RMI
Researched Medicines Industry Association

Submission to:

Medsafe

On the:

Proposed Clinical Trials Guidelines

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Contact
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Introduction

This submission is from The RMI, the association representing the following members:

Alcon New Zealand; AstraZeneca Limited; Bayer Schering Pharma; Boehringer Ingelheim NZ Limited; CSL Biotherapies (NZ) Limited; Dr Reddy's New Zealand Limited; Eli Lilly and Company (NZ) Limited; GlaxoSmithKline NZ Limited; Janssen-Cilag (New Zealand) Limited; Merck Sharp & Dohme (New Zealand) Limited; Mundipharma New Zealand Limited; Novartis New Zealand Limited; Pfizer New Zealand Limited; Roche Products (New Zealand) Limited; sanofi-aventis new Zealand limited; Wyeth (N.Z.) Limited

The RMI associate members are:

IMS Health (N.Z.) Limited and Quintiles Pty Limited.

In general, the RMI members support a move toward international harmonisation of clinical trail requirements.

There are a number of areas where the intention of the proposed guidelines should be clarified.

A number of requirements impose a substantial administrative burden, one particular example being the need to keep hard copies of all electronic records. Please review this need for hard copies of electronic records to be kept or refer this decision to the appropriate agency before publishing any requirements.

There are a number of minor improvements that could be made to the document, including:

- links to external websites are to the front pages of these websites, rather than to the web-page which contains the relevant information;
- consider alphanumeric referencing of each paragraph for ease of reference (as used in CPMP/ICH/135/95).

Section Two

Section 2.1

The guideline excludes the need for sponsors using medicines which already hold Ministerial consent under Section 20 to apply for approval under Section 30 for a clinical trial. The medicine consent however includes that the medicine be used with approved packaging; whereas clinical trial medicine is required to have the words: "To be used by qualified investigators only". This appears to be a conflicting area between the Medicines Act and the proposed guidelines. Please clarify the labeling requirements for medicines with consent under section 20

when used in clinical trials. This clarification should also make provision for these medicines to be used in a blinded fashion.

Section 2.1.1

Please clarify the third point under 2.1.1 which refers to "any substance" and appears to suggest that medicines which hold ministerial consent under Section 20 should also apply for approval under Section 30. A suggested alternative wording is: "If any substance usually considered to be a food, dietary supplement or cosmetic is administered to human beings for a therapeutic purpose as part of a trial…"

The last sentence under 2.1.1 refers the reader to "section 1.3", there is no section 1.3 in the proposal, this appears to be referring to section 2.3 of the proposed guidelines.

Section 2.1.2

Additional information to clarify structure on ethics committees would be very useful. Its clear that the ethics approval process is independent of Medsafe approval but the link to 'Operational Standards for Ethics Committees' goes direct to the document itself - the only identifier as to which authority issued this document is a statement that the document is available on the MOH website, which implies that the Ethics Committees are somehow managed by Medsafe. In addition there are two additional links in the ethics committee section, one of which is described as "National Ethics Committee Advisory Committee" but both go to the same webpage entitled "NZ Health and Disability Ethics Committees" so it is unclear as to what the NECAC is and how it links with HDECs and/or MOH.

Section 2.1.4

The paragraph dealing with new indications for an approved medicine does not describe any requirement for approval under Section 30 if the dosage used in the trial is different from that which holds consent under Section 20. Table 2.1.4 summarising the approval requirements however states that trials on new strengths of approved medicines should apply for approval under Section 30. Please describe the requirements for trials using dosages other than those holding consent.

Please provide clarity about requirements for approval for other types of trials including Major Adverse Clinical Outcomes (MACO) trials.

Section 2.2

Please provide details about all aspects of the process of self certification of clinical trial sites, such as: responsibility for certification; definition of a site; and staff to be included in certification. For example, does a trial site refer to a

hospital or to a department within the hospital in which the trial is run? Also personnel are likely to change on a regular basis and between different trials.

The link to a form in this section does not appear to link to a site certification form, but a clinical trial application form with a subsection relating to site certification. This suggests that the self certification process is to be repeated for each trial application. Please clarify the intention for a list of certified sites to be used.

Please advise the expected time taken from submitting a self certification form until this is reflected on the Medsafe website.

