Investigator's Code of Practice

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Version and Review Highlights

Version No.	Issue Date (DD/MM/YY)	Effective Date (DD/MM/YY)	Review Date (DD/MM/YY)	Highlights for the Issue
4	31/07/2024	01/08/2024	01/08/2027	1. Added Section 5.2 for handling of research data that involves identifiable patient data 2. Correction of typo errors and standardization of the term "clinical study" 3. Updated footnotes 1 and 3 4. Updated hyperlinks 5. All references to "subject(s)" are replaced by "participants" in line with the latest research ethics practice.

Table of Content

Related Document

Hospital Authority (HA) Guide on Research Ethics (for Study Site & Research Ethics Committee)

1. Objective

1.1 To document the expectations on responsibilities of Investigator(s) in the conduct of clinical trial and clinical research (collectively referred to as "clinical study") by the Hospital Authority ("HA").

2. Scope

2.1 Apply to clinical study[1] involving HA patients[2] or conducted within HA premises.

3. Investigator Responsibility

3.1 Fundamental responsibilities of investigator(s) are:

(i) Human participant protection (not limited to clinical care, see Annex I);

(ii) Compliance with regulatory, ethical and institutional requirements on research conducts; and

(iii) Fair conduct and fair reporting of clinical study, including comprehensive and accurate documentation of research procedures and data, and storage of study documents for the required duration.

3.2 The Principal Investigator ("PI") is ultimately accountable to the sponsor, institution (HA or University Medical Faculty as appropriate) for all study-related activities, including those delegated to others. The PI, therefore, has additional responsibilities of:

(i) Ensuring the clinical study is scientifically sound and ethically justified (see Annex II); and

(ii) Managing the research project and supervising the research team, to ensure the

[1] A clinical study means any systematic investigation in any medical or scientific discipline with the objective of answering question(s) that may contribute to establishment of theory(ies), principle(s) or generalizable knowledge by processing, analyzing and reporting of information collected from: (i) human beings (e.g. randomized controlled trial on a medical product or clinical procedure, or observational study following the progression of a disease); (ii) identifiable human materials (e.g. genetic analysis of archived human specimens); and/or (iii) identifiable human data (e.g. medical chart review or case series). It does not cover the use of innovative therapeutic interventions to benefit individual patients basing on clinical judgment or humanitarian grounds, or clinical audit with neither experimental design nor extra risk/inconvenience to routine care.

[2] Including research on materials of human origins, such as body tissue and fluid, including "waste" or "leftover" from diagnosis, treatment and post-mortem examination, or archiving such materials for future studies, and collation of records/data (whether prospective or retrospective) where there is a reasonable likelihood that such may link to the individuals' identifiable particulars or identifiers.

research is conducted according to protocol and study plan.

4. Investigator Competence

4.1 Investigator(s) must be qualified by training and experience for the respective tasks required by a given study. The PI must possess in-depth knowledge of the study including its background, preliminary studies, safety information, all details outlined in the research protocol, and investigator's brochure if applicable.

4.2 In therapeutic trials, the responsibility for the human research participant must rest with an appropriately qualified healthcare professional.

4.3 The PI should be familiar with the Declaration of Helsinki, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice (ICH-GCP Guideline) and Hospital Authority (HA) Guide on Research Ethics (for Study Site & Research Ethics Committee).

5. Research Project Management

5.1 The PI has overall responsibility in technical, administrative, fiscal and risk management of a given clinical study, s/he must:

(i) Obtain approvals from Research Ethics Committee/Institutional Review Board ("REC/IRB")[3], study site management (i.e. hospital and/or affiliating academia if applicable) and regulatory body (where applicable[4]) before commencing a Clinical Study;

(ii) Verify approvals have been obtained from all applying sites;

(iii) Liaise with sponsor, study team members, REC/IRB, Institution (study site) and

[3] Ethics review and approval is required for all research involving human participants including study on body tissue, fluid, records and data, which also applies to (i) prior collected data in a format linking to individual identifiers; (ii) 'waste' or 'extra' tissue / fluid; and (iii) collection and storage of 'extra' material for future study. If an activity exceeds the routine clinical care needs, or is intended to be published in a scientific journal as a study, then it falls under the domain of research, and hence, needs an ethics review. Quality assurance activity (e.g. clinical audit) that involves additional risk, burdens, intrusion of privacy and possibly overlap with research may require ethics review.

[4] According to the Regulation 36B of "Pharmacy and Poisons Regulations (Cap.138A)" under the "Pharmacy and Poisons Ordinance" (Cap. 138), and Section 129 "Chinese Medicine Ordinance" (Cap. 549), a Certificate for Clinical Trial or Medicinal Test is required for the purpose of conducting (or facilitating the conduct of) a clinical trial on human beings or a medicinal test on animals. The sponsor or the PI should obtain this certificate issued by the Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances: Certification of Clinical Trial/Medicinal Test) Committee (https://www.drugoffice.gov.hk/) or Chinese Medicines Board (http://www.cmchk.org.hk/) accordingly, and then submit a copy of it to the REC/IRB.

