the respondents are summarised below.

You can view the submissions that we have the permission to publish.

Respondent type	Total	Percent
As an individual	2	9%
On behalf of an organisation or group	21	91%
Not Answered	0	0%

Country	Total	Percent
New Zealand	13	56%
Australia	8	35%
Other	2	9%
Not Answered	0	0%

Respondent sector	Total	Percent
Member of the public/Participant in a clinical trial	0	0%
Clinical trial sponsor	10	43%
Clinical trial investigator	1	4%
Other clinical trial staff	2	9%
Healthcare professional	0	0%
Institution (eg, university, hospital)	0	0%
Industry organisation	5	22%
Manufacturer	2	9%
Supplier	0	0%
Importer	0	0%
Government	1	4%
Professional body	0	0%
Consumer organisation	0	0%
Regulatory affairs consultant	0	0%
Other	2	9%
Not Answered	0	0%

GRTPNZ: Clinical Trials

Definitions

Question 8: Do you have any comments on the proposed definitions?

11 respondents provided comments.

In general, the feedback supported the inclusion of definitions in the guideline. However, respondents pointed out inconsistencies between some definitions in the main guideline compared with definitions in the secondary documents.

Several respondents recommended adoption of definitions from the latest version of the ICH Guideline for Good Clinical Practice, ICH E6(R3). There were also comments to align with/include internationally accepted terminology and acronyms.

Some of the comments relating to specific definitions included:

- The definitions of 'signal' and 'significant safety issue' (SSI) are different to those in the GRTPNZ: Pharmacovigilance.
- The definitions of 'applicant' and 'sponsor' are not clear. Respondents commented that the two terms are not synonymous and also pointed out inconsistencies with the definitions in the Medicines Act 1981.
- The term 'subject' is no longer widely used in the clinical trial industry ('participant' recommended).
- Further clarity required for some definitions (eg, bioequivalence, biosimilar, contract).

Medsafe response:

Shortly after the consultation response period closed ICH E6(R3) was adopted (6 January 2025). Where possible Medsafe has updated all the definitions in the New Zealand guidelines to align with the ICH E6(R3) definitions.

Medsafe notes the comment around inconsistency of definitions in the secondary documents, therefore definitions have been removed from the secondary documents.

The definition of applicant has been updated to fully align with the definition in section 30(2) of the Medicines Act. The definition for sponsor is consistent with ICH E6(R3) definition. A separate definition for 'sponsor-investigator' has been added. We acknowledge that applicant and sponsor are not necessarily synonymous and the guideline has been updated. Note the guideline now refers to 'trial sponsor' to avoid confusion with sponsors for approved medicines (ie, marketing authorisation holders) who are referred to in other Medsafe guidelines.

A safety signal in a clinical trial setting differs to that in a post-market setting (which is covered in GRTPNZ: Pharmacovigilance). The definition of safety signal used in this guideline is taken from the ICH E2F DSUR guideline. The definition of significant safety issue used here is aligned with the Australian NHMRC guideline on safety monitoring and reporting in clinical trials involving therapeutic goods. No changes have been made to these definitions.

We agree that the terms 'trial subject' and 'contract' are outdated and have replaced them with 'participant/trial participant' and 'agreement' respectively, as per ICH E6(R3). The definition of bioequivalence has been amended to align with the GRTPNZ: Bioequivalence.

The definition of biosimilar has been amended to clarify that in this context the reference product does not necessarily need to be approved in New Zealand.

1. Legislation

Question 9: Is there additional legislation or guidance materials that are relevant and should be added?

7 respondents provided comments.

Additional legislation and/or guidance materials suggested were:

- European guidance on GCP for Advanced Therapy Medicinal Products (ATMPs)
- EMA ICH E2E Pharmacovigilance planning scientific guideline
- ICH E6(R3), to replace ICH E6(R2)
- Misuse of Drugs Act Section 2A Cannabis
- Guideline on the Regulation of Medicinal Cannabis in New Zealand
- Human Tissue Act 2008
- HDEC application template and guides
- SCOTT and GTAC terms of reference
- UK MHRA Good Clinical Practice (GCP) Guide 2023

One respondent recommended that references to original source documents should be used (eg, ICH document instead of the EMA adoption of ICH).

Medsafe's response:

The guideline now generally references ICH guidelines directly (ie, ICH E6(R3), ICH E2F and ICH E2A), rather than the EMA adoptions. In the event that further guidance or interpretation is required, we recommend EMA guidelines are used. The UK GCP guide has not been included to avoid potential conflicts from referencing multiple different sources.

We have included links to:

- Human Tissues Act
- Medical Cannabis Scheme guidelines
- European Commission guidelines on GCP specific to ATMPs
- HRC committees webpage.

As with all guidelines, where there are conflicts with New Zealand law, the New Zealand law takes precedence.

Note, the Medicinal Cannabis Scheme guidelines provide further information about the interpretation of legislation relating to medicinal cannabis (eg, section 2A and other relevant sections of the Misuse of Drugs Act). Additionally, as this guideline is not intended to provide a comprehensive overview of the ethics application process, we consider that additional links to HDEC application templates and guides are not needed. The EMA ICH E2A pharmacovigilance planning guideline has not been added, as information on safety monitoring and reporting has now largely been moved to the secondary guideline, which includes relevant links.

Question 10: Is there legislation or guidance materials that are not relevant and should be removed?

4 respondents provided comments.

Respondents recommended removing the MHRA/Health Canada's Guidance on how to increase transparency when presenting safety information in the DSUR: region-specific requirements for Canada and the UK.

Medsafe response:

We have removed reference to the MHRA/Health Canada guidance document.

2. Overview of the Regulation of Clinical Trials in New Zealand

Question 11: Do you agree with the updated definition of clinical trials?

Option	Total	Percent
Yes	12	52.17%
No	8	34.78%
Not Answered	3	13.04%

11 respondents provided comments.

Some respondents recommended alternate wording for the definition of clinical trial, including aligning with the definition in the ICH GCP guidelines. Several respondents requested further clarity on the points relating to observational trials or recommended removing these points.

Medsafe's response:

We have replaced the proposed definition with the ICH E6(R3) definition for clinical trial. Further clarification regarding the requirements for observational trials has been added to Table 4 of the guideline.

Question 12: Do you have any other comments on this section (section 2)?

11 respondents provided comments.

Respondents commented that not all trials require HDEC approval, therefore the statement that all trials must comply with HDEC requirements may not be correct. One respondent also commented that GCP requirements are not applicable to observational trials.

It was noted that for some clinical trials additional licenses and/or approval are required from different branches of Medsafe (for example Medicines Control or the Medicinal Cannabis Agency). It was suggested that applications to those agencies could proceed in parallel and these agencies provide guidance on timeframes for approval. In particular, concerns were raised that trials requiring a medicinal cannabis license may add at least another 60 days to the study start date. Further clarification on when additional approvals or licenses were required was also requested.

