National Policy and Guidelines for Human Research 2015

National Research Council of Thailand

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Preface

Thailand has been involved in human research for decades to address needs in medical or health issues and has actively participated in various international clinical trials for new drugs or vaccines licensing. Although international guidelines for conducting research have been implemented, there are no National Guidelines yet available in Thailand. Moreover, the laws governing human research are still being drafted. This National Policy and Guidelines for Human Research (2015) aims to fill these gaps. These Guidelines comprise types of research and study design, key players and their responsibilities, implementation, conflicts of interest management, research use of stored biomaterials and data, selected locally related laws and regulations and some issues of special consideration. The document results from the efforts of invited academics with expertise in human research in co-ordination with National Research Council of Thailand (NRCT) staff and we would like to acknowledge their commitment and tenacity. Special thanks are due to all cited references in our bibliography sections for providing with us rich resources for the drafting of the document.

On behalf of the NRCT, we hope that these Guidelines will be beneficial for both biomedical and behavioural/social science research areas.

Professor Emeritus Dr. Soottiporn Chittmittrapap)
Secretary-General
National Research Council of Thailand (NRCT)

1 General Introduction

1.1 Introduction

Research involving human subjects is necessary for achieving new knowledge, new therapeutic or preventive medical products, or strategies to prevent disease, to reduce illness and mortality, and to improve quality of life. History has progressively geared society towards more stringent laws and regulations on research involving human subjects to ensure both the safety of the research subjects and the credibility of the results. These mechanisms are designed to protect the participants, the researchers, and the institutions where research is conducted.

Thailand has been involved in clinical research for decades to address the needs of global or local medical and health issues

and has also participated in various international clinical trials for new drugs or vaccines licensing. Although the international guidelines for conducting clinical research, the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), Guideline for Good Clinical Practice (ICH GCP) in particular, have been implemented, there are no National Guidelines yet available. This National Policy and Guidelines for Human Research is therefore coordinated by the Office for Human Subject Research Standards (OHSRS) under the National Research Council of Thailand (NRCT). The main objectives are to secure the rights, safety and well-being of research subjects as well as the validity, reliability and integrity of the human research carried out in Thailand.

To develop the policy and guidelines for human research, an appointed NRCT working group has reviewed and referred to various related internationally-accepted documents from a range of sources, i.e. the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Guideline for Good Clinical Practice (ICH GCP), the World Health Organisation (WHO), and the United States National Institutes of Health (NIH) in order to make the initial draft. The draft has gone through a process of consultation with research communities and different stakeholders. The relevant input from

the consultation has been incorporated into the final guidelines which are then adopted by the NRCT. These guidelines should be useful for all parties involved directly or indirectly in human subject-related research. Of note, adherence to the Guidelines is mandatory for all the Royal Thai Government (RTG) funded research.

1.2 List of Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
CAB	Community Advisory Board
CAPA	Corrective Action and Preventive Action Plan
CIC	Conflicts of Interest Committee
CIOMS	Council for International Organizations of Medi cal Sciences
CMC	Chemistry Manufacturing Control
COI	Conflicts of Interest
CRF	Case Report Form
CRO	Contract Research Organisation
DHHS	US Department of Health and Human Services
DNA	Deoxyribonucleic acid
EC	Ethics Committee
EMA	European Medicines Agency
FDA	Food and Drug Administration
GCP	Good Clinical Practice

GMP	Good Manufacturing Practice
HIV	Human Immunodeficiency Virus
HM	Herbal Medicine
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Phar maceuticals for Human Use
ICTRP	International Clinical Trials Registry Platform
IDMC	Independent Data Monitoring Committee
IP	Investigational Product
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LAR	Legally Authorised Representative
NIH	US National Institutes of Health
NRCT	National Research Council of Thailand
OHRP	US Office for Human Research Protections
OHSRS	Office for Human Subject Research Standards
OPRR	US Office for Protection from Research Risks
ORI	US Office of Research Integrity
PI	Principal Investigator
QA	Quality Assurance
QMS	Quality Management System
RAC	Recombinant DNA Advisory Committee
REC	Research Ethics Committee

RNA	Ribonucleic acid
RTG	Royal Thai Government
SC	Stem Cell
SCOC	Stem Cell Oversight Committee
SOP	Standard Operating Procedures
TCTR	Thai Clinical Trials Registry
TM	Traditional Medicine
WHO	World Health Organization

2 Type of Research and Study Designs

2.1. Introduction

The value of research depends upon the integrity of study results. One of the ethical justifications for research involving human subjects is the social value of advancing scientific understanding and promoting human welfare by improving health care. But if a research study is so methodologically flawed that little or no reliable information will result, it is unethical to put subjects at risk or even inconvenience them through participation in such a study. Scientifically invalid research is unethical in that it exposes research subjects to risks without possible benefit; investigators and sponsors must ensure that proposed studies involving human subjects conform to generally-accepted scientific principles and

are based on adequate knowledge of the pertinent scientific literature.

The purpose of this chapter is to provide some brief basic background information on scientific research design, some of the research techniques used by researchers, and some ethical considerations raised by these designs and techniques.

2.2. Selected Research Methodology in Human Studies

The term “research” refers to a class of activities designed to develop or contribute to generalisable knowledge.

Biomedical research is simply known as medical research which is basic research, applied research, or translational research conducted to aid and supports the developing body of knowledge in the field of medicine.

In addition, to better understand the nature of health problems, social science research, which is an academic discipline concerned with society and the relationships among individuals within a society, may also be applied in human health studies.

2.2.1 Biomedical research

Biomedical investigations can be broadly categorised into two types: experimental studies and observational studies.

1) An experimental study is a study in which conditions are under the direct control of the investigator. While an observational study is an epidemiological study that does not involve any intervention, experimental or otherwise; such a study may be one in which nature is allowed to take its course with changes in one characteristic being studied in relation to changes in other characteristics. An observational study may be synonymously addressed as a non-experimental study.

In a typical experimental study, a study sample is selected for a planned trial of a regimen whose effects are measured by comparing the outcome of the regimen in the experimental group with the outcome of another regimen in a control (comparison) group. The control group consists of subjects with whom comparison is made against the experimental group. In order to avoid biases and confounding variables, members of the experimental and control groups should be comparable except in the regimen that is offered to them. The avoidance of bias is ideally achieved by randomly allocating individuals to groups, e.g., experimental and control regimens by chance. This process is called randomisation or random allocation. Most clinical trials use experimental studies.

If the investigator lacks full control over the allocation and/or timing of intervention in an experimental study, the study is recognised as a quasi-experimental study. Other options for

randomised studies may include, e.g., randomised block design, factorial design, before-after design, crossover design, etc., depending upon research questions.

When the observer(s) and/or subjects are unaware of the group to which the subjects are assigned the process is called blinding (masking). The main purpose of blinding is to minimise bias in the assessment of outcome(s). Blinding can be single-blinded (either the observer(s) or subjects are blinded), double-blinded (both are blinded), or triple-blinded (both and the analysis are blinded).

