

HOSPITAL AUTHORITY (HA) GUIDE ON RESEARCH ETHICS

(for Study Site & Research Ethics Committee)

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HA RE001 Hospital Authority Guide for Cluster Research Ethics Committees

HA RE002 Clinical Research Study Site Guide)

**Hospital Authority Research Ethics Committee
Hospital Authority**

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Related Documents: Supporting Form Templates

HA RE001F1	Declaration of Confidentiality Form
HA RE001F2	Reviewer's Conflict of Interest Declaration Form
HA RE001F3	Clinical Research Ethics Review Application Form
HA RE001F3b	Expedited Review Form for Multi-center Trial
HA RE001F4	Investigator's Conflict of Interest Declaration Form
HA RE001F5	REC Review Checklist
HA RE001F6a	REC Approval Form
HA RE001F6b	REC Clarification Form
HA RE001F6c	REC Disapproval Form
HA RE001F7	Protocol Amendment Application Form
HA RE001F8	Serious Adverse Event (SAE) Report Form
HA RE001F9a	Research Progress Report Form
HA RE001F9b	Research Final Report Form

1. Basic Considerations

- 1.1 Clinical trials and clinical research (collectively referred to as “**Clinical Research**”) are necessary if medicine is to progress. They contribute to the generation of knowledge and development of technology for healthcare advancement. Such objectives, however, do not take precedence over the interests of the research subjects (“**Research Subjects**”).
- 1.2 Clinical Research is premised on trust. At times, it places Research Subjects at risk for the good of the community. The community and the Research Subjects therefore have legitimate expectations that a system of protection should be in place. This paper sets out the system of protection within HA. The requirements have been developed with reference to overseas practice and local experience in Phase III and IV trials. HA expects that the requirements set out in this document should apply to Phase I,II, III and IV trials but, pending HAHO clarifications of the additional requirements to be imposed on Phase I and II trials, the Clusters are expected to impose additional requirements on their own volition to safeguard the safety of trial subjects.
- 1.3 One aspect of HA’s system is embodied in research ethics. Research ethics is a dynamic discipline rich in debate and competing discourses, manifesting through social conventions, professional code or law reflecting shared norms and values. Its ethical principles embrace the matters set out below.

2. Commonly Accepted Ethical Requirements in Clinical Research

- 2.1 In Clinical Research, the mandatory ethical requirements are the principles of the Declaration of Helsinki, and whenever applicable, the International Conference on Harmonisation – Good Clinical Practice Guidelines (“**ICH-GCP Guidelines**”). Legal requirements and local institution policies must also be complied with. Some of the more important requirements are:
 - (a) Clinical Research methodology must be scientifically valid and adequate in addressing the questions posed.
 - (b) Clinical Research design must minimize the potential risks to the Research Subjects, and its anticipated benefits must justify the potential risks.
 - (c) Equipoise must exist between different arms of a therapeutic trial comprising different interventions or different dosages.
 - (d) To ensure voluntary participation in Clinical Research, Research Subjects must be adequately informed of the experimental nature of the undertaking; the nature of the Clinical Research, its risks, burdens and benefits; and their rights to withdraw at any time, which will not affect the care they entitle.
 - (e) As each person weighs risks and benefits differently, we must respect other’s freedom to decide, based on his/her own value and belief, without coercion

and undue influence.

- (f) Selection of Research Subjects should be equitable, overuse of any group or individual should be avoided.
- (g) Special precautions should be taken to protect vulnerable Research Subjects.
- (h) Throughout a trial, Research Subjects should be provided with updated information about the Clinical Research (including adverse events) so that they are free to decide whether or not to continue.

3. HA's Obligations as a Research Institution

3.1 As a public healthcare provider, HA has to ensure that:

- (a) services are accorded priority;
- (b) Research Subjects' rights, safety and welfare are protected;
- (c) research is conducted ethically and lawfully amongst its staff;
- (d) public confidence is sustained by an environment that upholds scientific and ethical integrity; and
- (e) liabilities to HA be minimized.

