



Malaysia Addendum

General Comments

The Malaysia Addendum to the *Evaluation Instrument for Accreditation* is intended for use by organizations in Malaysia seeking accreditation; by site visitors evaluating organizations in Malaysia; and by accredited organizations in the US that conduct or oversee research in Malaysia. This Addendum includes Standards and Elements where Malaysian laws, regulations, and guidelines require significant additional protections beyond those defined in the *Evaluation Instrument* and is intended to be used in conjunction with the *Evaluation Instrument for Accreditation* ("Evaluation Instrument").

The Addendum is based on a review of the following laws, policies, and guidance:

- A Guide to Conducting Clinical Trials in Malaysia 1st Edition, Society of Clinical Research Professionals Malaysia (2016)
- Malaysian Guideline for Good Clinical Practice, 4th Ed. (March 2018)
- Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects, Ministry of Health Medical Review and Ethics Committee (2006)
- Malaysian Guideline for Independent Ethics Committee Registration and Inspection (2016)
- Malaysian Guideline for Application of Clinical Trial Import Licence and Clinical Trial Exemption (Edition 6.4)
- Malaysian Guideline for Safety Reporting of Investigational Products (2014)
- Medical Device Act (2012)

The Malaysian Guideline for Good Clinical Practice ("Malaysian GCP") has the same requirements as ICH-GCP (E6), except where noted below. Organizations that follow the Malaysian GCP should ensure requirements in ICH-GCP (E6) listed in the *Evaluation Instrument* are included in policies and procedures, as well as the additional requirements from the Malaysia GCP listed below.

Each Malaysia state and territory has separate legislation that may be relevant to the conduct of clinical trials. This Addendum does not include additional requirements under these laws.

This Addendum represents AAHRPP's current understanding of additional requirements covering organizations conducting or reviewing research in Malaysia.

We appreciate questions, concerns, and suggestions to improve this document. Please email accreditation@aahrpp.org.

Domain I: Organization

Standard I-1: The Organization has a systematic and comprehensive Human Research Protection Program with appropriate leadership.

Element I.1.A. The organization has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program.

All research involving human subjects must be overseen by a Human Research Protection Program. (Guideline Ethical Review of Clinical Research or Research Involving Human Subjects, MREC 2006)

The definition of research must cover all research activities (e.g., medical record review, behavioral health interventions not involving drugs or devices, or interviews with participants), not just those involving clinical trials of drugs and devices.

A human subject (in the context of research) is a living individual about whom an investigator obtains either:

- data through intervention (e.g., trial) with or without identifiable private information or
- interaction (e.g., physical examination, questionnaires) with the individual with collection of identifiable private information.

Element I.1.E. The organization has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants.

Researchers must complete a training program in Good Clinical Practices approved by the National Committee for Clinical Research (NCCR). (Malaysian GCP, Sections 1.6. and 4.1., and Malaysian Code of Responsible Conduct in Research, Section 4.1.)

- The content of the training must incorporate the curriculum as stipulated by the National Committee for Clinical Research (NCCR).
- Principle researchers involved in the study must be qualified by NCCR-approved training prior to engaging in research activity.

Element I.1.F. The organization has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process.

- Investigator-initiated research that does not involve international collaboration must be reviewed by a research review panel prior to submission to the MREC, per Malaysia NIH Guidelines for Conducting Research in Ministry of Health Institutions and Facilities. (A Guide to Conducting Clinical Trials in Malaysia, section 4.2.1.1.)

Standard I-7: The organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

Element I.7.A. When research involves investigational or unlicensed test articles, the organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.