2) An observational study may be retrospectively conducted by reviewing records from the past (e.g., birth and death certificates, medical records, school records, or employment records, etc.).

Observational studies can also be prospectively implemented by observing outcomes or events that occur subsequent to the identification of the group of subjects to be studied; they need not involve manipulation or intervention and involve only the collection of data.

Common observational studies may include, for example:

A cohort study is a study in which subsets of a defined population can be identified who are, have been, or in the future may be exposed or non-exposed, or exposed in different degrees,

to a factor or factors hypothesised to influence the probability of occurrence of a given disease or other outcome in the future (prospective cohort study, concurrent prospective study). This type of study usually has a long time-frame and a large study population. The study may start from the past (retrospective cohort study, non-concurrent prospective study, historical cohort study) using existing records about health or other relevant aspects at some time in the past that determine the current or subsequent status of the study population.

A case-control study is an epidemiological study of persons with a disease of interest (or other outcome variable) and a suitable control (comparison, reference) group of persons without the disease which are compared. The past history of exposure to a suspected risk factor is compared between "cases" and "controls".

A cross-sectional study (prevalence study) is a study that examines the relationship between diseases (or other health-related characteristics) and other variables of interest as they exist in a defined population at one particular time.

Although randomisation is the preferred method for assigning subjects to the various arms of a clinical trial, non-experimental methods, such as cohort and case-control studies to evaluate drugs and devices may often be justified scientifically and ethically.

Cluster sampling: A method of selecting subjects from a population in which each unit selected is a group of subjects rather than an individual. Clusters are usually selected through random sampling.

2.2.2 Social and Behavioural Science Research in Health Care

Identifying research questions in health care may also require social factors and questions that may contribute to action or change in behaviours to be taken into account. Thus, social science may contribute by answering these various questions. Unlike biomedical research, the potential risks to the research subject are not usually physiological, but researchers need to be aware of the dangers of exposing the subject to potential psychological or social harm or inconvenience. Such studies are carried out to ultimately benefit many individuals, though there is rarely a direct benefit for individual respondents; however, there is the opportunity for them to offer valuable information in a way that may contribute to improving many people's lives.

Study designs in social science may either be quantitative or qualitative depending on research questions. Interviews used in social science studies can be structured, semi-structured, or in-depth.

1) Quantitative research investigates social phenomena via statistical, mathematical, or numerical data or computational

techniques. Many approaches have study designs similar to those used in biomedical research described above.

A structured interview (also known as a standardised interview or a researcher-administered survey) is commonly employed in survey research. It aims to ensure that each interview is presented with exactly the same questions in the same order. While a structured interview has a rigorous set of questions which does not allow diversion, a semi-structured interview is open, allowing new ideas to be brought up during the interview as a result of what the interviewee says. The interviewer in a semi-structured interview generally has a framework of themes to be explored.

2) Qualitative research aims to gather an in-depth understanding of human behaviour and the reasons that govern such behaviour by investigating the why and how of decision-making, not just what, where, when. It thus uses smaller but more focused samples rather than large samples. Commonly used methods in qualitative research are described in brief as follows:

In-depth interviews are less structured than the structured and semi-structured interviews, and may cover only one or two issues, but in much greater detail.

A focus group is a group of people who are asked about their perceptions, opinions, beliefs, and attitudes towards a product,

service, concept, advertisement, idea, or packaging. Questions are asked in an interactive group setting where participants are free to talk with other group members. In this kind of study, there is a risk that confidentiality may be breached by participants in the discussion. Thus, subjects should be reminded that the identities of fellow participants and the information exchanged are confidential.

Participant observation is a type of data collection that aims to gain a close and intimate familiarity with a given group of individuals and their practices through an intensive involvement with people in their cultural environment, usually over an extended period of time.

Non-participant observation is a research technique whereby the researcher watches the subjects of his/her study, with their knowledge, but without taking an active part in the situation under scrutiny.

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Key Players and Responsibilities

3.1 Institution

3.1.1 Definition

Institution is defined as any public or private entity or agency (including medical or health care facility) where human research is conducted.

An institution has a major role in supporting and promoting the scientific integrity of the research and the protection of the human subjects.

3.1.2 Key Responsibilities

1) An institution should develop and implement quality standard policies and quality management systems which aim (i)

to support the effective conduct of high-quality research; and (ii) to ensure that the conduct of research is compliant with ethical standards, internationally accepted good clinical practice (ICH GCP), and applicable laws and regulations.

2) An institution must have an ethics committee (EC) to safeguard the rights, safety, well-being, and confidentiality of human subjects. The institution should ensure that the review and monitoring process of the EC is efficient and independent of sponsor, investigator, and institution.

3) An institution should support and promote education and training for their personnel who have key roles in research to ensure that they have adequate and appropriate knowledge and skills to perform their roles.

4) An institution should have effective and efficient processes to monitor the conduct of research in the institution and appropriate handling of non-compliance.

5) An institution should ensure that an effective compensation system is developed for research-related injuries.

6) An institution should establish the process in the appropriate management of conflicts of interest in the research.

7) An institution should support and promote the disclosure of their investigator-initiated and institution-funded human research.

3.2 Investigator

3.2.1 Definitions

The investigator is an individual who is responsible for activities and processes related to the conduct of human research at a research site (may also be referred to as study, trial, or investigational site).

The investigator has a primary role in protecting the rights, safety, well-being, and confidentiality of human subjects, including the quality and integrity of research data. The investigator may delegate any of his/her responsibilities to an appropriately qualified person; however, accountability remains with the investigator.

If a team of persons conducts human research, the investigator who is the responsible leader of the team may be named the principal investigator. An individual team member designated for critical research-related tasks and/or making important research-related decisions may be called a sub-investigator or co-investigator.

3.2.2 Key Responsibilities

General

1) The investigator should conduct the research in compliance with applicable ethical standards, ICH GCP, SOP, applicable laws and regulations. If any non-compliance occurs, the investigator

must ensure that appropriate corrective and preventive actions are taken and documented.

Qualifications

2) The investigator must be knowledgeable about applicable ethical standards, GCP, SOPs, laws and regulations.

3) The investigator must be knowledgeable about the research protocol, including the investigational product and/or intervention, the research process and procedures, and safety reporting (if any).

4) The investigator must ensure that (i) the research team members are aware of applicable ethical standards, GCP, SOP, applicable laws and regulations; and (ii) the individual team members are appropriately qualified and knowledgeable about designated research-related tasks.**Balancing the Potential Risks and Benefit of Human Research**

5) Before making a decision to conduct the research, the investigator must accurately evaluate potential risks and benefits to human subjects through a thorough review of the research protocol and other relevant information about the investigational product and/or intervention. The investigator must ensure that (i) the potential benefits for research subjects outweigh the anticipated risks to them; and (ii) the appropriate preventive and/or minimising

measures for the risks are defined in the research protocol.