3.2 HA should establish an ethics review and oversight mechanism through the Research Ethics Committee ("**REC**") structure, which is an added layer of protection for the Research Subjects. However, HA does not discharge its responsibilities completely by the establishment of the REC, it must continue to perform its obligation as a research institution.

3.3 REC is organized on two levels, HAHO and the Clusters.

(a) **HAHO Steering Committee on Research Ethics ("**HA REC**")**

HA REC is accountable to HA for:

- (i) establishing HA research ethics standards and guidelines;
- (ii) harmonizing research ethics standards and practices within HA and with affiliating academia;
- (iii) promulgating and monitoring the implementation of research ethics;
- (iv) administering a central database on Clinical Research for risk management; and
- (v) handling appeals against Cluster REC's decision.

(b) **Cluster REC**

The Cluster REC is responsible for conducting ethics review and overseeing the execution of study duties within the Cluster.

- 3.4 Besides ethics approval by Cluster REC, Clinical Research on HA patients or within HA facilities must also be approved by:
- (a) Study site management (i.e. the hospital + affiliating academia if applicable); and
 - (b) Regulatory body if applicable, e.g. Department of Health (DoH) which issues Clinical Trial Certificate as required by Law.

4. Responsibilities of the Study Site Management

- 4.1 At the study site ("Study Site"), all Clinical Research must, first of all, be approved by the Chief of Services ("COS") of the implicated department(s). The investigator has to submit the following documents (collectively "Application Dossiers") to the COS for approval before applying to the Cluster REC for an ethics review:
- (a) A duly completed and signed Application Form*;
 - (b) The research protocol;
 - (c) Investigator's brochure (if available);
 - (d) Consent form and information to be provided to Research Subjects (such as recruitment notice, invitation letter and safety information) in suitable language(s);
 - (e) Curriculum vitae and relevant experience of the principal investigator and other investigators;
 - (f) Other relevant documents, such as support from an academia for student projects;
 - (g) For sponsored Clinical Research or where commercial interest is involved (e.g. collecting data, evaluating a device, comparing different drugs, drug dosages or off label use of a licensed drug), the following documents must be submitted:
 - (i) Conflict of interest declaration by the investigator*;
 - (ii) Letter of Indemnity* for the standard indemnity agreement and procedure;
 - (iii) Draft Clinical Trial Agreement ("CTA")*;
 - (iv) A Certification of Clinical Trial or Medicinal Test (to be submitted when available at a later date) or other documents required by law; and
 - (v) The investigator should also state whether in his knowledge, the Clinical Research is to be conducted in other HA hospitals, and if so, the names of those hospitals.

Requirements under sub-paragraphs (g)(ii) and (g)(iii) do not apply to HA initiated Clinical Research.

* Use standard forms approved by the respective Cluster REC.