All IRBs in Malaysia that review drug-related trials must be registered with the National Pharmaceutical Control Bureau (NPCB) Independent Ethics Committee Compliance Program. (Malaysian Guideline for Independent Ethics Committee Registration and Inspection (2016); Guide to Conducting Clinical Trials in Malaysia, Chapter 1)

Policies and procedures must describe the process for confirming approval of a clinical trial import license (CTIL) and/or clinical trial exemption (CTX) prior to allowing research to commence. (A Guide to Conducting Clinical Trials in Malaysia, Section 3.2. and Malaysia GCP Sections 1.13 and 1.14, and Section 5.14)

- If the researcher is responsible for obtaining the CTIL and CTX, then the organization must confirm approval for each unique study drug prior to allowing research to start. This is not required if the sponsor is responsible.

The following products require a CTIL/CTX (Malaysian Guideline for Application of CTIL and CTX, Section 3):

- A product including placebo which is not registered with the Drug Control Authority (DCA) and are intended to be imported for clinical trial purpose.
- A product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form and when used for unapproved indication/when used to gain further information about an approved use for clinical trial purpose.
- A traditional product with a marketing authorization with indication for "traditionally used" when used for unapproved indication/therapeutic claims for clinical trial purpose.
- An unregistered product including placebo manufactured locally for the purpose of the clinical trial.

Trials must be registered with the national medical research register (NMRR) when research involves Ministry of Health (MOH) personnel, or conducted in a MOH facility, or funded by the MOH. (A Guide to Conducting Clinical Trials in Malaysia, Section 10.21.)

Element I.7.C. The organization has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article.

If the organization allows compassionate use of unapproved drugs as an extension to an approved clinical trial protocol, policies and procedures should describe eligibility and reporting. (Malaysia GCP, Section 8.1., and Guide to Conducting Clinical Trials in Malaysia, Section 8.4.):

- Only subjects who had previously enrolled in the approved clinical trial are allowed to continue the use of the unregistered medicinal product with the approval of the DCA. In such case, CTIL applicant shall apply for additional quantity for compassionate use in order to import the product via CTIL. The additional quantity for compassionate use program will only be approved for six months. If there is a need to continue the compassionate program for more than six months, the applicant is required to reapply for an additional quantity of investigational product.
- As the compassionate use program is an extension of a completed clinical trial and subjects will be provided with continued treatment with the unregistered product, all serious, unexpected adverse drug reactions should be reported to the Centre for Investigational New Product.
- In the event that the product to be used by the subjects of the completed clinical trial is registered with the DCA and commercially available, all suspected local adverse reactions should be reported to the Pharmacovigilance/ADR/Malaysian Adverse Drug Reactions Advisory Committee (MADRAC) Unit, Centre for Post Registration of Products in accordance with their established procedures.

Standard I-8: The organization works with public, industry, and sponsors to apply to the requirements of the Human Research Protection Program to all participants.

Element I.8.A. The organization has a written agreement with the sponsor that addresses medical care for research participants with a research-related injury, when appropriate.

If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and

financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence. (Malaysian GCP, Section 5.8.1.) It is a requirement of the independent ethics committee (IEC) or MREC that all ethics submission for clinical trials must include proof of trial indemnification either by insurance certificate or letter of indemnity. These documents should indicate the protocol title and number, period of coverage, and list of coverage for Malaysia sites among others. Insurance certificates that are renewed should be duly submitted to the ethics committee on an on-going basis. (A Guide to Conducting Clinical Trials in Malaysia, Section 7)

Standard I-9: The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization the rights and welfare of research participants are protected.

Organizations that are not part of the Ministry of Health without their own IRB may rely upon the central IRB for the Ministry of Health or designated universities to provide IRB review. (Malaysia GCP, Sections 3.2.7., 4.1., and 4.2.)

- When relying upon the MOH, the relying organization's policies and procedures must describe the roles of the organization and researchers when relying upon another organization's IRB (*Evaluation Instrument*, Standard I-9, items (1)(b)).

Domain II: Institutional Review Board or Ethics Committee

Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.

Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.

Organizations with local IRBs should publish the list of IRB members, including their area of expertise and experience. (Malaysian Guideline for Independent Ethics Committee Registration and Inspection)

Standard II-2: The IRB or EC evaluates each research protocol or plan to ensure the protection of participants.