6) During the conduct of the research, the investigator must be aware of any new information that is relevant to the continuing evaluation of potential benefits and risks to the subjects, and report that information to the EC.

7) The investigator must implement measures to prevent and/or minimise risks to the subjects, including safety monitoring. Informed Consent of Human Research Subjects

8) The Investigator must submit the subject information sheet and informed consent form to the EC for review and approval.

9) The investigator must secure EC approval of these documents before recruiting subjects.

10) The investigator/designee must obtain informed consent from subjects prior to performing any research-related procedure.

11) The investigator/designee must (i) provide the potential subjects with all information clearly and comprehensively in writing; (ii) evaluate if each potential subject understands the information and if there is any therapeutic misconception; (iii) provide ample time for each potential subject to ask questions and make decisions; and (iv) answer all questions that the potential subjects ask.

12) The investigator/designee must be aware of specific requirements for informed consent in research involving vulnerable subjects and minors, and subjects from whom obtaining written informed consent is not possible.

Protocol Compliance

13) The investigator must submit the research protocol and other relevant information to EC for review and approval.

14) The investigator must ensure that the research protocol receives documented approval from the EC prior to recruiting subjects.

15) The investigator must ensure that the conduct of human research is compliant with the current EC approved protocol.

16) If there is any protocol non-compliance, the investigator must ensure that appropriate corrective and preventive actions are performed, documented, and reported to the sponsor and EC.

Data Quality and Integrity

17) The investigator must ensure that the data reported in the Case Report Form (CRF) are accurate, legible, complete, contemporaneous, original, and attributable.

18) The investigator must ensure that data reported in CRFs are derived from and consistent with records in source documents. The records in source documents should be adequate to evaluate

the subject's participation and the conduct of the research. The source documents must be maintained and available for access.

19) The investigator must permit and facilitate monitoring and quality assurance procedures.

Protection of Confidentiality and Privacy of Human Research Participants

20) The investigator must implement measures to protect the personal and sensitive information of subjects and should ensure that the research team members are aware of these measures.

21) The investigator must ensure that subjects are informed about the measures to be used to protect their private information and records, and who will access their private information and records in what circumstances.

3.3 Ethics Committee

3.3.1 Definition

The Ethics Committee (EC) or Institutional Review Board (IRB) or Independent Ethics Committee (IEC) or Research Ethics Committee (REC) is an independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, confidentiality, and

well-being of human subjects involved in a trial and to provide public assurance of that protection.

3.3.2 Requirements

1) The legal status, composition, function, operations and regulatory requirements pertaining to the EC should allow the EC to act in agreement with the applicable local laws and regulation, ICH GCP and international guidelines.

2) The composition of EC members must include multidis ciplinary and multi-sectorial membership of both genders in compliance with local laws and regulations, ICH GCP and international guidelines.

3) The EC should be large enough to ensure robust discussion of protocols. It is recommended that the EC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a non-scientific area.

(c) At least one member who is independent of the institution/trial site.

4) A list of EC members and their qualifications and records of EC-related training as well as ICH GCP training must be maintained and updated.

3.3.3 Key Responsibilities

The EC's responsibility is to ensure the protection of the rights, safety, confidentiality, and well-being of potential participants as well as those participants involved in a trial. The EC provides public assurance of that protection by, among other things, reviewing and approving or rejecting the protocol and ensuring that the investigator(s) is/are suitable to conduct the trial, the facilities are adequate, and the methods and materials to be used in obtaining and documenting informed consent of the trial participants are appropriate.

The legal status, composition, function, operations, and regulatory requirements pertaining to EC differ among countries, but should allow the EC to act in accordance with ICH GCP.

1) The EC must safeguard the rights, safety, confidentially and well-being of all research subjects. Special attention should be paid to trials that may include vulnerable subjects.

2) The EC must review and maintain confidentiality of the proposed clinical trial, all documents submitted, and the qualifications of the investigators in accordance with the local laws and regulations, ICH GCP and international guidelines within reasonable time (optimally 2-4 weeks), and document its views in writing and the dates for the following:

(a) Approval/favourable opinion;

(b) Modifications required prior to its approval/ favourable opinion;

(c) Negative opinion/deferral

(d) Disapproval/negative opinion; and

(e) Termination/suspension of any prior approval/ favourable opinion.

When the research proposal is in doubt, the investigator must consult with the EC.

3) The EC must conduct continuing review of each ongoing trial at intervals appropriate to the degree of risks to human subjects, at least once per year.

4) In order to import non-registered investigational products into the country for research, the protocol must be submitted and approved by an EC recognised by the Thai Food and Drug Administration (FDA). Nonetheless, not every EC is eligible; there is a requirement for the study protocol to get approval from only an FDA-recognised EC.

3.3.4 Functions, Operations, Procedures, and Records

1) The EC must perform its functions according to a written

SOP, must maintain written records of its activities and minutes of its meetings, and must comply with the local laws and regulations, ICH GCP and international guidelines.

2) The EC must retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence, etc.) for a period of at least three years after completion of the trial and make them available upon request from the regulatory authority(ies).

3) It should be ensured that the EC promptly notifies the investigators/institution in writing (optimally within one week) concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

4) The EC must provide investigators, sponsors, or regulatory authorities with the written procedures and membership lists.

5.) The EC should have a good system or procedures for the coordinated review of multi-site research to facilitate the conduct of international health research.

3.4 Sponsor

3.4.1 Definitions

A sponsor is an individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

A sponsor-investigator is an individual who both initiates and conducts a clinical trial, alone or with others, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

3.4.2 Key Responsibilities

Investigators and Site Selection

1) The sponsor is responsible for selecting the investigator (s)/ institution (s) qualified by training and experience and with adequate resources to properly conduct the trial.

2) The sponsor must obtain the investigator's/institution's agreement to conduct the trial in compliance with ICH GCP, with the applicable regulatory requirement(s) and with the protocol agreed to by the sponsor and given approval/favourable opinion by the EC. The sponsor and the investigator/institution should sign

the protocol, or an alternative document, to confirm this agreement.

3) For multicentre trials, the sponsor should ensure that:

The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided and designed to capture additional data.

All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

Providing Trial Materials

Before entering an agreement with an investigator/institution to conduct a trial, the sponsor must provide the investigator(s)/ institution(s) with the protocol and an up-to-date Investigator's Brochure (IB), and should provide sufficient time for the investigator/ institution to review the protocol and the information provided.

1) Providing information on IP:

When planning trials, the sponsor must ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

The sponsor must update the IB as significant new information becomes available.

2) Manufacturing, Packaging, Labelling, and Coding of IP.

The sponsor must ensure that the investigational product (s) (IP) (including active comparator(s) and placebo, if applicable) is characterised as appropriate to the stage of development of the product (s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement (s). The IP must be packaged to prevent contamination and unacceptable deterioration during transport and storage (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor must inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers, etc.) of these determinations.