It is not clear whether the list of clinical trial sites will be audited or how sponsors would know that the information on the list published by Medsafe is current or accurate.

Will all the information submitted for trial site certification be accessible to sponsors? If this information is to be useful to sponsors as well as regulators, the process for gathering the information, as well as the type of information required should be better defined.

Please not that the provision and updating of this information is likely to generate an additional administrative burden on sponsors and as such should be expected to provide a useful information resource for sponsors.

Section 2.3

Section 2.3.3 states that payment should be made within 7 days of invoicing; it is unlikely that large companies will be in a position to reliably process payment within this time frame. Please consider extending this period.

Section 2.3.4 states that the applicant will be notified of the Director-General's decision within 45 days. Please clarify whether this refers to business days or calendar days.

Section Three

Please consider identifying the specific parts of the Medicines Act 1981 which are in conflict with the CPMP guideline.

The introductory paragraph in Section three refers to "certain modifications", please consider listing the modifications required.

The third paragraph of the introductory section refers to "Sections 1.8.1 to 1.8.5"; these sections cannot be found in either the Medsafe draft guidelines or CPMP/ICH/135/95. Please specify to which document these refer.

Section 3.1

The responsibilities described in the five points of section 3.1 are not all responsibilities of the same person, e.g. The sponsors contact with the ethics

committee is through the investigator; there is no direct contact between the sponsor and the ethics committee.

The second from last paragraph indicates that a monitor is an employee of the sponsor. At times however, a trial monitor may be a Clinical Research Associate (CRA), employed by a Clinical Research Organisation (CRO) rather than being an employee of the sponsor. Please make provision for this in the guidelines.

The fifth point should probably read as follows: "informing the Director-General of the identifying name or mark by which the trial ***medicine*** may be recognised…"

Section 3.2

Please note that section 4.6.4 of the CPMP/ICH/135/95 guideline states: The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s). Are there any New Zealand specific requirements relating to the storage of investigational products?

Section 3.3

Please clarify whether the trial sponsors and other parties involved in clinical trials are required to apply to the Chief Archivist for approval to destroy clinical trial records. Please advise the process to be followed for this application.

Please review the requirement that all computerised records be reproduced in hard copy, signed and dated. This represents an unreasonable administrative burden considering the volume of information generated in clinical trials. Also, there are adequately validated data-warehousing facilities available to ensure data are readily available when required.

As this topic is likely to fall outside of the Medsafe area of responsibility, it is considered that any requirements relating to keeping hard copies of electronic records should be the subject of a separate consultation by the agency responsible for administering the relevant section of the Health Regulations 1996.

Section 3.4

Please provide guidance about the reporting of adverse events for clinical trials which do not require approval under section 30 of the Medicines Act.

Please clarify whether SUSARs should be reported in unblinded trials, and whether the first three criteria should be the basis on which they are reported.

Please consider defining Important Medical Events (IME) criteria for reporting, or state that these reports are not required.

Please consider accepting reports of SUSARs by fax or email to reduce any delay in these reports being attended to.

Please advise whether adverse events in clinical trials are to be reported to the Centre for Adverse Reactions Monitoring, or whether reporting these to Medsafe is adequate.

The statement: "All (worldwide) serious adverse events which do not result in breaking the study code and which are not specified as study end points should be recorded and presented to Medsafe as part of the routine reporting required under the Section 30(7)(d) of the Act. A template reporting form is provided for this purpose." can be interpreted that Foreign SAE reports which result in breaking the study code have to be reported differently. However when you look at the template it states "Please note that Sponsors should only expedite reports (following ICH E2A guidelines) for any SAE for which unblinding of the patient's treatment has occurred at any NZ sites. No expedited reporting of individual SAEs at sites in other countries is required." (ie meaning that no foreign reports need to be reported on an expedited basis). Please clarify the intention in this section.

For the reporting required under Section 30(7)d of the Medicines Act, would Medsafe accept the format and periods of safety reports generated for other international regulators?

Summary

The RMI seeks the following outcomes for the proposed clinical trial guidelines:

1. Greater clarity around aspects of the guidelines identified in the body of this submission
2. That further consideration be given to the administrative burden imposed by certain requirements, particularly the need to keep hard copies of all electronic records.
3. Minor improvements in the presentation of the document which would improve the ability of people to use the document and may reduce time spent by Medsafe on queries about interpretation.