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1. Purpose

This procedure describes how continuing reviews of previously approved *CHH IRB* protocols are managed by the Ethics Committee.

The purpose of the continuing review is to monitor the progress of the entire study, not just the changes in it, to ensure continuous protection of the rights and welfare of research participants. Continuing review of the study may not be conducted through an expedited review procedure, unless 1) the study was eligible for, and initially reviewed by, an expedited review procedure; or 2) the study has changed such that the only activities remaining are eligible for expedited review.

2. Scope

This SOP applies to conducting any continuing review of study protocols involving human subjects at intervals appropriate to the degree of risk but not less than once a year. Depending upon the degree of risk to the participants, the nature of the studies, and the vulnerability of the study participants and duration of the study, the CHH IRB may choose to review or monitor the protocols more frequently.

3. Responsibility

It is the responsibility of the CHH IRB Secretariat to remind the CHH IRB and the principal investigators regarding study protocols that should be continuously reviewed. The Chairperson is responsible for determining the date of continuing review.

The CHH IRB is responsible for reviewing the progress made in the protocol, the occurrence of unexpected events or problems, and the rate of accrual of participants. The protocol informed consent documents and assent documents are examined to ensure that the information remains accurate.

The CHH IRB has the same options for decision making on a continuing review package as for an initial review package. The decision is made as *approval; needs clarifications and resubmission or disapproval*

4. Flow chart

No.	ACTIVITY	RESPONSIBLE PERSONNEL
I	Determine the date of continuing review	CHH IRB Secretariat and Chairperson
II	Notify the study team	CHH IRB Secretariat
III	Manage continuing review package upon receipt	CHH IRB Secretariat
IV	Notify the members of the CHH IRB	CHH IRB Secretariat
V	Prepare meeting agenda	CHH IRB Secretariat and Chairperson
VI	Protocol review process	CHH IRB Secretariat, Members and Chairperson
VII	Store original documents	CHH IRB Secretariat
VIII	Distribute documents to the study team	CHH IRB Secretariat

5. Detailed instructions

5.1 Determine the date of continuing review.

- Look through the document archives for the due date of continuing reviews.
- Plan for continuing review meeting at least two months ahead and as close as possible to the due date or the anniversary of the date of the original approval of the protocol.
- Consult the Chairperson for scheduling the Board meeting date.

5.2 Notify the principal investigator or the study team

- Inform the Study Team at least **two months in advance** of the due date for the continuing review by letter, fax, e-mail or other appropriate means.
- Fax, mail or e-mail also a Continuing Review Application Form (HRP-IRB-018, see ANNEX 1) to the Study Team to fill up.
- Keep the informed notice in the correspondence file.
- Allow the Study Team sufficient time to collate the information and to prepare a report package required for the continuing review.

5.3 Manage continuing review package upon receipt.

Receive a package of **Continuing Review Report** (CRR) for each protocol prepared and submitted by the Study Team.

- Upon receipt of the package, the Secretariat of the CHH IRB should perform the following:

5.3.1 Initial and date the submission package

- See SOP/008/05 for procedures on receipt of submitted packages.

5.3.2 Verify the contents of the package.

- **Continuing Review Application Form**
  - Check for complete information and for the presence of the required signatures (Chairperson of the *CHH IRB)*
  - See ANNEX 1 for the Continuing Review Application Form (HRP-IRB-018).
- **Continuing Review Memorandum** with progress report
  - Summarize the progress of the protocol since the time of the last review.
  - Include information about the number of participants enrolled to date and since the time of the last review, an explanation for any "yes" answers on the application form and a discussion of scientific development, either through the conduct of this study or similar research that may alter risks