In blinded trials, the coding system for the IP must include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

If significant formulation changes are made in the IP or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s)

(e.g. stability, dissolution rate, bioavailability, etc.) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product must be available prior to the use of the new formulation in clinical trials.

The sponsor must provide the IP after all required documentations (e.g. approval/ favourable opinion from EC and regulatory authority(ies)) are obtained, together with written instructions for the handling and storage of the IP. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused IP to the sponsor (or alternative disposition if authorised by the sponsor and in compliance with the applicable regulatory requirement (s)).

The sponsor must maintain records that document shipment, receipt, disposition, return, and destruction of the IP. The sponsor must ensure that the IPs are stable over the period of use and that there are sufficient quantities for reconfirmed specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent that stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement (s), whichever represents the longer retention period.

3) Compensation to Subjects and Investigators

The financial aspects of the trial must be documented in an agreement between the sponsor and the investigator/institution; when trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement (s). If required by the applicable regulatory requirement(s), the sponsor must provide insurance or must indemnify (legal and financial coverage) the investigator/ the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence. The sponsor's policies and procedures must address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

Documentation and Communication

1) The sponsor is responsible for securing written agreement from all involved parties and retaining all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s), or at least two years have elapsed since the formal discontinuation of clinical development of the IP.

The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

2) Before initiating the clinical trial, the sponsor should submit any required application to the appropriate authority for review, acceptance, and/or permission. Any notification/submission should be dated and contain sufficient information to identify the protocol.

3) The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/ institution's EC.

(b) A statement obtained from the EC that it is organised and operates according to ICH/ GCP and the applicable laws and regulations.

(c) Documented EC approval/favourable opinion and a current copy of the protocol, written informed consent form (s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the EC may have requested.

The sponsor should obtain from the investigator/institution documentation and dates of any EC re-approvals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

If the EC makes its approval/favourable opinion conditional upon change(s) in any aspect of the trial, such as modification(s) to the protocol, the written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/ institution a copy of the modification (s) made and the date approval/favourable opinion given by the EC.

4) The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/ institution(s) provide direct access to source data/ documents for trial-related monitoring, audits, EC review, and regulatory inspection.

5) The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, EC review, and regulatory inspection.

6) Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency (ies) as required by the

applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH GCP guideline for structure and content of clinical study reports.

Data Quality and Integrity

The sponsor is responsible for

1) Implementing and maintaining quality of the trials to ensure that the studies are conducted and the data documented/ reported in compliance with the protocol, ICH GCP, and the applicable regulatory requirement(s).

2) Appointing qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians, etc.) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and analysing and preparing interim and final clinical trial reports. The sponsor should establish an Independent Data Monitoring Committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

3) Maintaining a list of the individuals who are authorised to make data changes. Maintain adequate backup of the data.

Safeguarding the blinding, if any (e.g., maintain the blinding during data entry and processing). Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

4) Monitoring to ensure that:

(a) The trial is conducted and documented properly and verifying that the data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

(b) Any dose and/or therapy modifications are well documented for each of the trial subjects.

(c) Adverse events, concomitant medications, and inter-current illnesses are reported in accordance with the protocol on the CRFs.

(d) All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial. The monitor should submit a written report to the sponsor after each trial- site visit or trial-related communication.

5) Auditing

The sponsor should appoint individuals, who are qualified and independent of the clinical trials/systems, to conduct audits and ensure that the auditing is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports. The observations and findings of the auditor(s) should be documented.

Non-compliance with the protocol, SOPs, ICH GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance. If the monitoring and/or auditing identify serious and/or persistent non-compliance on the part of an investigator/ institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of non-compliance, the sponsor should promptly notify the regulatory authority(ies).

Safety Evaluation

1) The sponsor is responsible for the ongoing safety evaluation of the investigational product(s). The sponsor must promptly notify all concerned investigator (s) /institution (s) and the regulatory authority (ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the EC's approval/ favourable opinion to continue the trial.

2) Adverse Event Reporting

The sponsor must document all adverse events during the study period and expedite reporting to all concerned investigator (s)/institutions (s), to the EC and to the regulatory authority (ies) of all adverse events that are both serious and unexpected. The sponsor must submit to the regulatory authority (ies) all safety updates and periodic reports, as required by applicable regulatory requirement (s).

Premature Termination or Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The EC should also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the investigator/ institution, as specified by the applicable regulatory requirement(s).

A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a Contract Research Organisation (CRO), but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

3.5 Regulatory Authority on Human Subject Research

3.5.1 Definition

Regulatory authority is a regulatory agency authorised by the government; it is also known as the FDA, and is responsible to ensure that in a clinical trial the rights, safety, dignity, and well-being of subjects must be protected and the data generated must be reliable and robust.

3.5.2 General Guidance

1) The regulatory authority is responsible to ensure that the interests of the subjects always take priority over all other interests.

2) In order to avoid administrative delays for starting a clinical trial, the procedure to be used should be flexible and efficient, without compromising patient safety or public health.

3) The timelines for assessing an application dossier for clinical trials should be sufficient to assess the file, while at the same time ensuring quick access to new and innovative treatments.

4) The regulatory authority should ensure the administrative and facilitating processes are efficient and implemented in a timely manner to make sure the country remains an attractive place for conducting clinical trials.

5) The regulatory authority should efficiently assess all clinical trials applications within the given timelines.

6) A rapid yet in-depth assessment is of particular importance for clinical trials concerning medical conditions which are severely debilitating and/or life threatening and for which therapeutic options are limited or non-existent, as in the case of rare and ultra-rare diseases .

7) Clinical trials for the development of orphan medicinal products and of medicinal products addressed to subjects affected by severe, debilitating and often life-threatening diseases affecting no more than one person in 50,000 (ultra-rare diseases) should be fostered.

8) Unless otherwise justified in the protocol, the subjects participating in a clinical trial should represent the population groups, for example, gender and age groups, that are, in the future in general healthcare, likely to use the medicinal product that is investigated in the clinical trial.

9) In order to improve treatments available for vulnerable groups such as frail or older people, people suffering from multiple chronic conditions, and people affected by mental health disorders, medicinal products which are likely to be of significant clinical value should be fully and appropriately studied for their effects

in these specific groups, including requirements related to their specific characteristics and the protection of the health and wellbeing of subjects belonging to these groups.

10) The authorisation procedure should provide for the possibility to extend the timelines for the assessment in order to allow the sponsor or investigator to address questions or comments raised during the assessment of the application dossier. Moreover, it should be ensured that, within the extension period, there is always sufficient time for assessing the additional information submitted.