Respondents also requested clarification on the following.

- The roles and responsibilities of Medsafe and HRC in the approval process.
- Where allogenic vaccines, ATMPs and human cell therapy sits in relation to this guidance.
- The definition and requirements for rescue medicines.
- The requirements for unapproved comparator products (eg, what evidence of product quality needs to be provided if the product is manufactured by a different sponsor).
- The requirements where approved medicines are being used in addition to unapproved medicines (eg, what information about the approved medicine need to be included in the application).
- Whether editorial amendments to the protocol require approval.

Medsafe response:

As stated in section 2.6, all clinical trials must comply with HDEC requirements.This is not the same as a trial requiring HDEC approval. However, intervention studies (with few exceptions) will almost always require HDEC approval. It is expected that all studies requiring approval under section 30 will require HDEC approval, and trials must not start until ethics approval has been granted.

We note that ICH E6(R3) guidelines are specific to intervention trials. As this guideline primarily addresses these types of trials, we have not changed the wording.

This guideline is not about cannabis regulation or the operations of other Medsafe branches/agencies, and is not intended to provide a comprehensive overview of all New Zealand legislative requirements. Therefore additional information on the roles and responsibilities of different agencies has not been added. The guideline highlights that additional licensing or approvals may be required in some cases and refer the reader to the appropriate places should they need further information. If an applicant is not sure if additional approvals or licensing are required they should contact the relevant branch/agency for advice, as recommended in the guideline.

HRC conducts the scientific review of clinical trial applications and provides a recommendation to the Director-General of Health (the DG) on whether to approve the trial. The authority of the DG under section 30 of the Medicines Act has been delegated to Medsafe. Medsafe also does some of the administrative processing of clinical trial applications and issues outcome letters. This is described in section 3 of the guideline.

Allogenic vaccines, ATMPs and human cell therapy are considered to be medicines under the definition in the Medicines Act, therefore approval is required for these trials. The definition of investigational product has also been updated to align with ICH E6 (R3), which specifies that investigational products should be considered synonymous with drugs, medicines, medicinal products, vaccines and biological products.

With regard to 'rescue medicines', this section of Table 5 has been updated to clarify that the requirement for clinical trial approval applies if unapproved medicines are specified in the treatment protocol including as a comparator medicine or rescue medicine. This allows these medicines to be imported under the trial approval letter. A definition for rescue medicine has been added to the Definitions section of the guideline.

It is expected that the trial protocol will include information on standard treatment of care (concomitant medicines, supportive care, background therapy) including approved medicines. Additional information on approved medicines is not required in the clinical trial

application. For unapproved comparator/supportive products and placebos, evidence of product quality must be provided. Where the product is approved in another country, evidence of approval from a trusted regulator may be sufficient.

Protocol amendments have been removed from Table 5 of the guideline as they are addressed later in the guideline. Comments relating to protocol amendments are discussed in Question 23 of this document.

3. Application for Approval of a Clinical Trial Under Section 30 of the Medicines Act

Question 13: Do you agree with the updated criteria for fee waiver?

Option	Total	Percent
Yes	14	61%
No	3	13%
Not Answered	6	26%

6 respondents provided comments.

Comments were received on whether 'all' or at least one of the criteria listed in Table 6 must be fulfilled in order to be eligible for the fee waiver and that fulfilment of all criteria is very restrictive. It was also noted that Australasian-led group trials are being rolled out in multiple countries. The fee waiver criteria may increase barriers for New Zealand to participate in international collaborations.

There was a request for clarity on definitions of non-commercial trials, equity issues, unmet clinical need, and Australasia.

Medsafe response:

As stated in section 3.5.1, the trial must meet all of the criteria in Table 6 to be considered for a fee waiver. This has been further clarified in the table. The fee waiver is intended only to support innovative research which is likely to be of particular benefit to the New Zealand population, where funding may be limited. Not all academic research is expected to meet the criteria. Medsafe and HRC committees are funded solely through fees and do not receive any government funding for clinical trials regulation.

In response to the comments, we have removed the term non-commercial trial from this section of the guideline and have changed Australasia to Australia and New Zealand. It is up to the applicant to justify how their trial may benefit public health in New Zealand, and the bullet points in the first row of the table are provided as examples only.

No other changes to the criteria have been made.

Question 14: Do you have any other comments on this section (section 3)?

8 respondents provided comments, including the following.

- A request for clarification on whether the administrative processing of application refers to business or calendar days.
- Concerns that a change in the preferred route of communication (Ethics RM rather than email) may result in slow response times, noting that direct email contact with Medsafe has be advantageous.
- That trial medicines may be received and stored off-site rather than at the clinical trial site, noting that approval letters do not always include the delivery site address and whether system updates may be able to address this.
- A request to ensure that the standing committee recommendations are consistent with those outlined in the terms of reference.
- A request for clarification on the definition and responsibilities of the applicant, sponsor and importer.

Further comments were made on current application fees, the Ethics RM application form, public notification of trial approvals, and feedback from committees on how submissions could be improved.

Medsafe response:

All administrative time frames in the guideline have been updated to working days (see 'Medsafe Updates' below for more information on relevant legislative changes).

The information on communications channels has been updated where applicable to ensure prompt communication when required.

Medsafe notes that the delivery site address for the trial medicine is not always the same as the clinical trial site. In order for investigational products to pass border controls it is essential that the trial approval letter contains the correct investigators and trial sites including the delivery address if different to the main trial sites. It is the applicant's responsibility to check that the correct delivery sites are included in the approval letter and should contact Medsafe if this is not the case. No change to this requirement has been made, however text relating to delivery site addresses has been moved to section 5.3.4 of the guideline (distribution and supply of investigational product).

The section discussing recommendations of the standing committees has been simplified for clarity.

Comments on the definitions and roles of applicants, sponsors, and importers are addressed in Question 16 of this document. To avoid conflicts between different sections of the guideline, information relating to definitions of these roles has been removed from section 3 of the guideline and is outlined in section 5.

Clinical trial application fees were not consulted on and can only be changed through a fee consultation process. Feedback on the application form will be taken into consideration when the form is next updated. The requests for feedback on applications and publication of trials approved under section 30 are also noted.

4. Notification of Clinical Trial Sites

There were no questions in the consultation on this section of the guidelines. However, some comments were received which are relevant to section 4. These are addressed in Question 26 of this document.

5. Good Clinical Practice Requirements

Question 15: Do you agree with the recommendation for patient-centric clinical trial design and conduct?

Option	Total	Percent
Yes	17	74%
No	1	4%
Not Answered	5	22%

12 respondents provided comments.

In general, respondents agreed with the principles of patient-centric clinical trial design. It was noted this was already a requirement of GCP. However, there were concerns about this being a mandatory requirement for the clinical trial application.

There was a request for additional guidance on the documentation required, whether documentation is needed with the initial application, and whether patient input is required from New Zealand patients or if engagement with patients from other jurisdictions is acceptable.