Regulatory Bodies as required;

(iv) Ensure disclosure of all Conflicts of Interest;

(v) Ensure appropriate agreements (e.g. Clinical Trial Agreement ("CTA")) are completed and filed, if applicable;

(vi) Ensure competency of study team members in research conduct and care of participants;

(vii) Ascertain competency and safe operation of collaborating sites not managed by HA, especially if they are providing care to participants as part of the study;

(viii) Oversee research conducts to ensure research is carried out in a manner which is safe, efficient and ethical;

(ix) Ensure that written informed consent, as well as authorization for the use and disclosure of participant's health information, is obtained from each study participant prior to enrollment, unless these requirements are altered or waived by the REC/IRB;

(x) Control access to test articles and keep record of their use;

(xi) Ensure adequate and accurate records of all required observations and data during the study for each study participant;

(xii) Protect the privacy of participants and confidentiality of data. Safeguard the personal data of participants from being used for other purposes;

(xiii) Notify the REC/IRB of study changes, submit the required report for continuing review as specified by the REC/IRB approval letter, and prepare a final report to REC/IRB upon trial completion;

(xiv) Monitor participants' safety and well-being throughout the study. Coordinate and report all Suspected, Unexpected, Serious Adverse Reactions ("SUSARs")[5], occurred locally or overseas, to the sponsor (if available), REC/IRB, regulatory agency (if required by law) and the Legal Services Department of HAHO (when there is potential claim and legal implication). This should be done in a timely fashion[6]. Depending on the seriousness and study relatedness[7] of the adverse events, investigators should decide on the necessity to modify the study protocol, the informed consent form, and to update participants of the previously

[5] An adverse event is serious if it causes (i) death or a life-threatening event, (ii) hospitalization or prolongation of an existing hospitalization, (iii) persistent or significant disability or incapacity, (iv) congenital anomaly or birth defect, or (v) other harms judged by PI to be serious.

[6] ICH-GCP specifies immediate reporting of serious adverse event (SAE) to sponsor (para 4.11.1) and prompt reporting of all adverse drug reactions that are both serious and unexpected to the REC (para 3.3.8c).

[7] The SAE Report Form requires the PIs to estimate, at the time of reporting, of the causal relationship between study participation and the adverse event. 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 participant's clinical state, (iii) could not readily have been due to environmental or other interventions, (iv) follows a known pattern of response to intervention, and particularly if (v) it disappears or decreases with reduction in dose or cessation of intervention and (vi) recurs with re-exposure.

unknown/unexpected risk:

(xv) Permit appropriate monitoring bodies/authorities to inspect and monitor records of the study; and

(xvi) In the event that the PI resigns from the clinical study, the trial must be suspended until a new PI is approved by the REC/IRB, sponsor and Institution(s), i.e. hospital management or the University Medical Faculty as appropriate.

5.2 For clinical study involving identifiable patient data, in addition to the Personal Data (Privacy) Ordinance (Cap. 486), the PI should also comply with the Clinical Data Policy Manual of HA, especially:

(i) Section 3.1.1 – Authorized access

(ii) Section 3.1.1.2.2 – Access to Patient Data for Clinical Research & Teaching Purposes

(iii) Section 3.5 – Data Export

6. Archiving and Disposal of Study Documents

6.1 Study documents and related medical records must be kept for the period mandated by the ICH-GCP, regulatory requirements and/or CTA, whichever is longer, so that they can be accessed after completion/termination of a study, in case unforeseen side effects develop afterwards.

(i) The responsibility of keeping study documents, other than medical records, rests with the sponsor as well as the PI / study site. As such, the PI must maintain all essential documents throughout the study, and pass them to the respective department of the study site for storage upon completion/termination of the study.

(ii) The responsibility of keeping medical records remains with the hospital. As such, the PI should inform the hospital Medical Record Office of those medical records requiring extended storage and the storage period.

6.2 The ICH-GCP specified the documents essential for conducting clinical study (Section 8), and for how long (Section 5.5.11).

6.3 At the end of the required storage, study documents must be properly disposed to protect participants' privacy.

7. Use of Test Articles beyond the context of Study

7.1 Test articles that are not registered for sale in the market but approved for clinical study may be administered to a patient not involving in the study in exceptional conditions:

(i) participant is facing a life-threatening situation;

(ii) available treatments are unproven or unsatisfactory, or have failed; and

(iii) participant is not enrolled, or is not eligible to enroll in a study involving the test article.

7.2 Investigators proposing such use must seek endorsement within the study team, the sponsor, institution and report the use to the REC/IRB within 48 hours, giving details and justification for the use. If subsequent use is contemplated either in the same participant or in others, approval from the REC/IRB is necessary.

7.3 The above ethical considerations do not override legal requirements, hence, investigators must seek regulatory approval as is required.