11) In order to increase transparency in the area of clinical trials, data from a clinical trial should only be submitted in support of a clinical trial application if that clinical trial has been recorded in a publicly accessible and free-of-charge database which is a primary or partner registry of, or a data provider to at least the Thai Clinical Trials Registry (TCTR) (http://www.clinicaltrials.in.th/), or others like the World Health Organization International Clinical Trials Registry Platform (WHO/ICTRP) (http://www.who.int/ictrp/en/) or the US clinicaltrials.gov (https://clinicaltrials.gov/). Data providers to the WHO/ICTRP create and manage clinical trial records in a manner that is consistent with the WHO registry criteria. Specific provision should be made for data from clinical trials started before the date of application of this Regulation.

Remark:

This guidance is adapted in part from the Position of the European Parliament legislative resolution of 2 April 2014 on the proposal for a regulation of the European Parliament and of the Council on clinical trials on medicinal products for human use.

3.6 Volunteers

3.6.1 Definition

The volunteer or subject or trial subject participant or research subject participant is an individual who participates in research, either as a recipient of the investigational product (s) or as a control.

3.6.2 Selection and Recruitment of Volunteer

The potential volunteer/subject/participant should understand that ethically acceptable research will ensure that no group or class of persons bears more than its fair share of the burdens of participation in research and receives its fair share of the benefits of research. These benefits include the direct benefits of participation (if any) as well as new knowledge that the research is designed to yield. The clinical investigator has primary responsibility for recruiting subjects, ensuring that only eligible subjects are enrolled in the study, and obtaining and documenting the informed consent of each subject.

Selection of volunteers should be carried out in such a way that the burdens and benefits of the research will be equitably distributed. The exclusion of groups or communities that might benefit from study participation must be justified.

3.6.3 Responsibilities

1) After thoroughly considering information about the anticipated risks and benefits of the research and voluntary and free consent to participate in such research, volunteers should follow directions from the study staff as stated in the participant information sheet.

2) Women at risk of pregnancy during a clinical trial will need to use reliable birth control methods advised by the study doctor while in the study.

3) The volunteer should report or inform the researcher of any adverse events occurring during participation in the study.

4) The volunteer should keep the written informed consent provided by the researcher confidential.

5) The volunteer should inform the researcher when he/she wants to withdraw from the study and allow the researcher to do the follow up, when necessary.

6) All research with human volunteers is subject to the

oversight of an EC (although specific categories of research may be exempted or attract expedited review).

7) The volunteer should contact the EC when there is any deviation or non-compliance from what is stated in the information sheet prepared by the researcher or study staff.

3.6.4 Informed Consent of Volunteers

1) Informed consent is a process by which a prospective trial subject voluntarily confirms his/her willingness to participate in a particular trial, after having been informed of all aspects of the trial.

2) Informed consent is documented by means of a written, signed, and dated informed consent form.

3) Informed consent assures that the prospective human volunteer will understand the nature of the research and can knowledgeably and voluntarily decide whether or not to participate.

4) The prospective research volunteer should consider essential information in the written informed consent form and any other written information provided.

5) If the subject is unable to provide informed consent, the subject's Legally Authorised Representative (LAR) (unless required by local laws and regulations) is required.

6) Informed consent is an ongoing process, not a piece of paper, or a discrete moment in time.

The process of obtaining informed consent has been described in the Declaration of Helsinki (2013).

3.6.5 Means to Minimise Inappropriate Inducement to Participate in Research

1) The volunteer may be reimbursed for lost earnings, travel costs and other expenses incurred in taking part in a study; they may also receive free medical services.

2) The volunteer, particularly those who receive no direct benefit from research, may also be paid or otherwise compensated for inconvenience and time spent.

3) The payments should not be so large, however, or the medical services so extensive as to induce prospective volunteers to consent to participate in the research against their better judgement (''undue inducement'').

4) Payments to a subject should be rated pro-rata and not wholly contingent on completion of the trial by the subject.

5) All payments, reimbursements, and medical services provided to research volunteers must have been approved by the EC.

Acceptable and unacceptable recompense has been described by the Council for International Organizations of Medical Sciences (CIOMS). (See below)

6) Incompetent persons may be vulnerable to exploitation for financial gain by guardians. A guardian asked to give permission on behalf of an incompetent person should be offered no recompense other than a refund of travel and related expenses.

7) A volunteer who withdraws from research for reasons related to the study, such as unacceptable side-effects of a study drug, or who is withdrawn on health grounds, should be paid, or recompensed as if full participation had taken place.

8) A subject who withdraws for any other reason should be paid in proportion to the amount of participation.

9) An investigator who must remove a subject from the study for wilful non-compliance is entitled to withhold part or all of the payment.

3.6.6 Consideration of Benefits and Risks

1) It is very important that prospective volunteers should make the decision to participate in research based on information from the investigator that gives assurance that the potential benefits and risks of study participation are reasonably balanced and risks are minimised.

2) Interventions or procedures that hold out the prospect of direct diagnostic, therapeutic or prophylactic benefit for the individual volunteer must be justified by the expectation that they will be at least as advantageous to the individual volunteer, in the light of foreseeable risks and benefits, as any available alternative; otherwise interventions must be justified in relation to the expected benefits to society (generalisable knowledge).

3) The risks presented by such interventions must be reasonable in relation to the importance of the knowledge to be gained.

4) When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that does not hold out the prospect of direct benefits for the individual subject should be no more likely and not greater than the risks attached to routine medical or psychological examination of such persons. Slight or minor increases above such risks may be permitted when there is an overriding scientific or medical rationale for such increases and when the EC has approved them.

Acceptable Recompense. Research subjects may be reimbursed for their transport and other expenses, including lost earnings, associated with their participation in research. Those who receive no direct benefits from the research may also receive a

small sum of money for inconvenience due to their participation in the research. All subjects may receive medical services unrelated to the research and have procedures and tests performed free of charge.

Unacceptable Recompense. Payments in money or in kind to research subjects should not be so large as to persuade them to take undue risks or volunteer against their better judgement. Payments or rewards that undermine a person's capacity to exercise free choice invalidate consent. It may be difficult to distinguish between suitable recompense and undue influence to participate in research. An unemployed person or a student may view promised recompense differently from an employed person. Someone without access to medical care may or may not be unduly influenced to participate in research simply to receive such care. A prospective subject may be induced to participate in order to obtain a better diagnosis or access to a drug not otherwise available; the local EC may find such inducements acceptable.

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Implementation

4.1 The Quality of Human Research

The recommendations in this "National Policy and Guidelines for Human Research" are aimed to promote the conduct of high-quality human research in Thailand and assure the public of its quality. The quality of human research is defined as

1) Scientific integrity, accuracy, and reliability of data generated from human research; and

2) Compliance of the conduct of the human research with the ethical principles for human research, GCP and the related legal and regulatory requirements.

4.2 Shared Responsibility in the Quality of Human Research

Quality of human research is a responsibility that is shared

by the key stakeholders who conduct and oversee human research, including sponsors, institutions, investigators, research ethics committees, and regulatory authorities.