Element II.2.A. The IRB or EC has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB or EC. Such policies and procedures indicate that exemption determinations are not to be made by researchers or others who might have a conflict of interest regarding the studies.

The authority to exempt a proposed research study from MREC review and approval may be delegated to an individual or body in the local institution. For MOH facilities, this would typically be the local Clinical Research Committee. (Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects, Guideline 1)

- Prior to authorizing exemption from MREC approval, the local authorizing body must verify that the proposed research is registered with the National Medical/Clinical Research Register to allow the MREC to track and review the appropriateness of exemption from MREC review.
- An investigator lacking access to a local body to authorize the waiver may apply instead to the MREC for this purpose.

The following types of research or data collection are exempt from MREC review and approval (Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects, Guideline 1):

- Research not involving human subjects does not require review by an IRB and does not require consent.
- Study or data collection based entirely on data abstraction from existing medical or laboratory record with no interaction with the human subject concerned and with no collection of identifiable private information.
- Study based entirely on existing biological specimen with no interaction with the human subject concerned, with no collection of identifiable private information, and with no further processing of and/or testing on the specimen.
- Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures (questionnaires), interview procedures, or observation of public behavior and with no collection of identifiable private information.

Element II.2.G. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.

Policies and procedures must describe reporting requirements for researchers and requirements for reporting to regulatory agencies:

- All adverse drug reactions (ADRs) that are both serious and unexpected are subject to expedited reporting. This applies to reports from all clinical trials at Malaysia that require CTIL and/or CTX.
- There are situations in addition to single case reports of "serious" adverse events or reactions that may necessitate rapid communication to regulatory authorities; appropriate medical and scientific judgement should be applied for each situation. In general, information that might materially influence the benefit-risk assessment of a medicinal product or that would be sufficient to consider changes in medicinal product administration or in the overall conduct of a clinical investigation represents such situations. Examples include:
 - For an "expected," serious ADR, an increase in the rate of occurrence which is judged to be clinically important.
 - A significant hazard to the patient population, such as lack of efficacy with a medicinal product used in treating life-threatening disease.
 - A major safety finding from a newly completed animal study (such as carcinogenicity). (Malaysian Guideline for Safety Reporting of Investigational Products, Section 3.)
- In addition to the requirements under Malaysian law and guidelines, to conform to AAHRPP requirements, researchers must also report to the IRB other unanticipated problems involving risks to participants or others.

Standard II-3: The IRB or EC approves each research protocol or plan according to criteria based on applicable laws, regulations, codes, and guidance.

Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.

Consent documents must disclose the sources and components of investigational products that may be culturally unacceptable. (Malaysia GCP Section 4.8.10.)

Participants who are unable to read may use a thumbprint to document consent. (Malaysian GCP, Section 4.8.9.)

Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.

The MREC may waive the requirement to obtain individual informed consent from the human participants in the research provided the MREC finds and documents that:

- Participants would be exposed to no more than minimal risk and the requirement of individual informed consent would make the conduct of the research impracticable; or
- Participants would be exposed to no more than minimal risk and the study involves only publicly available data; or
- The study involves private data but is carried out under legislative or public health authority.
- A study involving a clinical or disease registry or database, or large-scale non-interventional observational study, would also qualify provided the data collection is based on existing medical or laboratory records, the risk is minimal, it is impractical otherwise to conduct such study, and the MOH is a sponsor of the registry or database or study.

(Guidelines for Ethical Review of Clinical Research or Research Involving Human Subjects, Guideline 2)

Standard II-5: The IRB or EC maintains documentation of its activities.

Element I.5.A. The IRB or EC maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, sponsor requirements, and organizational policies and procedures.

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least three years after completion of the trial and make them available upon request from the regulatory authority(ies). (Malaysian GCP, Section 3.4.)