to research participants

- **A written progress report/brief project summary** that includes the following or references other documents made available to the IRB:
  - The number of subjects accrued; (For multi-site studies, the number of subjects accrued at the local site and the number accrued study-wide, if available, should be provided.)
  - A brief summary of any amendments to the research approved by the IRB since the IRB's initial review or the last continuing review;
  - Any new and relevant information, published or unpublished, since the last IRB review, especially information about risks associated with the research;
  - A summary of any unanticipated problems.[11] In many cases, such a summary could be a brief statement that there have been no unanticipated problems (i.e., adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and Investigator's Brochure (if applicable));
  - A summary of any subject withdrawals from the research since the last IRB review, and the reasons for withdrawal, if known; and
  - A summary of any complaints about the research from subjects enrolled at the local site since the last IRB review;
- The **latest version of the protocol** and sample informed consent document(s) in use at the site;
- **Any proposed modifications to the informed consent** document or protocol;
- The current **Investigator's Brochure**, if any, including any modifications;
- Any **other significant information** related to subject risks, such as the most recent report, if any, from data monitoring committees (DMCs);
- **Aggregate information about relevant regulatory actions** occurring since the last review that could affect safety and risk assessments (e.g., withdrawal or suspension from marketing in any country on the basis of safety, reports of recalls and device disposition required by 21 CFR 812.150(b)(6)).

5.3.3 Photocopy the package.

- Make sufficient copies (for both members and reviewers) of the original continuing review package.

5.3.4 Store the continuing review package.

- Store the original package in the protocol specific file.

5.4 Notify the Members of the CHH IRB.

- Distribute the protocol progress report and the informed consent document to the CHH IRB.

5.5 Prepare meeting agenda.

- See SOP/017/05 for procedures on the preparation of meeting agenda.
- Place the review on the agenda for the meeting of the CHH IRB which coincides with the anniversary of the protocol effective date (original approval date).
- Distribute the materials to the CHH IRB members by the IRB Secretariat, according to Procedures for Maintaining Confidentiality of CHH IRB Documents at least one and a half to two weeks in advance of the scheduled meeting.
- Keep copies of "sent" e-mail, fax cover memos and/or letter accompanying posted materials in the Correspondence Section of the protocol specific file.
- Record and keep the CHH IRB members' response upon receipt of the agenda in the member correspondence file.

5.6 Protocol Review Process

5.6.1 Continuing Review Application Form

- Use the Continuing Review Application Form (HRP-IRB-018, see ANNEX 1) to guide the review and deliberation process.
- Sign and date the Continuing Review Application Form by the Chairperson of the CHH IRB after a decision has been reached.
  - ❖ The completed Continuing Review Applications Form is the official record of the decision reached by the CHH IRB for the protocol.
- Maintain and keep the form and minutes of the meeting relevant to the continuing review as part of the official record of the review process.

- **Risk Assessment**
  The submitted documents will be reassessed whether risks to the subjects have significantly altered to include whether;

1. Risks to subjects are minimized;
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may be expected to result;
3. Selection of subjects is equitable;
4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, and appropriately documented;
5. Where appropriate, the research plan adequately provides for monitoring the data collected to ensure the safety of subjects;
6. Where appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data;
7. Appropriate additional safeguards are included to protect vulnerable subjects; and
8. Where the study involves children, the research complies with 21 CFR part 50, Subpart D.

- **Adequacy of Informed Consent**

- **Local Issues**

  The reviewing IRB should consider local concerns during both initial and continuing review, including:

  1. Changes in the investigator's situation or qualifications (e.g., suspension of hospital privileges, medical license; involvement in numerous clinical trials);
  2. Evaluation, investigation, and resolution of complaints related to the research;
  3. Changes in the acceptability of the proposed research in terms of institutional commitments (e.g., personnel and financial resources, adequacy of facilities) and regulations, applicable state and local law, or standards of professional conduct or practice;
  4. Reports from third party observation of the research (including the informed consent process) carried out under 21 CFR 56.109(f); and
  5. Investigator concerns about trial conduct at the local site (e.g., study coordinator ineffectiveness, inability of subjects to understand sections of the informed consent document required by institutional policies).