Other comments included the following.

- This requirement is less relevant for some trials (eg, first in human and bioequivalence studies).
- This requirement is more relevant to clinical trial sponsors at the design phase of a clinical development programme and less relevant to the regulatory submission.
- No link to the New Zealand Health Strategy is included.

Medsafe response:

We note the inclusion of the patient perspective in the design of clinical trials is in line with GCP, as outlined in ICH E6(R3). However, we confirm that while patient and stakeholder engagement is desirable, it is not a mandatory requirement. The guideline has been updated to make this clear. This is an aspirational goal that we wish to encourage clinical trial applicants/sponsors in New Zealand to move towards, where feasible. At this stage there is no need to provide additional documentation with the clinical trial application.

The New Zealand Health Strategy is published on the Ministry of Health website. As this covers the health system more broadly, it is not included in the guideline. However, this patient-centric recommendation aligns with Priority 1, "Voice at the heart of the system".

Question 16: Do you agree with the way the applicant, sponsor, investigator and monitor have been defined?

Option	Total	Percent
Yes	14	61%
No	4	17%
Not Answered	5	22%

7 respondents provided comments.

It was highlighted that several of the terms in the definitions described at the beginning of the guideline differ from the definitions described in section 5.2.

Clarity was requested on the roles and definitions of investigators, applicant, sponsor and importer. Additionally, in the proposed guideline the terms sponsor and applicant were used interchangeably, however some respondents pointed out that these terms are not synonymous.

Respondents also commented on limitations of the outdated legislation, including ambiguities that are created because of differences in terminology between the Medicines Act and international GCP guidelines. There were concerns that the definition of applicant does not accurately reflect modern research practices. Examples include the following.

- A contract research organisation (CRO) running a trial on behalf of an overseas pharmaceutical company, taking on the role of applicant and acting as a 'local sponsor'.
- A New Zealand co-ordinating investigator or co-ordinating centre involved in an international, non-commercial, academic/investigator-led research collaboration, taking on the role of applicant and acting as a 'local sponsor'.
- An applicant may wish to appoint an importer to import the investigational products on their behalf, but the importer would not have any further involvement in the trial.

Respondents also requested more information on the applicant's ability to delegate responsibilities and questioned whether the applicant must be based in New Zealand.

Medsafe response:

The comments about conflicting definitions are noted, in particular regarding the applicant (as defined in the Medicines Act) and the sponsor (as defined by ICH). Therefore, this section of the guideline has been amended to more clearly outline legal roles and requirements as defined in the Medicines Act. We acknowledge the terminology in the legislation does not neatly align with international GCP guidelines.

Additional reference to Section 2 of the Act has been included in section 1.1 of the guideline for the definitions of 'importer', 'manufacture', 'pack', and 'sell'. Other definitions (such as investigator) have been aligned with ICH E6(R3) where possible.

We have also provided more clarity on who the applicant can be as well as guidance on delegation of activities. In accordance with Section 30(2) of the Act, the application must be made by the importer, manufacturer, or packer, or the intending manufacturer, packer, seller, or supplier of the medicine, in New Zealand (referred to as the applicant). Note that 'importer' includes not only the person importing goods, but also the person for whom and goods are imported. 'In New Zealand' means the applicant may be either an individual

resident in New Zealand or a New Zealand-registered company. Activities may be delegated, but the overall responsibility for activities specified in the Act remain with the applicant.

Question 17: Do you agree with the updated requirements for labelling, supplying, and distributing investigational products?

Option	Total	Percent
Yes	11	48%
No	8	35%
Not Answered	4	17%

12 respondents provided comments.

Several respondents commented that the labelling requirements in Section 30 of the Medicines Act are not aligned with Annex 13 of the PICs GMP guideline and the requirements in other countries. In particular, the requirement for the following words to be included on the label: "To be used by qualified investigators only". Respondents commented that this was potential barrier to clinical trials being conducted in New Zealand. Respondents requested words of a similar meaning to be allowed (eg, for clinical trial use only) which was included in previous versions of the guideline.

Regarding the requirement to include information on procedures addressing the use of the IP in the trial protocol (or other relevant documents), a respondent noted that the protocol and investigators brochure contain only high level information on handling, storage, dispensing and administration of the IP and detailed information in the pharmacy manual may not be available at the time of the initial clinical trial application. They questioned if this level of detail was necessary for a clinical trial application. There was also a comment that delegation is not required for some activities (eg, disposal of an IP).

It was also noted that many sites used for vaccine studies (or products requiring cold storage) are already cold chain accredited or have a robust cold chain policies. The conditions of the storage and management of IPs are defined by the sponsor/manufacturer, and it would be more appropriate that sites conform to the appropriate study specific requirements set by the sponsor rather than the national standards which are more targeted towards immunisation providers.

Respondents queried whether a Product Specification File is required for products manufactured overseas or only products manufactured in New Zealand. It was also noted that ATMPs may have differing specifications based on the individual product, and a recommendation was made to follow EMA guidance which allows for out of specification release where the patient may come to significant harm if the treatment is not received.

Other comments included the following.

- A request for clarification on the level of detail and type of documentation required to be provided in the clinical trial application on the quality of the IP (eg, is information in the Investigator's Brochure sufficient, or is something like an Investigational Medicine Product Dossier [IMPD] expected).
- A recommendation to change the maximum period of supply for controlled drugs from 1 month to 30 days.

- A request for clarification about whether "Keep out of reach of children" should be included as per PIC/S GMP Guide Annex 13, except when the product is for use in trials where the product is not taken home by the participant.
- A request for clarification on the definition of repacking, including whether trial sites are able to dispense and pack from bulk IP without a licence or if this considered repacking.
- Disagreement with adoption of the entire Part 5 of the Medicines Regulations 1984 for clinical trials, such as section 35(4). There was also a request for clarity on who is responsible for ensuring the regulations are met (eg, if it is the sponsor's responsibility).

Medsafe response:

We note the significant comments received during this consultation regarding the Medicines Act requirement for "To be used by qualified investigators only" to be included on the label. The guideline has been updated as a result of these comments. Proposed labels should continue to be submitted for review as part of the clinical trial application.

In response to the comments received on the handling, storage, dispensing and administration of the IP, we have removed the paragraph that recommended procedure documents be submitted as part of the clinical trial application. The statement about delegation has also been removed. We also acknowledge that the manufacturer/sponsor will have specific storage requirements and cold chain procedures for their IPs. The requirement to follow the National Standards for Vaccine Storage and Transport has been removed. Information over and above that typically included in the Investigator's Brochure and/or trial protocol is not required to be routinely provided as part of the clinical trial application.

Manufacturers of IPs in New Zealand are required to hold the usual manufacturing documentation, as outlined in the NZ Code of GMP. We recognise that ATMPs may have unique requirements and recommend contacting Medsafe if specific advice is required (GMP@health.govt.nz). Medsafe is unable to comment on overseas regulatory requirements for manufacturers outside of New Zealand.