To accomplish the goals of this recommendation, all the key stakeholders need to commit to their shared responsibility in the quality of human research by implementing Quality Management System (QMS) for the processes and activities related to the conduct and/or oversight of human research for which they are responsible.

4.3 Aims of Quality Management System (QMS) for Human Research

QMS should be aimed at

1) Management and continual improvement of the quality and effectiveness of processes and activities related to the conduct and oversight of human research

2) Assurance of the compliance of the conduct of the research with the ethical principles for human research, ICH GCP and the related legal and regulatory requirements

3) Assurance of the protection of subjects participating in the research and the quality and integrity of the research data

4) Enhancement of the partnership among the key stakeholders

4.4 Implementation of QMS for Human Research

4.4.1 Management Leadership and Commitment to the Quality of Human Research Is Essential

The management practices of each key stakeholder should demonstrate their active commitment to the QMS for human research in a practical manner by carrying out the following responsibilities:-

1) Clearly defining and establishing the organisation's quality policy and quality objectives in the conduct and/or oversight of human researches

2) Promoting the quality management of human research, which includes the quality plan, quality control, quality assurance and continual quality improvement for processes and procedures related to the conduct and/or oversight of human research

3) Promoting involvement of people at all levels of the organisation in the quality management of human research

4) Providing adequate resources for the implementation and continuous improvement of the QMS. The resources required for QMS include financial resources, human resources, and infrastructure and work environment

5) Ensuring that the responsibilities and authority of the personnel in each organisation involved in human research, are

defined and communicated within the organisation

6) Establishing clear internal communication lines and promoting good two-way communication among both internal and external stakeholders

7) Appointing a senior person with management authority (given-title may be "Quality Manager") to ensure that the QMS is effectively and efficiently maintained

8) Regularly reviewing the performance of QMS

4.4.2 Roles and Responsibilities and Training Requirements of Personnel Involved in Human Research Should be Defined and Promoted

All the key stakeholders should

1) Define, document and update their organisational structure and functions

2) Define, document and update the roles and responsibilities of personnel in each function, and the qualifications, competencies and training required for each role

3) Provide effective training and education to their personnel to develop their competencies and awareness of the organisation's quality policy and quality objectives in carrying out human research; and

4) Establish practices to recognise the contribution and effort of their personnel in the achievement of quality in human research

4.4.3 Process and Procedures Related to the Conduct and Oversight of Human Research Should be Defined and Documented

All the key stakeholders should:

1) Understand and clearly define processes and procedures related to the conduct and oversight of human research in addition to the interconnection and interaction between those processes.

2) Determine criteria and methods needed to ensure that those processes and activities are effective and conform to the organisation's quality policy and quality objectives in human research; and

3) Develop, maintain, and update the documentation related to those processes and activities including quality policy, quality objectives, SOP, work instructions, checklists, and forms.

Following are the processes and procedures that each key stakeholder should include in their QMS.

a.) Sponsors

Sponsors should develop, implement, and maintain

written procedures for activities pertaining to the role of sponsor, including but not limited to:

- Creating, reviewing, approving and updating the research protocol, informed consent document, IB, CRFs, and other research-related documents
- Assessing and selecting qualified investigators and site personnel
- Shipping, handling, and accounting for all supplies of the IP and other products
- Monitoring and reporting safety concerns
- Collecting, verifying, validating, storing, protecting, analysing, and reporting research data to ensure the quality and integrity of data and of the final research report
- Filing, maintaining and archiving essential documents as defined in the ICH GCP
- Monitoring the conduct of research to ensure its compliance with the research protocol, ICH GCP and applicable regulations.
- Auditing, to determine if the monitoring is being appropriately carried out and the systems for quality control are operational and effective.

b.) Investigators and institutions

Investigators/institutions should develop, implement, and maintain written procedures for activities pertaining to the

role of investigator/institution, including but not limited to:

- Communicating with the EC during the setup, conduct, and closeout of research
- Recruiting and retaining research subjects
- Obtaining, recording, and updating informed consent
- Managing, recording, and reporting serious and non-serious adverse events
- Storing, dispensing, disposing, and accounting for the IP
- Preparing and recording source documents
- Filing, maintaining, and archiving essential documents as defined in the ICH GCP
- Managing and reporting protocol non-compliance, serious violation and urgent safety matters

c.) Research Ethics Committees (EC)

Research ethics committees (EC) should develop, implement, and maintain written procedures for their operations, including but not limited to:

- Constitution and selection process of the EC, and the membership qualifications and training requirements
- Initial and continuous review processes for a research protocol
- Review of safety reports and other significant risk and benefit information

- Review of the final report of the approved research
- Communicating with investigators and institutions
- Handling non-compliance with the research protocol, ethical principles for human research, ICH GCP and the related legal and regulatory requirements
- Maintaining confidentiality of research data
- Handling Conflicts of Interest (COI) in the conduct of human research

d.) Regulatory Authorities (FDA for IP, OHSRS, NRCT for Governmental Funded Research)

Regulators should consider developing, implementing, and maintaining written procedures for activities pertaining to the regulation of human research and as required by Good Review Practices. Those activities may include but are not limited to:

- Submitting, reviewing, and approving regulatory authority applications and safety reports
- Communicating with sponsors and other key organisations
- Conducting GCP inspections and communicating findings to the inspected parties
- Enforcing rules and regulations including the notification of violation and assessment of penalty, appeals procedure, and the final notice of violation and penalty assessment order

4.4.4 Documentation of QMS should be implemented and maintained at all levels in the organisation.

Documentation is an essential part of the QMS for the conduct of human research. Documentation may be in various formats including paper-based, electronic, and photographic media. There are two primary types of documentation in the QMS, i.e., instructional documents and records/reports.

1) Instructional documents provide direction and requirements for the conduct and oversight of human research. Those documents include documents of organisational structure and function, quality policy, quality objectives, quality plan, SOP, work instructions, checklists, and forms.

2) Records/reports provide evidence of the compliance of key research activities undertaken and their results with the requirements of quality standards and regulations. The records/ reports include the essential documents as defined in ICH GCP.

Documentation aims to

1) Help all key research activities to be implemented and to ensure that research data are recorded in a consistent manner

2) Help monitor and evaluate compliance of the performance or results of key research activities with the requirements of quality standards and regulations

3) Help evaluate the quality of research data generated

4) Help evaluate effectiveness of the QMS; and

5) Facilitate internal and external communications, and knowledge-sharing

All the key stakeholders should implement good documentation practices, and control of documents and control of records in the QMS.