8. Availability of Study Article after Study

8.1 Participants are entitled to appropriate medical care after completion of study. In general, they should continue to receive test articles that are proven to be beneficial in their treatment until these articles are made available commercially, especially if it is life-saving or has enormous effect on participant's quality of life, and there is no alternative effective treatment. Arrangement of test article supply or lack of it after study completion should be explained to research participants in the consent process. This is especially important if it is foreseen that a test article may not be financed by the public health service due to budgetary reasons.

References

(i) Declaration of Helsinki[8]
(ii) ICH[9]-GCP[10]
(iii) EC Clinical Trials Directive 2001/20/EC[11]
(iv) Clinical Trial Regulation EU No. 536/2014[12]
(v) GMC Guidance on Good Practice in Research[13]

[8] The most widely accepted ethical principles for medical research involving human subjects established by the World Medical Association. https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
[9] International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use. Scientific and regulatory standards in clinical research on medicinal products agreed between EU, Japan and USA. http://www.ich.org/home.html
[10] Good Clinical Practice. A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. https://www.ich.org/page/efficacy-guidelines
[11] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32001L0020&qid=1610347513340
This Directive will be repealed by Regulation EU No. 536/2014.
[12] https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0536&qid=1610347513340
[13] GMC guidance on the role and responsibilities of doctors is available on its website. http://www.gmc-uk.org/guidance/ethical_guidance/5992.asp

Annex 1: Rights of Research Participants

Investigator must respect and protect rights of research participants. The obvious ones include:

i) Self-determination: Participation in research must be voluntary, i.e. no undue influence, no coercion, and participants are free to withdraw from research at any time without reprisal.

ii) Respect for human dignity: Participants' culture and belief must be respected.

iii) Right to information and care: Participants should receive appropriate medical care during and after study. They should be updated throughout the research of new information that may be relevant to their willingness to continue participation in the research.

iv) Privacy: Participants' privacy must be protected. Ensure data confidentiality, keep disclosure to the minimum necessary and anonymize data whenever possible. Keep abreast with, and abide by legal requirement[14,15] and on personal data privacy.

v) Compensation for injury: Participants should be compensated for and taken care of research-related injuries.

vi) Non-exploitation:

- Vulnerable participants should not be included in research unless the research is necessary to promote the health of the study population and it cannot be performed on other, less vulnerable participants.
- Selection of research participant should be equitable such that no individual or group should be overburdened without the acquisition of potential benefits.

[14] Personal Data (Privacy) Ordinance (Chapter 486). https://www.elegislation.gov.hk/hk/cap486?pmc=1&m=1&pm=0

[15] Code of Practice on the Identity Card Number and other Personal Identifiers. https://www.pcpd.org.hk/english/data_privacy_law/code_of_practices/code.html

Annex 2: Justification for Clinical Study

i) Clinical study has value as measured by its potential in improving healthcare or furthering knowledge, or both. Nonetheless, development of treatment and furthering of knowledge do not take precedence over the interests of research participants.

ii) Trial design and methodology are scientifically valid and adequate. Some practical considerations are:

- Are the research questions clearly framed, and are they being addressed according to present state of knowledge and clinical practice context?
- For trials with an experimental design, is it possible to frame the research question in the form of a testable null hypothesis[16]?
- Is the use of control or placebo groups adequately addressed?
- In therapeutic trials comparing treatment interventions, does clinical equipoise[17] exist between the different interventions?
- How relevant are the study endpoints in reflecting patients' concern?
- Is the likely effect size worthy of the expenditure of effort, time and other resources?
- Are the methods and procedures involved valid and reliable?
- Are the types of statistical/analytical method to be used suitable for the trial?
- Does the sample size provide adequate levels of significance and power to detect meaningful differences between the comparison groups?
- Is the study timeframe reasonable and is it practical to recruit the planned sample size within the timeframe?
- Does the research design deal with potential biases adequately and to what extent can one generalize the study findings?
- Are there sufficient resources (budget, personnel and facilities) to support the research?
- Are there adequate provisions to identify safety issues and minimize risk to participants?

iii) Risk-benefit analysis: Anticipated benefits[18] must justify foreseeable risks[19].

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[16] It is theoretically impossible to prove a hypothesis to be right. Only the converse can be done, as a single robust contradicting observation will cast serious doubt, if not negate a hypothesis. A testable hypothesis is one that is falsifiable, i.e., it is possible to conceive of results or observations that contradict the predictions of the hypothesis. This is the rationale of "*Null Hypothesis*".

[17] Clinical equipoise is a concept referring to a collective professional uncertainty about the comparative therapeutic merits of each arm of a clinical trial.

[18] Only benefits directly traceable to the study article should be included. Do not count factors such as participants may receive more attention, better facilities, etc.

[19] This may not be limited to the risks of study article, as a research may involve additional invasive procedures. However, risks associated with the research should be distinguished from the risks of therapies the participants would receive even if not participating in research.