Sufficient information is required to demonstrate that the IP is of acceptable quality to give to participants. The required information is detailed in the application form and includes information on the chemical and pharmaceutical properties, formulation, stability and shelf life, storage recommendations and evidence the product meets the required specifications. The applicant may identify the location of this information in the Investigator's Brochure or protocol, or supplementary documentation may be provided. An IMPD is not specifically required if the relevant information is available elsewhere. Evidence of GMP certification should be provided. As noted in the question 12 response, evidence of product quality should also be provided for unapproved comparator/supportive products. Where the product is approved in another country, evidence of approval from a trusted regulator may be sufficient.

As per the Misuse of Drugs Act 1975, the maximum period of supply is reported in months not days. No change to this timeframe has been made.

Repacking includes any act of taking a medicine out of its original container or packaging and enclosing it in a new container or packaging. Dispensing and packing from bulk IP will generally require a licence, as outlined in section 17 of the Medicines Act.

Part 5 of the Medicines Regulations is included in the current guidelines and has not been changed in this update. The regulations outline measures to ensure medicines are stored and

handled in sanitary conditions and protected from contamination. Therefore they are considered relevant to clinical trials and no changes are planned. For further interpretation refer to GRTPNZ: New Medicine Applications (eg, quality control of packaging materials). The responsibility for ensuring the requirements of the regulations are met lie with the person(s) involved in carrying out specific activities. Refer to the regulations for more information.

Question 18: Do you have any other comments on this section (section 5)?

9 respondents provided comments.

There was a query as to whether GMP is an absolute requirement for investigational products, noting this may be difficult for FIH Phase 1 studies and limit the development of products in New Zealand. The respondent stated that Annex 13 says that products should be manufactured in accordance with the principles of GMP, but not that the product is fully certified as GMP. They recommended aligning with Australia, where GMP-like products can be used for Phase 1 trials.

One respondent suggested adding that investigational medicines should be stored, handling and shipped in strict adherence to sponsor requirement. Recommendations for changes to the information to be included on labels were also made.

Comments already addressed in previous questions are not repeated here. Comments on site accreditation are addressed in Question 26.

Medsafe response:

The law requires that IPs manufactured in New Zealand require a manufacturing licence regardless of the phase of a trial. Compliance with the NZ code of GMP (the Code) is a requirement for licensing. Annex 13 of the Code considers differences between IPs and medicines with marketing authorisation and these differences are considered when issuing manufacturing licences. We recommend contacting Medsafe early in the development process for advice on GMP certification (GMP@health.govt.nz).

IPs manufactured overseas should comply with the regulatory requirements and guidance of the country of manufacture. We expect IPs manufactured overseas to be manufactured to a high standard consistent with GMP and appropriate evidence of this (eg, GMP certification) should be provided with the clinical trial application.

Wording relating to storage, handling and shipping of investigational products has been added as suggested. To avoid confusion from conflicting information, Medsafe has removed Table 8 (information that should be included on labels) and referred the reader directly to Annex 13 for these requirements.

6. Records and Reporting

Question 19: Do you agree with waiving the requirement for reporting suspected unexpected serious adverse reactions (SUSARs) for sponsors with a pharmacovigilance system

Option	Total	Percent
Yes	16	70%
No	3	13%
Not Answered	4	17%

10 respondents provided comments.

Respondents were generally supportive of removing the requirement for SUSARs reporting for sponsors with a pharmacovigilance system. However, further guidance on the type and level of detail required about the pharmacovigilance system in the trial initial application was requested. The following were also suggested.

- Medsafe provides a template or form for the pharmacovigilance system information.
- Details of a pharmacovigilance system could be submitted to Medsafe separately (ie, following the initial application), as they may not be available at the time of submission.
- The pharmacovigilance system could be considered at the sponsor/applicant level rather than the study level to help streamline the process and avoid duplication.
- Whether this waiver will apply to trials that are already in progress at the time the guideline comes into effect.
- Pharmacovigilance systems accepted by Medsafe should conform to international guidelines such as the ICH Guideline of Pharmacovigilance Planning and this expectation should be clearly stated in the guideline.
- The waiver of SUSAR reporting should not occur unless Medsafe can confirm the pharmacovigilance system is adequate/fit for purpose. There was concern that the current proposal has limited information and could allow for inadequate systems to be adopted leading to risks with SUSAR management and reporting.

One respondent noted that the main topic of interest may be with international trials, as SUSARs will likely not be dominated by events occurring in New Zealand. There was also a request for clarity on who will review the submitted information on pharmacovigilance systems.

Comments on reporting timelines and records are addressed in question 21 and 24, respectively.

Medsafe response:

Regarding the requirements of a pharmacovigilance system, Medsafe expects that a high functioning pharmacovigilance systems would meet ICH GVP practices. Medsafe has provided additional guidance (Box 1) on the expectations of a pharmacovigilance system. Additionally, we have specified that this applies only where the sponsor holds all relevant safety information (ie, worldwide) for the investigational product, as these sponsors will be best placed to perform an analysis of these reports.

We agree with the recommendation to avoid duplication in notification of the pharmacovigilance system. We propose that details of the pharmacovigilance system are notified to Medsafe once (unless there are major changes). However, Medsafe should still be notified about every new trial which will be covered by the system where the applicant or sponsor intends not to submit expedited reports for SUSARs. The guideline has been updated. We consider it appropriate for Medsafe to review the information provided on pharmacovigilance systems (rather than the HRC committee) as Medsafe has an established pharmacovigilance team.

The guideline has been updated with information on how to notify Medsafe via email (separate to the SCOTT application). This would also apply to trials that are already in progress.

At this stage, we do not plan to produce a template for submission of the pharmacovigilance system information. However applicants should provide an overview or executive summary that describes how the system meets the requirements outlined in the guideline.

Note, due to comments received noting duplication of information of safety information in the main guideline and the secondary document 'Clinical trial Safety Monitoring and Reporting for Investigational Products' (see question 32), these sections of the main guideline have been significantly condensed. The secondary document is now the primary source of information on safety monitoring and reporting.

Question 20: Do you agree with the updated list of reportable actions/issues?

Option	Total	Percent
Yes	18	79%
No	1	4%
Not Answered	4	17%

5 respondents provided comments.

While most respondents agreed with the updated list of reportable actions/issues, there were several suggestions or requests for clarification about serious breaches, including the following.

- A request for clarification about the types of serious breaches that require notification, who reports serious breaches, and how serious breaches are reported.
- Whether serious breaches refer to findings in New Zealand only or globally and if site and sponsor findings are included.
- Recommendation to include the definition of serious breach in the guideline
- Recommendation to remove 'major audit findings' from the list of examples of serious breaches.
- Recommendation to only require serious breaches relating to the investigational product to be reported.

Other comments included the following.

