

- 1. Title**
Investigator's Code of Practice in Undertaking Clinical Research
- 2. Purpose**
Clinical research is made possible through trust between participants and investigators. Since the benefit of research is not always certain, it is crucial to ensure that the research is not contrary to the participants' best interest. The responsibilities which investigators have towards human research subjects reflect basic ethical values such as honesty, beneficence, fairness, respect for human dignity and autonomy. This document sets out the standards expected of investigators performing clinical research¹ within the Hospital Authority (HA).
- 3. Scope**
This document applies to clinical research² and does not cover clinical audit with no experimental design or the use of innovative therapeutic interventions to benefit individual patients basing on clinical judgment.
- 4. Basic Principles**
 - i) Research should have value as measured by its potential in improving healthcare and/or furthering knowledge. However, development of treatment and furthering of knowledge shall not by themselves take precedence over patient interest, i.e. anticipated benefit must justify risk.
 - ii) Equipoise must exist between treatment interventions to be compared.
 - iii) Hypothesis of research must be testable³.
 - iv) Research must be conducted in an ethical manner, i.e. in accordance to the Declaration of Helsinki, ICH-GCP, local regulations and institution policy whenever applicable.
- 5. Rights of Research Participant**
 - i) Participation in research must be voluntary. Research participants shall never be coerced or placed under undue influence throughout study.
 - ii) Participants are free to withdraw from research at anytime without reprisal.
 - iii) Participants' culture and belief must be respected.
 - iv) Participants should be updated throughout the research of new information that may be relevant to their willingness to continue participation in the research.
 - v) Participants should be compensated for and taken care of research-related injuries.
 - vi) Selection of research participant should be equitable in that no individual or group should be overburdened without the acquisition of potential benefits. Over-use of patient groups or individuals should be avoided.
 - vii) 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. Investigators should give consideration to their vulnerability and be careful not to exert undue influence on these subjects.
 - viii) Whenever applicable, seek participants' consents to inform their personal physicians (and other clinicians responsible for their care) of their involvement in the research and provide these clinicians the necessary information for their continuing care.
 - ix) Participants are entitled to receive appropriate medical care after completion of study. In general, they should continue to receive the test articles that are proven to be

¹ The decision to develop a Code of Practice for research investigators was endorsed in the Medical Service Development Committee meeting held on 15/12/2003 (MSDC-P181). This document should be used in conjunction with our other guidance documents listed in section 14.

² This also covers human genome, pre-implantation and human embryo research.

³ 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*".

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. In all cases, the arrangement of test article supply or lack of it after study completion should be explicitly explained to participants in the consent."

- x) In all cases, the arrangement of test article supply or lack of it after study completion should be explained to participants beforehand.
- xi) Protect the privacy of participants and confidentiality of data. Keep disclosures to the minimum necessary and anonymize the data whenever possible. For information that are sensitive, seek consent to its disclosure. Keep abreast with, and abide by, statute and common law requirements on personal privacy, e.g. CAP486 Personal Data (Privacy) Ordinance. The above principle also applies to record-based research without directly dealing with human subjects.

6. Consent for Research

- i) Informed consent is a process that involves giving a subject adequate information concerning the research, providing adequate opportunity for the subject to consider all options, responding to the subject's questions, ensuring that the subject has comprehended this information, obtaining the subject's voluntary agreement to participate and, continuing to provide information as the subject or situation requires. The process should provide ample opportunity for the investigator and subject to exchange information and ask questions.
- ii) Subject giving consent must be competent, has adequate information and understanding, and agrees voluntarily, i.e. free from coercion, fear or deceit to the offer. Principles established from case law on informed consent for medical intervention often define competency in giving or withholding consent by a person's ability in (a) comprehending presented information clearly, in particular issues and circumstances relating to giving the consent, (b) retaining the information long enough to consider, and (c) weighing the information in balance to arrive at a decision. Age as a relevant indicator of likely intellectual development and maturity is often the first factor to consider in seeking consent. Nonetheless, assessing mental capacity is a matter for professional judgment and the Law has not set a dividing line basing on age. Although adults are assumed to be competent until proven otherwise, minors (i.e., age <18 years) do have legal capacity to consent if they can fulfill the above requirements. It is important to note that competence is not an all or none phenomenon, as the capacity to consent will depend on the nature of the proposed intervention and the ability of the patient to understand its specific implications. A mentally incapacitated adult who could understand the procedure and its implications can consent to or refuse that procedure. (See excerpt from FDA's IRB Guide⁴)
- iii) Additional requirements regarding information to be given to research subjects are provided in the ICH GCP Guideline E6, Section 4.8.10. In brief, this should cover research aims, methods, nature of involvement, anticipated benefits, risks and discomforts, right to not participate or withdraw consent at any time, data