4.2 Administrative approval

- (a) By signing the Application Form, the COS endorses the Clinical Research as both scientifically and ethically sound. S/he also confirms that:
- (i) Services priority of the department will not be affected;
 - (ii) Research team is competent;
 - (iii) The investigator has sufficient resources to conduct the Clinical Research safely;
 - (iv) Therapeutic intervention(s), if any, can be performed by appropriate personnel proficient in managing conditions that may arise; and
 - (v) The Study Site has sufficient facilities to support the Clinical Research; and
 - (vi) If the Clinical Research is sponsored, the CTA has been approved (or under process) by the HAHO Legal Services Section and an approved Letter of Indemnity is in place (or under process).
- (b) If in doubt, the COS should submit the Application Dossiers to the hospital management. Before approving the Clinical Research, the hospital management has to satisfy itself that:
- (i) Service priority of the hospital will not be adversely affected by the Clinical Research;
 - (ii) The hospital has in place sufficient facilities/resources to conduct the Clinical Research safely and to manage conditions that may arise;
 - (iii) If the Clinical Research is sponsored, the CTA has been approved (or under process) by the HAHO Legal Services Section and an approved Letter of Indemnity is in place (or under process); and
 - (iv) The Cluster Chief Executive (“**CCE**”) or his/her designate’s approval is required if the Clinical Research involves testing of an article for unlicensed indications, which exposes the hospital to unknown risks.
- (c) In negotiating a CTA with the sponsor:
- (ii) The hospital management can approach the Legal Services Section for pre-approved HA CTA template and/or pre-approved drug company CTA templates.
 - (iii) Other than where a pre-approved CTA is used, the hospital management has to liaise with sponsors and Legal Services Section for amendments and approval of CTA.
 - (iv) If the Clinical Research is a multi-centre trial, the principal investigator’s hospital is responsible for ensuring the approval of CTA and that the Letter of Indemnity is in place for all HA Study Sites. The principal investigator should notify the Legal Services Section that s/he is co-ordinating the approval for all HA Study Sites.

- (d) HA may charge administrative costs for the approval of the sponsored Clinical Research and the archiving of the Study Site records.

4.3 Following the administrative approval by the line management, the Application Dossiers should be submitted to Cluster REC for ethics approval.

5. **Cluster REC**

5.1 **Functions of Cluster REC**

The Cluster REC has jurisdiction over the institutions within its cluster. While it is accountable to the CCE, it should function as independently as possible. It is responsible for

- (a) ethics approval of Clinical Research and proactive monitoring until their completion or termination;
- (b) harmonizing ethical requirements and procedures with the affiliating academia, if applicable;
- (c) advising the hospitals and HA on matters pertaining to research ethics, for example, the need to:
 - (i) submit data to a central database on Clinical Researches for risk management and exposure assessment; and
 - (ii) notify HA REC on premature termination of Clinical Research due to safety concerns;
- (d) establishing and maintaining Standard Operating Procedures and Record Forms for ethics review and Clinical Research oversight in compliance with HA requirements;
- (e) recruiting Cluster REC members, coordinating training and maintaining members' records, e.g. appointment letters, confidentiality undertakings, conflict of interest declarations and training records.

5.2 **Powers of Cluster REC**

The Cluster REC has the power to oversee all Clinical Research within its cluster, including:

- (a) approving, disapproving, requiring modification or amendment of any Clinical Research;
- (b) monitoring progress of Clinical Research through study progress reports and serious adverse events ("**SAE**") reports;
- (c) terminating or suspending any Clinical Research; or
- (d) initiating an audit.

Cluster REC can charge for its services and compensate its members. Payment

should never be dependent on a favourable decision.

5.3 Matters within the Purview of Cluster REC

- (a) The following types of activities must be submitted to Cluster REC for ethics approval:
 - (i) Clinical Research with humans as Research Subjects. This may include quality assurance activities that involve additional risk, burden or intrusion of privacy that are not part of the routine care.
 - (ii) Research on materials of human origins, such as body tissue and fluid, including “waste” or “leftover” from diagnosis and treatment, or archiving such materials for future studies;
 - (iii) Collation of records/data (whether existing or to be collected) where there is a reasonable likelihood that such may link to the individuals’ identifiable particulars or identifiers; and
 - (iv) Clinical Research on cognitive / mental phenomena.
- (b) When there is an ambiguity on whether an activity is clinical research, the Cluster Management has authority to decide if it should go through ethics review and monitoring.