- If withdrawal of an IP from development for specific indications or all indications should be reported.
- A recommendation to include 'premature discontinuation of the clinical trial for any reason' as a reportable action/issue.

Comments about the definition of significant safety issue (SSI) have been addressed in question 8.

Medsafe response:

The definition of serious breach has been included in the main document under definitions. The guideline now includes a link to the EMA guidelines for the notification of serious breaches, which includes examples of the types of breaches that should be reported to Medsafe. The list of examples (including major audit findings) has been removed from the guideline as readers should refer directly to the EMA document.

We do not agree with the recommendation that only serious breaches relating to the IP should be reportable to Medsafe. Any breaches that could have a serious impact on the trial participants or impact the benefit-risk balance of the trial should be reported.

Serious breaches occurring at New Zealand trial sites should be reported. However, if a serious breach occurs overseas that could impact the New Zealand trial or New Zealand participants, this should also be reported.

The guideline has been updated to include reporting method (via email or Ethics RM). The sponsor has the primary responsibility for monitoring and reporting of serious breaches (or the local sponsor or applicant in New Zealand). However, anyone that has a concern about a trial or suspects a serious breach (eg, investigators or other third party) can report it to Medsafe via email (askmedsafe@health.govt.nz).

Withdrawal of the investigational product from continued development for any reason that may be relevant to the indication under investigation should be notified.

Applicants are already required to notify Medsafe when a trial ends (refer to section 6.6 of the updated guideline), including if it ends prematurely. Therefore, this has not been included in this section of the guideline. If the trial ends early due to a safety concern, we expect this to be captured in the existing reporting requirements for SSIs/USMs.

Question 21: Do you agree with the updated reporting timelines?

Option	Total	Percent
Yes	18	79%
No	1	4%
Not Answered	4	17%

5 respondents provided comments.

Clarification was requested on whether, for global sponsors, the reporting timelines start from the awareness date of the local sponsor or applicant. Respondents queried if notification timelines start from the date at which the sponsor is first made aware of an issue or at the point when the issue is formally designated/assessed by the sponsor.

There was a request for the inclusion of SSI examples or to link to secondary documents.

Medsafe response:

The reporting timelines for SSIs and other reportable issues is from the date of the local sponsor or applicant first being made aware of the issue (ie, the date of first awareness). Note, reporting timeframes are given in calendar days.

Reporting of SSIs/USMs has moved from this guideline to the safety monitoring secondary document in response to comments about duplication. Examples are included in the secondary document.

Comments on annual safety reporting are addressed in question 22.

Question 22: Do you agree with the requirements for periodic safety reporting/development safety update reports (DSURs)?

Option	Total	Percent
Yes	19	83%
No	0	0%
Not Answered	4	17%

5 respondents provided comments.

Respondents generally agreed with the requirements for period safety reporting/DSURs. Clarification was requested on the preparation/submission of progress reports versus annual safety reports (eg, whether 6-monthly progress reports and annual safety reports are submitted as one document or independently of each other, whether the DSUR can be used for the 6-monthly progress report).

There was a comment that the submission of DSURs would streamline the study progress reporting.

Other comments included the following.

- A recommendation that the DSUR Executive Summary be provided rather than the full report.
- A suggestion for annual safety reports to align with the TGA clinical trials guideline.
- Clarification requested on how to submit annual safety reports.

Medsafe response:

The comment on aligning with annual reports as per the TGA clinical trials guideline is noted. The guideline proposes annual safety reporting, however the requirement for 6-monthly progress reporting cannot be changed (without a change to the legislation) as this is a requirement specified in Medicines Act. However, we have clarified in the guideline that the annual safety report/DSUR may serve as one of the 6-monthly progress reports to streamline this process as much as possible. A standard progress report will still need to be submitted for the other 6 month report.

The guideline has been updated to specify that the DSUR executive summary may be submitted, rather than the full DSUR. However, the full DSUR should be made available if requested.

Progress reports and annual safety reports should be submitted through Ethics RM.

Question 23: Do you agree with the requirements for notifying trial protocol amendments or other changes to a trial?

Option	Total	Percent
Yes	15	65%
No	3	13%
Not Answered	5	22%

7 respondents provided comments.

Clarification was requested regarding the type of protocol changes that require submission/approval. The following comments were made.

- Small administrative changes should be sent as a notification and should not require approval.
- Request to align with HDEC requirements.
- Request for confirmation that urgent safety measures can be implemented immediately prior to approval.
- Request for clarification on types of investigator changes that require submission/approval (eg, only coordinating and/or principal investigators or are sub-investigator changes also in scope).

There was also request for clarification on whether acknowledgement of the notification of updates to the Investigator's Brochure (IB) must take place before implementation, or if it can be implemented as soon as it is released by the sponsor.

The paragraph about naming of specific key persons/delegation logs (section 6.4.1, 3rd paragraph) was considered redundant, as this information is decided at a site level rather than in the trial protocol.

One respondent requested information on the review process for amendments, and suggested a scope of review for amendments requiring HRC committee review versus Medsafe review be included.

Medsafe response:

The guideline has been updated to clarify that only substantial amendments to the trial protocol should be submitted for approval. The definition for substantial amendment aligns with the HDEC definition. Examples of substantial amendments have been included in the guideline, but note this is not an exhaustive list.

We confirm urgent safety measures can be implemented prior to approval. However, they must be reported to Medsafe as soon as possible, and no later than seven calendar days after taking such measures, as outlined in the secondary document on safety monitoring and reporting.

All coordinating investigators and principal investigators (referred to in the guideline as investigators) require approval. This does not apply to sub-investigators.

Approval does not need to be sought prior to implementing minor changes to the IB. However, changes to the IB that are related to a substantial protocol amendment should be submitted as part of the substantial amendment.

The paragraph on delegation logs (section 6.4.1, 3rd paragraph) has been removed from the updated guideline.

Protocol amendments are reviewed by Medsafe medical advisors. However, the submission process is via Ethics RM (using the 'SCOTT PAF' form).

Question 24: Do you have any other comments on this section (section 6)?

11 respondents provided comments.

Comments/questions that have not already been addressed in previous questions include the following.

- For paediatric studies, the data requirements may vary and information pertaining to these studies can be found in the NEAC guideline.
- Who is the responsible person for record keeping?
- The mechanisms for submitting individual case safety reports (ICSRs) (request for further option to receive CIOMs reports via email or using other technologies such as E2B).
- Requirements for reporting of SUSARs for placebos.
- Requirements for reporting SUSARs for approved medicines used in clinical trials (eg, concomitant medicines)
- Medsafe's process for requesting SUSARs, for those that do not need to be routinely submitted.
- Request to add that there is no requirement for investigators to print, review and file SUSARs/DSURs once the sponsor confirms the report has no bearing on participant safety or trial conduct.
- Whether Medsafe should be notified if there is a change in the global sponsor of a trial?

