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INVESTIGATOR' S CODE OF PRACTICE

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HOSPITAL AUTHORITY GUIDE ON RESEARCH ETHICS: FOR STUDY SITE AND
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1. Objective

To document the expectations on responsibilities of Investigator in the conduct of clinical trials by the Hospital Authority (HA).

2. Scope

Apply to clinical trial¹ involving HA patients² or conducted within HA premises.

3. Investigator Responsibility

- i) Fundamental responsibilities of investigators are:
 - Human subject protection (not limited to clinical care, see Appendix 1);
 - Compliance with regulatory, ethical and institutional requirements on research conducts;
 - Fair conduct and fair reporting of clinical trials, including comprehensive and accurate documentation of research procedures and data, and storage of trial documents for the required duration.
- ii) The Principal Investigator (PI) is ultimately accountable to the Sponsor, Institution (HA or University Medical Faculty as appropriate) for all trial-related activities, including those delegated to others. The PI, therefore, has additional responsibilities of
 - ensuring the trial is scientifically sound and ethically justified (see Appendix 2);
 - managing the research project³ and supervising the research team, to ensure the research is conducted according to protocol and study plan.

4. Investigator Competence


- i) Investigator must be qualified by training and experience for the respective tasks required by a given trial. The PI must possess in-depth knowledge of the trial including its background, preliminary studies, safety information, all details in the research protocol, (and Investigator's Brochure if applicable.)
- ii) In therapeutic trials, the responsibility for the human research subject must rest with an appropriately qualified healthcare professional.
- iii) The PI should be familiar with the Declaration of Helsinki, ICH-GCP⁴ and HA policy on clinical research.

¹It 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. However, 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 clinical research, and hence, needs an ethics review.

²Including 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.

³In a multi-centre trial, the lead PI has the overall responsibility in managing the research while site PIs are responsible for research activities at the site.

⁴International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; E6(R2) Guideline for Good Clinical Practice.

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5. Research Project Management

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

- i) Obtain approvals from REC/IRB⁵, study site management (i.e. hospital and affiliating academia if applicable) and regulatory body (where applicable⁶) before commencing a trial.
- ii) Verify approvals have been obtained from all collaborating sites.
- iii) Liaise with Sponsor, collaborators, REC/IRB, Institution (study site) and Regulatory Bodies as required.
- iv) Ensure disclosure of all Conflicts of Interest.
- v) Ensure appropriate agreements (e.g. Indemnity Agreement) and contracts (e.g. Clinical Trial Agreement/CTA) are completed and filed.
- vi) Ensure competency of research 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 subjects as part of the trial.
- 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 subject'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 subjects and confidentiality of data. Safeguard the personal data of subjects from being used for other purposes.

⁵ Ethics review and approval is required for all research involving human subjects 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. Ethical approval is usually not required in analysis of existing or secondary data if no identifiers are recorded that link the data to the subject. Quality assurance activity (e.g. clinical audit) that involves additional risk, burdens, intrusion of privacy and possibly overlap with research may require ethics review.

⁶ Under the Law of Hong Kong, Regulation 36B under Chapter 138A "Pharmacy and Poisons Regulations" of the "Pharmacy and Poisons Ordinance", and Section 129 "Clinical Trials and Medicinal Tests" of Chapter 549 "Chinese Medicine Ordinance", 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/eps/do/en/doc/guidelines_forms/Guidance_Notes_en_Version.pdf?v=ksql0wi) or Chinese Medicines Board (http://www.cmchk.org.hk/pcm/pdf/CT_Cert_GL_e.pdf) accordingly, and then submit a copy of it to the respective REC.

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- 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 subjects' safety and well-being throughout study. Coordinate and report all Suspected, Unexpected, Serious Adverse Reactions (SUSARs)⁷, 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 fashion⁸. Depending on the seriousness and study relatedness⁹ of the adverse events, investigators should decide on the necessity to modify the study protocol, the consent form, and to update subjects of the previously unknown/unexpected risk.
- xv) Permit appropriate monitoring bodies/authorities to inspect and monitor records of the trial.
- xvi) In the event that the PI resigns from the trial, 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.


6. Archiving and Disposal of Trial Documents

- i) Trial 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 trial, in case unforeseen side effects develop afterwards.
 - The responsibility of keeping trial documents, other than medical records, rests with the Sponsor as well as the PI / study site. As such, the PI must maintain all essential trial documents throughout the trial, and pass them to the respective department of the study site for storage upon completion/termination of a trial.
 - 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.

⁷ 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.

⁸ ICH-GCP specifies immediate reporting of 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).

⁹ 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 subject'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.

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- ii) The ICH GCP Guidelines are specific about which documents are essential for the conduct of a clinical trial (Section 8), and for how long (Section 5.5.11: The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor [i.e. as agreed in the CTA.]
- iii) At the end of the required storage, trial documents must be properly disposed to protect subjects' privacy.