Document control procedures include:

1) Reviewing and approving the documents before issuing

2) Updating, reviewing, and re-approving the documents as necessary

3) Versioning the documents to ensure that changes and the current revision status of documents are identified

4) Ensuring availability of the current version of documents at points of use; and preventing unintended use of obsolete documents

5) Ensuring that external documents are identified and their distribution is controlled; and

6) Archiving and retention of documents

The record control procedures include:

1) Ensuring that the records are accurate, legible, complete, original and attributable; and are updated at the time each action is taken

2) Ensuring that the records are traceable and any alteration of the records is signed and dated; and

3) Identification, storage, protection, retrieval, retention, and disposal of the records

4.4.5 Implementation of monitoring, quality assurance and non-compliance management systems is essential to ensure compliance of key research activities with the quality standards; and to accomplish quality objectives and effectiveness of the QMS

1) Monitoring System

All the key stakeholders should develop and implement simple and effective monitoring systems for each human research project.

The objectives of the monitoring system are as following.

(a) To verify and ensure that the research is conducted, recorded, and reported in accordance with the protocol, Standard

Operating Procedures (SOP) and/or work instructions, ICH GCP and the related legal and regulatory requirements

(b) To ensure that progression of the research is in accordance with the research plan

The extent and type of monitoring activities are determined by the level of risk associated with the conduct of each human research project. The level of risk depends on purposes, type and complexity of human research, vulnerability of study population, nature of intervention, research procedures, and assessment tools.

To have an effective monitoring plan, those risks should be evaluated initially and continually throughout the conduct of human research.

2) Quality Assurance (QA)

All the key stakeholders should develop and implement a QA system in the QMS.

QA embodies the planned and systematic actions that are established in the QMS to ensure that the quality requirements of processes and procedures in the QMS have been fulfilled; to prevent non-compliance of key research activities with the quality standards; and to identify opportunity for continuous quality improvement of the QMS. The key activities of QA include developing

the QA plan, conducting internal/external audit and analysing the quality performance of the QMS.

The audit must be independent and evidence of the performance and results of human research must be systematically reviewed and evaluated objectively to determine: the level of fulfilment of the quality requirements of the process and procedures in the QMS; and to verify the compliance of the conduct of human research with ICH GCP and the applicable regulatory requirement(s).

After the audit process is completed, the audit report, including audit findings and improvement opportunities, should be issued to the auditee. The auditee must develop and implement the CAPA (Corrective Action and Preventive Action Plan) for the audit findings; and report the CAPA and outcomes of the action plan. The auditor must review and verify the CAPA. The audit should be closed out once the resolutions of the audit findings are satisfied.

3) Non-Compliance Management System

All the stakeholders should develop and implement effective non-compliance management system in the QMS.

Effective management of non-compliance is a key activity for the continuous quality improvement of human research.

Managing non-compliance is interrelated with the monitoring and QA activities. The non-compliance management system includes the following activities:-

(a) Assessing the risks of an instance of non-compliance

(b) Monitoring and identifying the non-compliance

(c) Developing comprehensive corrective action to correct and eliminate the root causes of the detected non-compliance

(d) Developing effective preventive action to eliminate the root causes of potential future non-compliance

4) Management review

Top management should review the report of quality performance of the QMS including the audit report at least annually. Improvement opportunity should be identified and continuous improvement of the quality and effectiveness of the QMS should be promoted at all levels of the organisation.

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Conicts of Interest Management

5.1 Definition

Conflict of Interest (COI) is a specific financial or non-financial benefit that will be gained directly or indirectly by one or more of the members of investigators, institutions, or EC. Such interests may increase a risk of bias or poor judgement that may affect the rights and welfare of human subjects and/or the integrity of the research outcomes.

5.2 Types of COI

1) Financial COI: includes, but not limited to, any of the following monetary gains, for example, salary payment, honorarium, fee (for consultation or speaker), travel support, intellectual property

rights, licensing agreement or equity (an ownership interest in a company in the form of stocks).

2) Non-Financial COI: includes, but not limited to, any of the following personal gains, for example, personal benefits from publications, acquisition of grant, personal conflict (individual preferences, prejudices or competing interests), or advancement of academic position, etc.

5.3 Management of COI

The main purpose is to identify and eliminate or reduce COI to ensure that the study design, conduct, and report of research will be free from bias or poor judgement to avoid/reduce any risk to the human subjects or the integrity of the research outcomes. There are principles to be considered on the COI management that include:

1) It is in the best interests of individual and relevant parties to recognise significant COI and to take steps to avoid or prevent those conflicts to avoid affecting the rights and welfare of human subjects and/or the integrity of the research outcomes.

2) Each institution should adopt these national guidelines or generate its own policies and guidance to prevent the negative impact of either an individual's or an institution's COI on the participants' rights and welfare or on the integrity of the research.

3) In all cases, good judgement, openness of process and reliance upon objective, third party oversight can effectively minimise the potential harm to subjects and safeguard the integrity of the research.

4) In a case where COI cannot be completely avoided, public disclosure of financial COI should be made, such as in the informed consent process, at the scientific or public presentation of the study results, or in published scientific articles or media.

5.4 Roles and Responsibilities

5.4.1 Institution

1) Institutions clearly need to have their own guidelines or adopt these guidelines and procedures for managing COI among their employees, and also need to manage their own COI.

2) Institutions should ideally consider establishing a Conflicts of Interest Committee (CIC) to ensure any significant COI will be properly managed and monitored. This is a useful body for an institution to have and is helpful in keeping the EC from bearing the burden of becoming the main group for considering such issues.

3) If there is no CIC, the institutions should assign this function to their EC and support the EC in performing this role and responsibility.

4) Institutions should establish educational programmes on financial COI as part of their educational requirements for clinical investigators and EC members.

5) Institutions should make their financial COI policies and related documents, forms, etc. available online.

6) In a setting when the institution has either a financial stake or other interest in the outcome of the research, to protect the integrity of the CIC or EC process,

(a) The institution should ensure that the review board is free to make its decisions and conduct its oversight activities in an autonomous manner and free from institutional pressures to follow a preferred course of action.

(b) A few outsiders who have no interest in the outcome of the research or the business interests of the institution should be included among EC members.

7) When institutions consider entering into such business agreements, they should consider establishing an independent advisory and oversight committee (institutional CIC), if one does not already exist, to determine whether the financial arrangements represent a COI, and if so, how those conflicts should be managed.

8) An institution may consider providing its own definition of "significant COI" or may consider adapting a definition from any

well established guidelines, such as the US Department of Health and Human Services (DHHS) Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators, February 2013.

5.4.2 Investigator

a) It is desirable to avoid COI whenever possible.

b) Investigators should consider the potential effect that having a financial relationship of any kind with a commercial sponsor of a clinical trial or on interactions with research subjects.

c) If there is a significant COI, or uncertainty about its significance, the investigator should inform or consult the institution's CIC or equivalent body, such as the EC.

d) Any agreements between investigators and a sponsor should be reviewed by the Institution's CIC or equivalent body, such as the EC.

e) Investigators should participate in educational and training programmes concerned with both financial and non-financial COI issues including those that are required by their institutions.

f) Public disclosure of significant financial COI should be made either in the informed consent process when recruiting participants, or when presenting or publishing the study results.