Medsafe response:

A reference to the NEAC standards is already included in section 1.2 of the guideline. Section 6.1 focuses on the legislative requirements and no changes have been made.

While the trial sponsor is generally considered responsible for the overall management of trial data, all trial staff have a professional responsibility to ensure record keeping meets required standards. For example, trial staff involved in collecting study data are responsible for ensuring information is accurately recorded and appropriately stored.

The secondary safety guideline has been updated to provide more options for reported ICSRs. These align with the reporting methods in GRTPNZ: Pharmacovigilance. We confirm that for adverse events associated with approved medicines that are used during a trial (eg, concomitant medicines, rescue medicines), these should be reported as outlined in the GRTPNZ: Pharmacovigilance. Adverse events associated with placebos are not generally expected to meet the criteria for reporting to Medsafe (ie, due to relatedness). However, there are limited circumstances when reporting may appropriate (eg, for a SUSAR arising from a quality issue). The secondary document on safety monitoring and reporting has been updated.

In the situation where Medsafe requests further information on a trial (including information on SUSARs), Medsafe will contact the individual named as the contact person supplied in the application form. Where there is a change to the contact person for the trial in New Zealand, Medsafe should be notified of this change.

The current guideline does not specify any requirement for investigators to print, review and file SUSARs/DSURs. As this is not changing, no updates have been made to the guideline. Sponsors are expected to have their own policies for managing these internal processes.

Medsafe should be notified if there is a change in the global sponsor, as this many impact the ongoing conduct of the trial in New Zealand.

7. Medical Device Trials

Question 25: Do you agree with the inclusion of this new section?

Option	Total	Percent
Yes	19	83%
No	0	0%
Not Answered	4	17%

7 respondents provided comments.

Respondents were generally in agreement with the addition of the new section on medical device trials. However, respondents asked for clarity on the definition of a medical devices to avoid confusion. Additionally, use of the phrase 'clinical trials involving medical devices' in the guideline was considered unclear. Respondents queried the following.

- Are tubes, kits and other equipment such as wearables and data collection tools are considered to be devices that should be notified, if they are being used in clinical trials?
- Are trials of medicines that involve devices (eg, autoinjectors, ambulatory pumps, software/apps) required to be notified via devices@health.govt.nz if the information is already included in the clinical trial application?

Respondents noted that the lack of device regulation may potentially put participants at risk, and that currently only HDEC is responsible for reviewing these trials. It was recognised to be an issue outside of this guideline, but it was suggested that Medsafe considers how HDEC can be supported.

Medsafe response:

The definition of medical device can be found in the section 3A of the Medicines Act. If applicants are not sure if their product is a medicine or medical device they should contact Medsafe for advice (devices@health.govt.nz).

Medsafe have renamed the heading to 'Clinical Trials of Medical Devices' and the wording throughout the guidelines has been amended. This section intends to cover clinical trials where a medical device is being investigated (eg, clinical trials of investigational medical devices). Equipment such as tubes/kits that are used in a trial are not considered investigational medical devices. The guideline has been updated to provide additional clarity on these issues.

8. Further comments

Question 26: Do you have any further comments on this guideline?

11 respondents provided comments.

Several comments were received about the inclusion of 'signed and dated CV' for investigators and 'signed agreement between involved parties' in Appendix 1.1. Respondents commented that the rationale for these changes were not clear and raised the following concerns.

- Requiring CVs to be signed and dated could slow down the application process, noting that this is not standard practice and is not a requirement of ICH GCP.
- Requiring CVs to be provided for sub-investigators will add significant administrative burden, noting that sub-investigators often change during the course of a study.
- Requiring signed agreements to be provided could lead to a significant delay in trial start up timelines, as these may not be finalised at the time of the initial application. Additionally, signed agreements may contain commercially sensitive information.

One respondent suggest that a signed investigator consent form (ie, letter of intent or protocol signature page) would be sufficient as an agreement to conduct the trial. Another respondent suggested that the signing of the application form by the investigator in Ethics RM should suffice as them confirming awareness of the protocol (and similarly, for newly added or replacement investigators).

Other comments on the guideline that have not been answered in previous questions include the following.

- Recommendation to include annual safety report in Appendix 1.2.
- Request for clarification on which documents can be included with the 6-monthly progress reports (eg, updated GMP certificates and labels), noting they are currently listed separately.
- Suggestion to split the list of required documents into those requiring prior approval before implementation and those requiring notification only.

One respondent also commented that section 4 (notification of clinical trial sites) is narrow and not suitable to determine the suitability of investigators and institutions/trial sites. They recommended an accreditation process should be considered.

Medsafe response:

We have removed the need for signed and dated CVs. However, CVs should be current (within 6 months). A CV template has been created to assist and will be made available on the Medsafe website. The use of this template is optional. The requirement to submit CVs for sub-investigators has been removed. However CVs for principal investigators (referred to in the guideline as investigators – ie, at each investigator site) and the coordinating investigator is still required. This is a legislative requirement in section 30 of the Medicines Act.

The requirement for signed agreements between parties has been removed. However, details of the proposed trial sites must still be included in the application. This is a legislative requirement in section 30 of the Medicines Act.

The annual safety report has been added to the list of required documents.

Medsafe will consider updating templates. The current forms can be accessed via Ethics RM.

Further suggestions for improvements to the Appendix are noted. We will be reviewing and updating forms/templates on Ethics RM, which should provide additional clarity.

The comments on an accreditation process are noted but not within the scope of this guideline. Any such process would likely require significant resource and possibly legislative change.

Secondary GRTPNZ documents

9. First-In-Human and Early Phase Clinical Trials

Question 27: Do you agree that additional guidance for FIH and early phase clinical trials is needed?

Option	Total	Percent
Yes	14	61%
No	4	17%
Not Answered	5	22%

9 respondents provided comments.

Most respondents considered the additional document on considerations for first in human and early phase clinical trials would be helpful. It was noted that the guidance may be more helpful to newer sites looking to enter the FIH and early phase arena, rather than established sites, and that some of the information specified in the guideline is generally already included in FIH and early phase protocols.

One respondent suggested that appropriate oversight of the Clinical Trial Notification system may be sufficient, rather than creating an additional guidance document.

Clarification was requested about whether the considerations in the guideline were mandatory. It was noted that mandatory requirements would make it difficult for new sites to become established in early phase research in New Zealand.

Medsafe:

As supported by several respondents, Medsafe has included the additional guidance document on FIH and early phase clinical trials.

The guideline is considered complementary to the current clinical trial notification system. As noted in question 26, significant changes to the trial site notification system are not currently possible.

The considerations in this guidance document are not mandatory requirements. However, individuals or organisations involved in the conduct of FIH, or early phase trials should ensure a high standard for participant safety is met and can be clearly demonstrated. The guideline is intended to support this.

Question 28: Do you consider the guidance in this document to be broadly applicable to all types of FIH and early phase trials?

Option	Total	Percent
Yes	14	61%
No	4	17%
Not Answered	5	22%

4 respondents provided comments.