7. Use of Test Articles beyond the context of Research

- i) Test articles that are not registered for sale in the market but approved for clinical trial may be administered to a patient not involving in trial in exceptional conditions:
 - subject is facing a life-threatening situation, and
 - available treatments are unproven or unsatisfactory, or have failed, and
 - subject is not enrolled, or is not eligible to enroll in a trial involving the test article.
- ii) Investigators proposing such use must seek endorsement within the research team, the Sponsor, Institution and report use to the REC/IRB within 48 hours, giving details and justification of use. If subsequent use is contemplated either in the same subject or in others, approval from the REC/IRB is necessary.
- iii) The above ethical considerations do not override legal requirements, hence, investigators must seek regulatory approval as is required.


8. Availability of Study Article after Research

Subjects 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 subjects 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.

9. Reference

- i) Declaration of Helsinki¹⁰
- ii) ICH¹¹-GCP¹²

¹⁰ 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/>

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- iii) EC Clinical Trials Directive 2001/20/EC (relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use)¹³. The EU Clinical Trial Directive 2001/20/EC will be replaced by the Clinical Trial Regulation EU No. 536/2014 when the Regulation becomes applicable during 2019¹⁴
- iv) GMC Guidance on Good Practice in Research¹⁵

¹¹ 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>

¹² 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.


http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2_Step_4_2016_1109.pdf

¹³ All EU Member States should have the Directive implemented in national regulations by May 2004. <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF>

¹⁴ The Clinical Trial Regulation EU No. 536/2014 was adopted and entered into force in 2014 and the Regulation will come into application during 2019.

https://www.therqa.com/assets/js/tiny_mce/plugins/filemanager/files/Committees/Good_Clinical_Practice_GCP/Clinical_Trials_Regulation_EU_No_5362014.pdf

¹⁵ GMC guidance on the role and responsibilities of doctors is available on its website. http://www.gmc-uk.org/guidance/ethical_guidance/5992.asp

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Appendix 1 Rights of Research Subjects

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

- i) Self determination: Participation in research must be voluntary, i.e. no undue influence, no coercion, and Subjects are free to withdraw from research at any time without reprisal.
- ii) Respect for human dignity: Subjects' culture and belief must be respected.
- iii) Right to information and care: Subjects 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: Subjects' 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^{16,17} and HA policy^{18,19,20,21,22} on personal data privacy.
- v) Compensation for injury: Subjects should be compensated for and taken care of research-related injuries.
- vi) Non-exploitation:
 - Vulnerable subjects 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 subjects.
 - Selection of research subject should be equitable such that no individual or group should be overburdened without the acquisition of potential benefits.

¹⁶ Personal Data (Privacy) Ordinance (Chapter 486). <https://www.elegislation.gov.hk/hk/cap486?pmc=1&m=1&pm=0>

¹⁷ Code of Practice on the Identity Card Number and other Personal Identifiers (1st Revision, April 2016)

https://www.pcpd.org.hk/english/data_privacy_law/code_of_practices/files/picode_en.pdf

¹⁸ Clinical Data Policy Manual. http://informatics.home/mediawiki/index.php/Clinical_Data_Policy_Manual_-_Table_of_Content_version_Sept_06


¹⁹ Information Technology Circular No. 11/2016 - Confidential and Personal Data Security. <http://ha.home/circular2/IT-2016-11.pdf>

²⁰ Information Security Policy and Procedure Manual for Hospital Authority (Nov 2014, pending review in Nov 2017) http://hacgl.home/it/getDMSPDF.aspx?FileUrl=http://hadms.home/HAHO/itd/PDF%20DMS%20Document/cfd19b96-a916-472b-bf31-64d6637c0c44/Information%20Security%20Policy%20and%20Procedures%20Manual_1.pdf

²¹ Information Technology Circular No. 3/2016 - Electronic Communications Policy. <http://ha.home/circular2/IT-2016-03.pdf>

²² A Practical Guide to IT Security for Everyone Working in Hospital Authority (May 2008)

<http://infosec.home/PoliciesAndGuidelines/PracticalGuideToITSecurity.aspx?Menu=Guidelines&Lang=en-US>

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Appendix 2 Justification for Clinical Research

- i) Clinical research 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 subjects.
- 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 hypothesis²³?
 - Is the use of control or placebo groups adequately addressed?
 - In therapeutic trials comparing treatment interventions, does clinical equipoise²⁴ 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 benefits²⁵ must justify foreseeable risks²⁶.

²³ 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*".

²⁴ Clinical equipoise is a concept referring to a collective professional uncertainty about the comparative therapeutic merits of each arm of a clinical trial.

²⁵ Only benefits directly traceable to the study article should be included. Do not count factors such as subjects may receive more attention, better facilities, etc.

²⁶ 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 subjects would receive even if not participating in research.