5.4 The Composition of Cluster REC and Review Structure

- (a) The Cluster REC should have enough members with diverse background, serving for a term not exceeding 3 years but eligible for re-appointment. Members who do not have prior REC experience should undergo training.
- (b) Review Structure
 - (i) Panel Review

Ethics review should normally be conducted in a meeting by a panel of at least five reviewers, who collectively have the ability and experience to evaluate the scientific, medical and ethical aspects of the proposal. One of the panel members shall chair the meeting. Specifically, a panel shall comprise:

 - (aa) ≥ 1 reviewer who has scientific or healthcare background;
 - (bb) ≥ 1 reviewer who has neither scientific nor healthcare background;
 - (cc) ≥ 1 reviewer who is not affiliated with the institution, i.e., the hospital cluster and/or medical faculty of the academia as applicable, nor is part of the immediate family of such a person; and
 - (dd) both male and female reviewers whenever possible, especially in the case of an international trial which it may fall under the scrutiny of an overseas regulatory body.

- (ii) Experts can be invited to provide scientific, legal or ethics input but they are not entitled to vote. To facilitate their contribution, they should have access to the Application Dossiers.
- (iii) Application Dossiers should be sent to reviewers and invited experts at least 7 days before a panel review meeting.
- (iv) Expedited Review
 - (aa) Expedited review is permitted for Clinical Research that
 - (aa1) does not involve additional clinical intervention (drug or invasive procedure) or carry no more than minimal risk to the Research Subjects, and
 - (aa2) does not include vulnerable subjects, and
 - (aa3) does not raise sensitive privacy concerns.
 - (bb) Expedited review is also permitted for cross-cluster multi-center Clinical Research previously approved by another Cluster REC.
 - (cc) The Cluster REC Chairman may perform the expedited review or assign the task to one or more experienced Cluster REC members. In an expedited review, the reviewers can exercise all authorities of the REC except disapproval, which shall only be made in a panel review.

5.5 Confidentiality Undertaking and Conflict of Interest Declaration

Reviewers and experts invited to provide scientific, legal or ethics input are required to sign the Confidentiality Undertaking* and Conflict of Interest Declaration*.

** Use standard forms approved by the respective Cluster REC.*

5.6 Review Procedure and Records

- (a) The Cluster REC should adopt a structured review process is to address all important considerations
- (b) Reviewers who have conflict of interest in any application should abstain from the meeting. Only Cluster REC members who have participated in the review and deliberation can vote. The Cluster REC must ensure that a quorum always exists in a panel review.
- (c) The Cluster REC should document the review process, and maintain records for each application that permit the subsequent evaluation of the review and the decision. Such documents, organized in ways to facilitate easy retrieval, must be retained for at least 3 years after the completion or termination of the Clinical Research.
- (d) Cluster REC records should be made available to the hospital management,

HA REC and relevant monitoring authority upon request.

5.7 Review Considerations

Besides the mandatory ethical and legal requirements, the Cluster REC must also consider the following aspects:

- (a) whether the Clinical Research has a reasonable prospect of improving healthcare or furthering knowledge;
- (b) whether the design and methodology of the Clinical Research (including statistics and sample size) are adequate in addressing the research question;
- (c) whether the research team is competent in the area of Clinical Research and the study site is suitably equipped;
- (d) whether the Clinical Research has a favourable risk-benefit ratio. In considering the risk-benefit ratio, the Clinical REC should consider:
 - (i) The risks linked to the Clinical Research as distinct from those associated with standard care. The assessment of the risks should not be limited to the study article(s) since the Clinical Researches may involve additional invasive procedures, e.g., additional organ biopsies.
 - (ii) Whether the foreseeable risks are minimized to the extent possible?
 - (iii) Whether there are adequate provisions for monitoring risks and early detection of adverse outcome in the Research Subjects?
 - (iv) Whether the risk undertaken justifies the use of an independent data monitoring committee (IDMC) to ensure safety of Research Subjects as a whole?
 - (v) Whether the necessary expertise is available to carry out the Clinical Research and to manage the possible adverse outcomes?
 - (vi) Whether the anticipated benefits to the Research Subjects (excluding extraneous ones such as free service, more attention and expert care, etc.) outweigh all risks and burdens of the Clinical Research?
- (e) The Cluster REC should consider if the Research Subjects are selected on the bases of scientific principles and study goals, and not by convenience, vulnerability, privilege, or other irrelevant factors. In so far as consistent with scientific principles and study goals, a certain population group should not be overburdened. It is also important to ensure that treatment allocated to groups within the Clinical Research is reasonable and fair.
- (f) The Cluster REC should review and approve all informed consent documents to ensure that adequate explanation, prepared in language suitable for the Research Subjects' understanding, will be given. Basic requirements on information to be given to Research Subjects are set out in ICH-GCP Guideline E6, Section 4.8.10, which include, but is not limited to, the followings:

- (i) The research institution and investigators;
- (ii) The purpose of the study;
- (iii) Which aspect of study is experimental;
- (iv) Details of study relevant to Research Subject's willingness to participate, e.g. nature of intervention and invasiveness, use of placebo, method of assignment to different arms and its probability, duration of involvement, sample size, likelihood of premature termination, etc;
- (v) The foreseeable risks and discomforts to Research Subjects, including embryo, fetus and nursing infant, if applicable;
- (vi) Any expected benefits (must specify if none is expected);
- (vii) The rights to refuse or withdraw at any time without reprisal;
- (viii) Alternative treatments if Research Subject refuses to participate in, or withdraws from, the study;
- (ix) Possible scenarios where the Research Subject's participation may be terminated;
- (x) Anticipated expenses to be borne by, or payment to be made to, Research Subjects;
- (xi) Means of contact for query and urgent medical attention to adverse outcomes;
- (xii) The risk of inducement, such as payment to Research Subjects; and
- (xiii) The protection of subjects' privacy and data confidentiality (subject to study monitoring and audit needs).

5.8 Ethics Review Decision and Validity

The decisions of the Cluster REC should be documented in writing which specifies:

- (a) The review structure, i.e., panel or expedited review.
- (b) The documents (which should be uniquely identified by name, version number and/or date) reviewed.
- (c) Conditions of approval, the violation of which invalidates the ethics approval granted, e.g.
 - (i) Requirements to be met before subject recruitment can commence, such as the submission of an Indemnity Agreement, a Certificate of Clinical Trial and/or a Clinical Trial Certificate issued by DoH as indicated.
 - (ii) Adherence to the approved Application Dossier, and that any amendment to be made requires re-approval by the Cluster REC.
 - (iii) Clinical Research oversight requirements, particularly of adverse event reporting and study progress reporting.
- (d) Reasons for disapproval, suspension or termination of a Clinical Research.

5.9 Appeal against Cluster REC Decisions

- (a) If the Cluster REC disapproves a Clinical Research, the investigator can EITHER modify and resubmit the research proposal OR appeal to HA REC within 30 days of the Cluster REC decision.
- (b) HA REC can assign a panel of no less than three members to review the Cluster REC decision. The HA REC, by so doing, does not perform another ethics review. Its decision is EITHER to “uphold the Cluster REC decision” OR “revert back to Cluster REC for another ethics review”.

6. Clinical Research Oversight / Monitoring

- 6.1 Cluster REC must continuously review or monitor all approved Clinical Research until completion or termination.
- 6.2 The investigator must adhere to the Cluster REC decision and recommendation, and s/he:
 - (a) should not deviate from, or change, the protocol without the prior written Cluster REC approval, except
 - (i) when it is necessary to eliminate immediate hazards to Research Subjects;
 - (ii) if such deviation or change is purely logistical or administrative;
 - (iii) in both cases, the deviation or change must be reported to Cluster REC as soon as possible;
 - (b) should report research progress to the Cluster REC at intervals as indicated in its decision, or if no interval is indicated, report yearly. Such reporting is necessary for the Cluster REC to consider whether the approval status can be maintained;
 - (c) should coordinate timely reporting of adverse events to the sponsor (if applicable), Cluster REC, regulatory body (if required) and the Legal Services Section of HAHO (if there is a risk of claim). This should be done in a timely fashion. Depending on the seriousness and study relatedness of the adverse events, investigators and the Cluster REC should decide on the necessity to modify the study protocol, the consent, and to update subjects of the previously unknown / unexpected risks. As a general guide, the study relatedness of an adverse event increases if it (i) has a reasonable temporal relationship to intervention, (ii) could not readily have been produced by the Research Subject's clinical condition, (iii) could not readily have been due to environmental or other interventions, (iv) follows a known pattern of response to the study article, and particularly if (v) it disappears or decreases with reduction in dose or cessation of the investigational article and (vi) recurs with re-exposure; and
 - (d) should report new information that may be relevant to a Research Subject's