One respondent commented that the guidance document is more applicable to specialist Phase 1 units, rather than trials conducted within a hospital setting (such as for a ATMP product).

Another respondent noted the definition of early phase trials in the guideline may not be accurate in relation to early phase trials conducted in oncology indications that may have clinically relevant endpoints (eg, Phase 2a trials). The respondent suggested changes to the definition to reference conventional trial phase classifications.

Medsafe response:

Medsafe notes comment about specialist Phase 1 units. However, we consider the general principles in this document would still apply to trials conducted in a hospital setting.

The description of early phase trials in the document is based on the description in the Australian clinical trial handbook. We consider this to be appropriate for the intended scope of the document.

Question 29: Do you agree with the requirement for a risk assessment as described in 'general considerations?

Option	Total	Percent
Yes	14	61%
No	4	17%
Not Answered	5	22%

10 respondents provided comments.

Respondents commented that risk assessment for clinical trials is an integral part of the trial design and protocol development. There was a comment noting that this information is generally included in FIH and early phase trial protocols. Another respondent noted risk assessment for individual clinical trials is a fundamental responsibility of the trial site and principal investigator.

Further clarification on the contents of a risk assessment was sought and the provision of risk assessment templates and/or formatting for the submission was recommended. One respondent requested clarification on who performs the risk assessment.

Instead of a risk assessment, some respondents recommended the extension of the site self-certification scheme to all FIH/early phase sites to enable the applicant to confirm the sites have the appropriate facilities and processes in place.

Medsafe response:

The risk assessment does not necessarily need to be a standalone document. If relevant information is already included in the protocol (or other relevant document), it is acceptable for applicants to indicate where in the application this information can be found. The applicant should be able to demonstrate that sufficient risk assessment has been carried out (eg, at the level of trial design, selection of trial sites, etc) in order for the trial to be safely conducted in New Zealand. The wording in the guideline has been updated for clarity.

To allow flexibility for applicants to provide information relevant to their trial, we do not intend to provide a template. The information required is likely to differ depending on specific features of the trial and medicines being investigated.

The existing Clinical Trial Site Notification scheme can be used to notify any site that intends to run FIH trials, and this is recommended in the guideline.

Question 30: Do you agree with the proposed level of experience required for clinical trial sites and investigators wishing to conduct FIH trials?

Option	Total	Percent
Yes	11	48%
No	7	30%
Not Answered	5	22%

9 respondents provided comments.

In general, respondents agreed with the overall level of experience required for trial staff. However, several respondents raised concerns with the requirements for trial sites, particularly the feasibility of requiring FIH sites to have been audited. Respondents commented that the criteria proposed in section 4.1 are exclusionary and may deter new sites from participating in FIH trials, particularly as Medsafe does not conduct GCP inspections. It was also mentioned that the experience of the trial staff is more important.

One respondent requested further guidance on the requirements for standard operating procedure (SOP) development, specifically an SOP on risk assessment and mitigation. There was also a request for more clarity on Medsafe's expectations of an expert advisor.

Comments on the self-certification and accreditation schemes have been previously addressed in other questions.

Medsafe response:

Medsafe supports new trial sites being able to participate in FIH or early phase trials while ensuring the safety of participants. Following the concerns raised on the feasibility and practicality of auditing, we have removed this requirement from the guideline. However, it is still expected that early phase clinical trials will have previously been conducted at a trial site before FIH trials are conducted at the site.

The example of an expert advisor was given as a possible mechanism for mitigation of gaps in investigator experience. As this will be unique to each trial/situation, no further detail is provided, and other types of mitigations may also be appropriate.

Medsafe does not plan to provide further guidance on how to develop a quality system, including SOPs. It is outside of Medsafe's remit to provide this type of guidance.

Question 31: Do you have any other comments on the contents of this document (First in Human trial guidance)?

8 respondents provided comments.

Comments/questions that have not already been addressed in previous questions include the following.

- Informing hospital emergency personnel when dosing is occurring is unnecessary. It is more important that thorough immediate and ongoing information is provided at the time of an emergency transfer or presentation to hospital.
- Requests for clarity on items in the bullet point list in section 4.1.4.
- Handling and storage of IP should be in accordance with the protocol.
- Recommendation to add ability of Medsafe to audit facilities.
- Self-certification of trial sites and this document should be aligned.

It was commented that the wording in section 4.1.4 should be updated to reflect that IPs may be stored off-site rather than at the clinical trial unit and that specifics on the handling and storage of the IPs should be in compliance with the protocol.

Medsafe response:

The recommendation to inform relevant hospital and emergency personnel when dosing is occurring has been removed. However, the clinical trial unit should still have a clearly documented procedure for transferring patients in the case of a medical emergency.

The section on storage and handling of the IP (section 4.1.4) has been simplified and now states that handling and storage of the investigational product should be in accordance with the trial protocol and manufacturer requirements. The bullet point list of examples of additional requirements has been removed.

There is currently no legislation enabling regulatory audits of clinical trial facilities.

Medsafe plans to review and update the self-notification of trial sites form.

10. Clinical Trial Safety Monitoring and Reporting

Question 32: Do you agree that additional guidance on safety monitoring and reporting in clinical trials is needed?

Option	Total	Percent
Yes	17	74%
No	3	13%
Not Answered	3	13%

11 respondents provided comments.

Most respondents agreed that a standalone document on safety monitoring and reporting is needed.

As previously noted, several respondents recommended that safety information in the main guideline should be streamlined to minimise duplication of information. Alternatively, some respondents suggested the inclusion of this information into the main guideline and removal of the secondary document.

Other comments included the following.

- Request for clarity on who is responsible for assessing if an event is a SUSAR or SSI (ie, the sponsor or investigator).
- Request for clarity on reporting processes such as the management of site-specific safety issues and the coordination of safety communications between sponsors, investigators and ethics committees to support effective implementation.
- Suggestion to include that coordinating centres that report on behalf of the sponsor can be located outside of New Zealand.

Medsafe response:

As previously noted, duplicated information has been removed from the main guideline document. The main guideline now refers to this secondary document for information on safety monitoring and reporting.

The sponsor is primarily responsible for determining and reporting SUSARs and SSIs and reporting to Medsafe. The investigator is responsible for capturing and assessing AEs in accordance with the trial protocol, which will include an assessment of seriousness and causality. The wording has been amended in the guideline to provide additional clarity.

It is expected that processes will be in place to manage site-specific safety issues and the coordination of safety communications between relevant parties. It is outside of Medsafe's remit to provide this type of guidance.

The guideline does not specify that coordinating centres must be located in New Zealand. Therefore, no changes have been made.

Comments on the medical monitor are addressed in question 33.

Question 33: Do you agree with the roles and responsibilities of entities involved in clinical trials in New Zealand outlined in the guideline?

Option	Total	Percent
Yes	19	83%
No	0	0%
Not Answered	4	17%

8 respondents provided comments.