- **Trial Progress**
    1. **Total Subject Enrollment**. The sponsor has primary responsibility for monitoring the study. However, the IRB's responsibility to protect human subjects should include the IRB's review of trial progress. For example, expected rates of enrollment and dropout are generally identified for most studies. A marked difference between the actual and expected rates of enrollment or dropout, either at an individual site or in the study as a whole, may indicate a problem requiring further investigation.
        a. As part of its initial review, the IRB will have approved the protocol, which typically includes the number of subjects expected to be enrolled at a particular site. An investigator who enrolls more subjects than the number allowed at that site may have violated the study protocol or conditions set by the IRB or FDA.
        b. Information about the number of subjects enrolled in the overall study may allow the IRB to ascertain whether enrollment is consistent with the planned number of subjects described in the approved protocol. If enrollment in the study as a whole is too low (either because subject enrollment is too low or subject withdrawal is too high), there may not be justification to continue exposing subjects to the risks of the test article because the study itself may no longer be expected to provide sufficient data to answer the scientific question at hand. (See 21 CFR 56.111(a)(2).)
        c. To address low enrollment issues, an IRB may recommend that the reasons behind the lagging enrollment be explored and appropriate steps be

taken to remedy the situation (e.g., proposals for modification of recruitment practices, adjustment of inclusion criteria and evaluation of reasons for excessive withdrawal). In a multi-site study, participating sites might be enrolling subjects at different times. In this case, information about enrollment across all sites may reaffirm that there is sufficient rationale to continue a clinical investigation at an individual site despite low local enrollment. IRBs should note that once the study is completely enrolled, the study should not be unduly prolonged.

2. Subject Withdrawals. Subjects may withdraw from studies for various reasons (e.g., serious adverse events, conflicts with site staff, transportation problems). IRB continuing review procedures should provide for review of the number of subjects who withdrew from the research at the local site as compared to other sites, and a summary of the reasons for the local withdrawals.

3. Information about subject withdrawals may be available in IRB or institutional files, or obtained from other sources (e.g., complaint files, sponsor, clinical investigator, contract research organization (CRO)). IRB review of this information may shed light on problems related to the conduct of the research at the local site.

5.6.2 Preliminary Communication of the Decision

- Verbal Communication of the Decision
  - The Chairperson notifies the Director of Chong Hua Hospital verbally of the decision and the reasons for the decision as soon as possible after the meeting, but no later than one working day.
- Preliminary Written Communication of the Decision
  - The Chairperson must send an electronic version of the completed Continuing Review Application Form to the

Secretariat and to the Medical and Scientific Director within one working day whenever possible, but no later than 5 working days after the review has taken place.

- The Secretariat, in turn, forwards this to the study team (by e-mail). "Sent" or "Received" e-mails are filed in the protocol file under "Correspondence".

5.6.3 Final Documentation and Communication of the Decision

- Complete the printed version of the Continuing Review Application/ Assessment Form by the Chairperson of the CHH IRB:
  - Sign and date the printed version of the form containing the decision and return this to the Secretariat.
  - Complete the process within 5 working days of the CHH IRB meeting.
- Complete the original version of the Continuing Review Application Form by the Chairperson:
  - Sign and date the original version of the form.
  - The Secretariat must sign and date the form.

5.7 Store original documents.

- Place the original completed documents with the other documents in the Continuing Review Package in the protocol file.

5.8 Distribute documents to the Study Team.

- Distribute copy version of the completed Continuing Review Application/Assessment Form to the Principal Investigator within **7** working days.

6. Glossary

Approved Protocols — Protocols that have been *approved without stipulations* or *approved with recommendations* by the CHH IRB may proceed.

Protocols that have been *approved with stipulations* by the CHH IRB may not proceed until the conditions set by the CHH IRB in the decision have been met. Protocols should be amended and submitted to the CHH IRB within *one* month for re-review.

7. ANNEX

HRP-IRB-018: Continuing Review Application Form

CHONG HUA HOSPITAL
Healing with Passion. Caring with Compassion.