⁴ "Special provision may need to be made when comprehension is severely limited - for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g., infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails pro-providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm. The third parties chosen should be those who are most likely to understand the incompetent subject's situation and to act in that person's best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject's best interest."

confidentiality, sources of funding, any possible conflicts of interest, institutional affiliations of the researchers, compensation, indemnity, insurance etc. A quick reference is provided in the REC Review Checklist (HA RE001F5) which incorporates most of the ICH GCP requirements on consent for research.

- iv) Consent should be in a written format save in exceptional circumstances where specific approval not to obtain consent or written consent has been given by the REC⁵.
- v) Consent should not contain any exculpatory language that ask participants to waive (or appear to waive) any of their legal rights, or to release the investigator, sponsor, or study site from liability for negligence.
- vi) Communicate in terms that the participant can understand. Consent document should be written in a language suitable for the intended participants. Bear in mind the difficulties facing lay persons in understanding scientific and medical concepts and weighing the risk and uncertainty. Provide supporting information leaflet where possible and give participant opportunities to ask questions and to express any concerns s/he may have. Participant must understand that s/he is being asked to participate in a research in which the outcome is yet to be established.
- vii) Financial cost to be charged and payment to participant must be explained and stated clearly in the consent / information sheet.
- viii) Special situations:
 - Research into treatment in emergencies: In an emergency where consent cannot be obtained, treatment can be given only if it is limited to what is immediately necessary to save life or avoid significant deterioration in the patient's health. This may include treatment that is part of a therapeutic research project, where the risks of the new treatment are not believed to exceed the known risks of standard treatment. If, during treatment, the patient regains capacity, the patient should be told about the research as soon as possible and their consent to continue should be sought. If it is possible, you should discuss the situation with relatives and/or partners of the patient unless you have what you judge to be good reason to believe that the patient would wish otherwise. You must always respect the terms of any valid advance refusal that you know about, or is drawn to your attention. If there is time, you may want to seek the opinion or advice of another member of the research team to discuss the course of action you are intending to take.
 - Consent to archive samples of body tissues or fluids research: The extent and purpose must be indicated in the consent as clear as possible. This applies whether the material is obtained solely for research or retained following a treatment procedure or post-mortem examination, saves in exceptional circumstances that qualify for waiver and endorsed by the REC.
 - Consent to use existing records for research: Consent is required save in circumstances where research cannot practicably be carried out without the waiver and it involves no more than minimal risk to subjects and the waiver will not adversely affect the rights, safety and welfare of subjects, then the REC may consider to waive the consent requirement.

7. Research Design

- i) Research questions should be carefully selected, clearly framed and stated in advance.
- ii) Study should address the research questions according to present state of knowledge and put into clinical practice context as far as possible.
- iii) The design and methodology must be scientifically valid and adequate in addressing the questions posed. Important considerations include:
 - Is the research question well defined?
 - Is it possible to frame the research questions in terms of a testable null hypothesis?
 - Is selection of research subjects equitable?
 - Is the use of control or placebo groups adequately addressed?

⁵ See Hospital Authority Guide for Cluster Research Ethics Committees.

- Are the study endpoints relevant and reflect 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?
 - 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?
 - Are the types of statistical / analytical method to be used suitable for the research?
 - 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?
- iv) There are adequate provisions to identify safety issues and minimize risk to participants.

8. Benefit Risk Analysis

- i) Risk-benefit analysis involves a series of considerations:
- Identify the risks associated with the research, as distinguished from the risks of therapies the subjects would receive even if not participating in research.
 - Risk can be seen as the combination of the probability of occurrence of harm and the likely severity of that harm.
 - Determine that the risks will be minimized to the extent possible.
 - Identify the probable benefits to be derived from the research.
 - Determine that the risks are reasonable in relation to be benefits to subjects, if any, and the importance of the knowledge to be gained.
 - Determine if the measures available are suitable and sufficient for early detection and effective management of possible adverse outcomes.
 - Risk-benefit analysis should be more stringent in non-therapeutic than therapeutic research, and in research involving vulnerable subjects.