willingness to continue participation in the Clinical Research.

7. **Special Considerations** (for both Study Site Management and Cluster REC)

7.1 Research Collaboration

- (a) Collaborating parties, being separate legal entities, shall agree upon each one's obligations and bear responsibility over the acts of their employees.
- (b) When a HA hospital (or a medical faculty facility) is the principal site of a multi-center study, the lead principal investigator (i.e. principal investigator of the principal site) is responsible for the overall conduct of the Clinical Research. S/he shall serve as the point of communication with the sponsor, other participating sites (and their respective Cluster RECs) and any internal or external agencies.
- (c) When a HA hospital (or a medical faculty facility) is a participating site of a multi-center study, the local Cluster REC shall ascertain if the principal site has been granted ethics approval before reviewing the participating site protocol.

7.2 Student Project

- (a) In addition to the stipulations in this document, student projects must be formally approved by the academia in writing and by such approval, the academia accepts responsibility for all project-related liabilities.
- (b) The student must be under suitable and sufficient supervision by the academia.
- (c) Student projects shall not expose Research Subjects to additional health (including psychological) hazards or involve vulnerable subjects.

7.3 Testing of an Article for Unlicensed Indications

Since off-label use may involve additional health risk (to subjects) and financial risk (to organization), hospital management must take into account:

- (a) Availability of safety information and overseas practice in using the investigational article beyond licensed indications, especially if there has been reported use as in the proposed trial.
- (b) The rationale for testing the article in the proposed trial.
- (c) Whether the manufacturer is aware of the trial and its possible roles and contributions.

7.4 Use of an Investigational Article Beyond the Context of Clinical Research

- (a) Investigational articles that are not registered for sale in the market (e.g. unlicensed drugs, biologics or devices) but approved by a Cluster REC for Clinical Research (beyond phase I and II) may be administered to a patient

outside the approved trial only in very exceptional circumstances:

- (i) when the patient is facing a life-threatening situation;
 - (ii) available treatments are unproven or unsatisfactory, or have failed; and
 - (iii) the patient is not enrolled, or is not eligible to enroll in a Clinical Research involving the test article.
- (b) Emergency use of investigational articles in this context must be endorsed by the supervising specialty team head or COS (in accordance with the local hospital policy) and reported to the hospital management and implicated Cluster REC within 48 hours, giving full details and justification of use.
- (c) If subsequent use is contemplated either in the same patient or in others, approval from the both hospital management and the Cluster REC will be necessary. Note that management and ethical compliance do not override legal requirement and investigators / clinicians must consult regulatory body to ascertain whether the use of the article is under legal control.
- (d) Consent to use an investigational article beyond the context of research must be formally documented in the patient's medical records. Copies of the authorization consent documents should also be submitted to the Cluster REC for reference.

8. Handling of Complaints

- 8.1 Complaints on Clinical Research, whether in respect of incompetence, negligence, misconduct or otherwise, should be investigated promptly at the hospital level.
- 8.2 If there is a genuine concern on the safety of Research Subjects, the hospital should suspend the Clinical Research while the complaint is being investigated.
- 8.3 Cluster REC and HA REC should be notified of the complaint and the investigation findings.