CONTINUING REVIEW APPLICATION FORM

Form HRP-IRB-018

DATE FILED:

PROTOCOL No.: ASSIGNED No.: ☐☐☐ / ☐☐☐☐-☐☐

PROTOCOL TITLE:

PRINCIPAL INVESTIGATOR:

1. ACTION REQUESTED:
   - ☐ Renew - New participant accrual to continue
   - ☐ Renew - Enrolled participant follow up only
   - ☐ Terminate - Protocol discontinued

2. AMENDMENTS SINCE THE LAST REVIEW?
   - ☐ NO
   - ☐ YES (Describe briefly in attached narrative)

3. PROTOCOL PARTICIPANTS SUMMARY:
   - _____ Accrual ceiling set by IRB
   - _____ New participants accrued since last review
   - _____ Total participants accrued since protocol began

4. ACCRUAL EXCLUSIONS
   - ☐ NONE
   - ☐ MALE
   - ☐ FEMALE
   - ☐ OTHER (specify):_____

5. IMPAIRED PARTICIPANTS
   - ☐ None
   - ☐ Physically
   - ☐ Cognitively
   - ☐ Both

6. HAVE THERE BEEN ANY CHANGES IN THE PARTICIPANT POPULATION, RECRUITMENT OR SELECTION CRITERIA SINCE THE LAST REVIEW?
   - ☐ NO
   - ☐ YES (Explain changes in attached narrative)

7. HAVE THERE BEEN ANY CHANGES IN THE INFORMED CONSENT PROCESS OR DOCUMENTATION SINCE THE LAST REVIEW?
   - ☐ NO
   - ☐ YES (Explain changes in attached narrative)

8. CHANGE IN PRINCIPAL INVESTIGATOR?
   - ☐ NONE
   - ☐ DELETE:_____
   - ☐ ADD: _____

9. IS THERE NEW INFORMATION FROM SIMILAR RESEARCH THAT MIGHT AFFECT THE RISK/BENEFIT RATIO OF THE HUMAN SUBJECTS INVOLVED IN THIS PROTOCOL?
   - ☐ NO
   - ☐ YES (Discuss in the attached narrative)

10. HAVE ANY UNEXPECTED COMPLICATIONS OR ADVERSE EVENTS BEEN NOTED SINCE LAST REVIEW?
    - ☐ NO
    - ☐ YES (Discuss in the attached narrative)

11. HAVE ANY PARTICIPANTS WITHDRAWN FROM THIS STUDY SINCE THE LAST IRB APPROVAL?
    - ☐ NO
    - ☐ YES (Discuss in the attached narrative)

12. HAVE ANY PARTICIPATING INVESTIGATORS BEEN ADDED OR DELETED SINCE LAST REVIEW?
    - ☐ NO
    - ☐ YES (Identify all changes in the attached narrative)

13. HAVE ANY NEW COLLABORATING SITES (INSTITUTIONS) BEEN ADDED OR DELETED SINCE THE LAST REVIEW?
    - ☐ NO
    - ☐ YES (Identify all changes and provide an explanation of changes in the attached narrative)

14. HAVE ANY INVESTIGATORS DEVELOPED EQUITY OR CONSULTATIVE RELATIONSHIP WITH A SOURCE RELATED TO THIS PROTOCOL WHICH MIGHT BE CONSIDERED A CONFLICT OF INTEREST?
    - ☐ NO
    - ☐ YES (Append a statement of disclosure)

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CONTINUING REVIEW APPLICATION FORM

Form HRP-IRB-018

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CONTINUING REVIEW APPLICATION FORM

Form HRP-IRB-018

SIGNED

_____ Date: _____
Principal Investigator

IRB Comment/Decision:

- ☐ Needs Clarification
- ☐ Approval
- ☐ Disapproval

SIGNED

_____ Date: _____
Chairperson, *CHONG HUA HOSPITAL IRB*

8. References

- World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000.
- International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996.
- Associated SOP# FE 007, 024, and 028.
- CFR 312.53(c)(1)(vii), 312.60, 312.66, 812.36(c)(viii), 812.100, 812.110(b), 812.40, and 812.43(c)(4)(i). [10] Some of this information may come from the sponsor, who would have access to data across all study sites. Sponsors may provide information directly to IRBs or to the clinical investigators who in turn would share it with the IRBs.
- IRB procedures must ensure that there is prompt reporting to the IRB of unanticipated problems involving risks to human subjects or others (21 CFR 56.108(b)(1)). See "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs--Improving Human Subject Protection,"
- http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126572.pdf.accessed 28 April 2016.