9. Research-related Liability

Clinical research is a high-risk activity and collaborative efforts between investigators, study site authority and REC are required to contain its risk and liabilities, which could involve health hazard (to research subjects) and financial and legal risk (to sponsor, investigators, study sites). This underpins the need for ethical code of practice and control over research conducts.

10. Research Investigator

- i) Investigators must be qualified by education, training and experience⁶ to perform the respective tasks required by the study. Supporting evidence should be made available when required.
- ii) In therapeutic research, the responsibility for the human research subject must rest with a medically qualified person.
- iii) The principal investigator (PI) assumes overall responsibility of study, in:
- Liaising with sponsor (if applicable), to settle appropriate sharing of liability and responsibility for subject injury, ownership of data, and the autonomy and rights to publish in academic journals. Contracts with sponsor should not place the study site (and parent organization such as HA or University) in unfavorable position.
 - Ascertaining competency and safe operation of collaborating study sites not under the control of HA, especially if they are providing study related clinical care to research subjects.
 - Seeking necessary approvals including ethical review.
 - Communicating with the study site authority, REC and other bodies with regulatory

⁶ Experience refers to familiarity with the appropriate use of the investigational product and understanding about the potential adverse effects.

- authority.
 - Ensuring competency of research team members in research-related activities and care of participants.
 - Ensuring data quality, accuracy and confidentiality.
 - Addressing liability and indemnity issues.
 - Overseeing research conducts, i.e. research is carried out in a manner which is safe, efficient and ethical.
- iv) If the PI leaves HA (or the University Medical Faculty) during study and is unable to continue carrying out the duty required, then s/he must hand over the duty to a suitable co-investigator and report change to the respective REC, the person-in-charge of the implicated clinical service at the study site and the funding body if required.

11. Regulatory, Administrative and Ethical Reviews

- i) A Certificate of Clinical Trial or Medicinal Test⁷ issued from the Department of Health is required for phase I, II and III drug trials⁸.
- ii) No clinical research is allowed without approval by a recognized REC and endorsement from the study site authority. HA has established a research ethics committee (REC) in each hospital cluster to review and monitor clinical research involving HA facility, HA staff or HA patients. The REC has authority in:
 - Approving, requiring modifications in (to secure approval), or disapproving the research.
 - Approving changes to research proposals and consent document.
 - Monitoring research progress including serious adverse event reports.
 - Terminating / suspending any prior approved studies.
 - Initiating audits when indicated.
- iii) The PI shall seek endorsement from the Head of Department / Chief of Service (or equivalent) and submit the following documents to the respective Cluster REC for review⁹.
 - A completed ethical review application form of the respective Cluster REC
 - The research protocol* (and investigator's brochure* if available)
 - Written informed consent forms* and any written information to be given to research participants (in suitable languages)
 - Recruitment advertisement* if any
 - The investigator's current curriculum vitae (and other documentation evidencing qualifications if required by the REC)
 - Declarations of conflict of interest by all investigators
 - Indemnity agreement (± insurance policy certificate if available)
 - Any other documents required by the REC in order to fulfill its responsibilities
- iv) Investigators should control access to the test articles and keep record of its use.
- v) Investigators may be required to clarify queries raised by the REC.
- vi) Investigators shall abide by the REC decision and recommendation but may appeal to the HA REC for arbitration if disagree.

⁷ 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", the latter subject to exemption under Regulation 34 under Chapter 549F "Chinese Medicine Regulation", 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. Normally, the sponsor often the importer of the test article should apply for this certificate from the Department of Health (Pharmaceuticals Regulation and Import/Export Control Section) and pass a copy of it to the PI for informing the respective REC. The effective date of Chapter 549 and 549F is pending.

⁸ Since the Government is in the process of developing administrative and regulatory control over medical devices, investigators should monitor the development and consult the Medical Device Control Office of DOH for requirements in using investigational devices in clinical research.

⁹ Refer to update requirements in the latest revision of the Hospital Authority Guide for Cluster Research Ethics Committees (HA RE001).

** Document should have title, version / revision number and effective date for unique identification.*

12. Use of Test Articles beyond the context of Research

- a) Test articles that are not registered for sale in the market but approved by an REC 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.
- b) Investigators proposing such use must seek endorsement within the research team, the study site authority and report use to the implicated REC 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 will be necessary.