Respondents generally agreed with the roles and responsibilities described in this document.

Respondents requested clarification on the timeframes for investigators reporting SSIs and SUSARs to their institution. It was suggested to add 'as per institution's requirements', to allow flexibility for the institution on the reporting and oversight requirements.

Other comments included the following.

- A suggestion to include the role of the medical monitor.
- A suggestion to remove the word 'independent' in reference to independent individuals (eg, medical monitor), noting that they are not always independent but work for the sponsor.
- Safety reports should be assessed by the regulator and not the HDEC.

Comments on reporting adverse reactions associated with another supplier or manufacturer's medicine are addressed in question 34.

Medsafe response

We acknowledge that institutions may have different reporting requirements and the recommendation regarding reporting timeframes has been incorporated into the guideline.

The medical monitor is referenced in section 3.1 of the guideline. We consider that additional information on this role is not required at this time. Regarding the independence of medical monitors, we accept that the level of independence may vary. Independent oversight is considered desirable but is not mandatory. No changes have been made.

Medsafe and HDEC consider the impact of new safety information from different perspectives. Note HDEC does not require reporting of ICSRs.

Question 34: Do you have any comments on the reporting requirements for clinical trials involving medicines?

13 respondents provided comments.

Several respondents requested clarification on the requirements for reporting adverse reactions associated with another manufacturer's or supplier's medicine used as an active comparator in a trial. The requirement of having an agreement in place was considered to be unfeasible and inconsistent with standard practice. Some respondents recommended aligning with the requirements in the TGA guidelines or ICH E2A guideline.

Clarification on the requirements for reporting of adverse reactions was also requested for:

- blinded SUSARs
- follow-up information for ICSRs
- cross-reporting of SUSARs from a different study investigating the same IP
- if investigators are required to report USMs to the institution.

One respondent queried if a trial is temporarily halted, whether Medsafe should be notified when the study restarts.

Medsafe response:

The paragraph on reporting of adverse events for another supplier's or manufacturer's product has been amended. We have removed the recommendation that a specific agreement between parties is needed. Sponsors should decide in advance how these events will be reported.

We confirm that blinded SUSARs should not be reported to Medsafe as the investigational product involved is not known, as specified in section 4.1.1. Study unblinding procedures should be followed when determining whether unblinding should occur.

There are no specific timelines for reporting follow-up information. Ideally, this would only be reported once follow-up was complete to avoid submitting numerous reports for the same event.

If a SUSAR occurring in another trial has implications for the safety of the investigational product more broadly, this should trigger reporting of an SSI.

Medsafe should be notified before a trial is restarted after a temporary halt (and approval is required). This has been added to the guideline.

Several of the comments have been addressed in previous questions:

- Definition of SSI – question 8
- Pharmacovigilance system – question 19
- Reporting timelines – question 21
- DSUR/progress report – question 22
- Trial amendments – question 23 (note that that reporting of amendments is now primarily covered in the main GRTPNZ: Clinical Trials)
- Adverse event reporting methods – question 24
- Adverse events associated with placebo – question 24

Question 35: Do you have any comments on the reporting requirements for clinical trials involving medical devices?

7 respondents provided comments.

Respondents requested clarity on the following.

- Whether reporting of safety issues to Medsafe for device trials is mandatory or preferred, and if Medsafe will be expecting sponsors to report for these trials.
- Whether reporting is applicable for trials where medical devices are used but are not the subject of investigation in the trial.

One respondent suggested the removal of reference to DSURs from section 5.3 as these are not generated for medical devices.

Other respondents commented that devices were a gap in the current regulatory legislation, noting safety monitoring and reporting guidelines were not enforceable.

Medsafe response:

Medical device trials are not regulated by the Medicines Act, therefore the recommendations and timeframes for safety reporting to Medsafe are considered desirable but are not mandatory.

We confirm that annual safety report for medical device trials do not need to be submitted to Medsafe. However, annual safety reporting to HDEC is required. Reference to DSURs has been removed.

Section 5 is primarily aimed at clinical trials investigating medical devices (ie, investigational medical device trials). This has been clarified in the guideline. Reporting of ICSRs, SSIs and USMs in medical device trials are strongly encouraged but are not mandatory.

Issues with other devices used in a trial should be reported as per the standard process. Refer to the Medical Device Adverse Event Reporting on the Medsafe website for more information.

Question 36: Do you have any other comments on the contents of this document (safety monitoring and reporting)?

9 respondents provided comments.

The majority of comments have already been addressed in previous questions and are not repeated here.

One respondent recommended updates to the appendix to include 6-monthly progress reports and a summary for reporting responsibilities for medical devices.

Medsafe response:

We have added 6-monthly progress reports to the appendix for completeness. However, sponsors/applicants should refer to the main GTPRNZ Clinical Trials guideline to understand the full legislative requirements for these.

As device reporting is not mandatory, we have not added a separate appendix for devices. However, the recommendations for devices mirror medicines.

Other Comments

Question 37: If you have any further comments that have not been covered in the previous questions, please provide them here.

13 respondents provided comments.

Comments that have not already been addressed in previous questions include the following.

- Suggestion to add "for example a pharmacist" to the sentence in section 5.3.3 which specifies who can repack medicines (a person who is the holder of a packing licence or is otherwise authorised to pack medicines).
- Suggestion to include NZ trial registration and results disclosure requirements in the guideline.
- Observation that clinical trial sites listed on the "Notified Clinical Trial Sites" webpage are out of date/inaccurate. It was also suggested that Medsafe consider publishing/requesting a generic email address for each site.

Respondents also recognised the current limitations to the Medicines Act for the approval of clinical trials in New Zealand. It was recommended that future updates to the legislation should align where possible with other major regulatory territories.

Medsafe response:

The guideline has been updated with additional information on packing medicines for use in clinical trials.

Information on registration of clinical trials on a trial registry has been added to section 2.6 of the guideline as this is a condition of HDEC approval for intervention trials. Applicants should refer to the HDEC website for more information.

It is the responsibility of the site to ensure that the site notification remains up to date. The guideline has been updated to emphasise this responsibility. We will consider publishing email addresses for each site on the webpage.

The comments on the limitations of legislation and recommendations for future legislation are noted.

Medsafe Updates

The following changes to the guideline have also been made in response to queries received by Medsafe and legislation changes that have occurred since the consultation closed.

- The Medicines Amendment Act 2025, which came into effect on 19 November 2025, introduces the following change to section 30(4) of the Medicines Act: replace “45 days” with “32 working days”. Timeframes for clinical trial approval have been updated accordingly in the guideline.
- Medsafe recommends that clinical trial participation is recorded in an individual’s medical record. This is to ensure health professionals who are involved in patient care outside of the trial setting (eg, the emergency department) are aware of the patients involvement in a clinical trial. The investigator’s contact information should also be included. Section 6.2 in the updated guideline contains this recommendation.