13. Study Organization and Monitoring

- i) The success of a study depends on
 - Knowledge and competency of research team members
 - Scientific validity of study design
 - Logistic arrangement of study details
 - Budget control over cost and expenses
 - Study reporting integrity; efforts to ensure accuracy and completeness of all key data critical to the interpretation findings and their maintenance to allow future audits
 - An appropriate level of monitoring to ensure safety of research participants¹⁰.
 - Effective management of risk and liability
 - Good information flow between PI, sponsor, REC, study site authority, regulatory authority (if appropriate), other investigators and the participants.
- ii) Adhere to REC decision and recommendation. Do not deviate from, or make changes to the study protocol and other vetted documents without prior approval from the REC and trial sponsor, except when it is necessary to eliminate immediate hazards to research subjects or when the change involves purely logistical or administrative issues, and to notify them promptly of such changes.
- iii) Report adverse events as soon as possible to all participants who are or may be affected, to the clinicians responsible for their medical care, to the sponsor (in sponsored trials), to the local REC, to the Legal Services Section of HAHO if there potential claim and legal implication, and to regulatory agency if required by law¹¹.
- iv) Report study progress (including termination of study) and new information that may be relevant to a subject's willingness to continue participation in the study to the REC.
- v) A research project once started should be completed as far as possible, unless findings indicate risk to participant is unjustified in relation to the anticipated benefit, or a pre-determined stop rule is fulfilled.
- vi) Retain essential research documents and records in a secure and safe manner for up to at least 3 years after completion of study or after the last approval of a marketing application for drug trials, or as demanded by applicable local regulations, or by an agreement with the sponsor, whichever is longer. Records made during research may only be disclosed to people outside the research team in accordance with participant consent, REC's guidance, or to personnel authorized by the study site authority or law on specific purposes. Access of personal information by the research subjects should follow the law.

¹⁰ All clinical trials require safety monitoring but not all of them require an independent data monitoring committee (IDMC). IDMC is generally indicated in controlled therapeutic trials where mortality or major morbidity serves as an endpoint.

¹¹ According to ICH-GCP, principal investigator has to report research-related serious adverse effect to REC and sponsor if applicable within 24 hours after occurrence of the event.

14. Sponsorship, Income and Conflicts of Interest

- i) Be open and honest in all financial and commercial matters relating to the research.
- ii) Investigators should act in the participants' best interest and be particularly careful not to allow his/her judgment to be influenced, or seen by others to be influenced, by financial, personal, political or other external interests at any stage of the research, and not to offer payments at a level which could induce participants to take risks that they would otherwise not take.
- iii) Investigators must inform REC of all research-related incomes (lump sum or per capita fee for contracted clinical trial, recruitment incentives, etc.) and declare possible conflicts of interest, such as equity ownership (stocks, stock options, etc.), patent rights, royalties, consultancy / advisory fees and other honoraria, donations and gifts to institution (e.g. endowed chairs) and research team including informal benefits (e.g. sponsorship to attend scientific meeting and entertainment, etc.)
- iv) All members in the research team and the participants have the right to be informed about the way in which the research is being financed and managed.

15. Related Documents¹²

- i) HA RE001 Hospital Authority Guide for Cluster Research Ethics Committees
- ii) HA RE002 Clinical Research Study Site Guide

16. Reference

- i) Declaration of Helsinki¹³
- ii) ICH¹⁴-GCP¹⁵
- 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)¹⁶
- iv) GMC Guidance on Good Practice in Research¹⁷

¹² Available in: <http://www.ha.org.hk/> (internet) or <http://ha.home/visitor/> (HA intranet)

¹³ The most widely accepted ethical code for human research established by the World Medical Association. <http://www.wma.net/e/policy/b3.htm>

¹⁴ International Conference on Harmonization of technical requirements for registration of pharmaceuticals for human use. Scientific and regulatory standards in clinical research on medicinal products agreed between EU, Japan and USA. http://www.ich.org/UrlGrpServer.jsr?@_ID=276&@_TEMPLATE=254

¹⁵ 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.fda.gov/cder/guidance/959fnl.pdf>

¹⁶ All EU Member States should have the Directive implemented in national regulations by May 2004. http://europa.eu.int/comm/research/science-society/ethics/legislation_en.html#02

¹⁷ GMC guidance on the role and responsibilities of doctors is available on its website <http://www.gmc-uk.org/standards/research.htm>