5.4.3 EC

a) The EC Chair should ask its members if they have any potential financial COI related to any of the protocols that the EC is about to consider.

b) The EC should have clear procedures for disqualifi cation of its members, including the Chair, from deliberating/voting on all protocols for which there is a potential or actual financial COI.

c) EC members and staff should participate in education and training activities related to financial COI issues including those required by their institution.

d) When an institution official or CIC or its equivalent determines that a potential Institutional conflict is problematic, the EC should review the institution's financial relationship to the sponsor of a specific study and determine whether the study should be permitted to be carried out at the Institution. If so, the EC should consider how this should best be managed, including what modifications might be needed to the protocol or to the consent form.

e) All ECs should be aware of the source of funding and funding arrangements for each protocol they review, and the

source and arrangements for the funding of the EC when reviewing each protocol.

f) When the institutional official or CIC or its equivalent determines that an investigator has a potential COI that cannot be eliminated, and must be reduced or managed in some way, the EC should consider not only what modifications might need to be made to the protocol or the consent forms, but also other approaches as appropriate.

g) If a financial COI of the institution and/or investigator cannot be eliminated, what the financial arrangement is and how that conflict is being managed should be disclosed in the consent document.

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Research Use of Stored Biomaterials and Data

6.1 Definitions

1) Clinical specimens: include e.g., blood, body fluids, cells, tissues, proteins, or genetic materials (Deoxyribonucleic acid [DNA] or Ribonucleic acid [RNA]) obtained from patients or study subjects.

2) Clinical or bio-data: includes e.g., personal identifiable information (Thai citizen identification number, hospital number, etc.), demographic data, medical records, psychosocial or behavioural data, clinical information such as laboratory results, medical imaging, and genetics or genomic data collected from patients or study subjects.

3) Human subject: means an individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual, and or (2) identifiable confidential information.

4) Repository: Activities that involve three components: (1) the collectors of clinical samples; (2) the repository storage and data management facility or centre; and (3) the recipient investigators.

6.2 Recommendations

6.2.1 Research use of stored biomaterials and data should be subject to oversight by an EC

1) The EC should review and approve the protocol and ensure adequate provisions to protect the privacy of subjects and maintain the confidentiality of data.

2) A confidentiality agreement should be obtained from the investigators to protect confidentiality of repository specimens.

6.2.2 Review processes for biomaterials or data access request: The following should be considered both by the EC and the relevant authority:

1) The experience and qualifications of the investigators

2) Ethical considerations

3) The investigators' familiarity with the characteristics, limitations, and strengths of the dataset/bio-specimens

4) The adequacy of the proposed research design

5) The adequacy of the research environment

6) The adequacy of the investigators' funding resources to support the proposed study and

7) The adequacy of the investigators' agreement on data sharing as stipulated in the data/resource sharing plan

6.2.3 In the case of clinical specimens or data being submitted to the repository without any identifiable private data or information about the individual from whom the material was obtained, permission to access the information or specimens should be obtained from the authorised person of the institution and the EC (either for expedited review or an exemption).

6.2.4 The guidelines should be applied to all studies, regardless of funding sources.

6.2.5 Recipient investigators remain subject to applicable laws or regulations and institutional policies which provide additional protections for human subjects.

6.2.6 In addition, social and behavioural science studies should adopt this guideline.

Bibliography

Coded Private Information or Biological Specimens: Issues to Consider in the Research Use of Stored Data or Tissues, Operation of Biological Repositories: OPRR Memoranda (1996, 1997), NIH. http://www.hhs.gov/ohrp/policy/biodata/, accessed: 22-Feb-15

Guidance on Research Involving Coded Private Information or Biological Specimens, OHRP, DHHS 2008. http://www.hhs.gov/ohrp/policy/cdebiol.html, accessed: 22-Feb-15

The National Institute of Mental Health (NIMH) Repository and Genomics Resource (RGR), accessed on 21 September 2014 from https://www.nimhgenetics.org/access_data_biomaterial.php, accessed: 22-Feb-15

7 Related Local Laws, Regulations, Rules, and Guidelines

This chapter lists selected laws and regulations that may be applicable to human research in Thailand. Please be aware that there may be laws, regulations, or rules that may be applicable to research other than those referred to in this section. Items appearing in this chapter begin with laws, followed by regulations, rules, and guidelines respectively. Please also note that this English version summarises the essence of each item and is not a word-by-word translation. The footnotes in Thai state the actual legal/official statements of each article.

7.1 The National Health Act BE 2550[1] (AD 2007) requires only written informed consent in advance prior to initiating an experiment in

[1] พระราชบัญญัติสุขภาพแห่งชาติ พ.ศ. 2550

humans.[2] It also regards health data as personal, confidential information which cannot be released with the risk of causing damage in the absence of the person's consent.[3] Violations could result in up to six months imprisonment and/or a ten thousand baht fine.[4]

7.2 The Medical Profession Act BE 2525[5] (AD 1982) and the Rule of the Medical Council on the Observance on Medical Ethics BE

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[2] มาตรา 9 ในกรณีที่ผู้ประกอบวิชาชีพด้านสาธารณสุขประสงค์จะใช้ผู้รับบริการเป็นส่วนหนึ่งของการทดลองในงานวิจัยผู้ประกอบวิชาชีพด้านสาธารณสุข ต้องแจ้งให้ผู้รับบริการทราบล่วงหน้า และต้องได้รับความยินยอมเป็นหนังสือจากผู้รับบริการก่อน จึงจะดำเนินการได้ ความยินยอมดังกล่าวผู้รับบริการจะเพิกถอนเสียเมื่อใดก็ได้

[3] มาตรา 7 ข้อมูลด้านสุขภาพของบุคคล เป็นความลับส่วนบุคคล ผู้ใดจะนำไปเปิดเผยในประการที่น่าจะทำให้บุคคลนั้นเสียหายไม่ได้ เว้นแต่การเปิดเผยนั้นเป็นไปตามความประสงค์ของบุคคลนั้นโดยตรง หรือมีกฎหมายเฉพาะบัญญัติให้ต้องเปิดเผย แต่ไม่ว่าในกรณีใด ๆ ผู้ใดจะอาศัยอำนาจหรือสิทธิตามกฎหมายว่าด้วยข้อมูลข่าวสารของราชการหรือกฎหมายอื่นเพื่อขอเอกสารเกี่ยวกับข้อมูลด้านสุขภาพของบุคคลที่ไม่ใช่ของตนไม่ได้

[4] มาตรา 49 ผู้ใดฝ่าฝืนมาตรา 7 หรือมาตรา 9 ต้องระวางโทษจำคุกไม่เกินหกเดือนหรือปรับไม่เกินหนึ่งหมื่นบาท หรือทั้งจำทั้งปรับความผิดตามมาตรานี้เป็นความผิดอันยอมความได้

5 พระราชบัญญัติวิชาชีพเวชกรรม พ.ศ. 2525

2549[6] (AD 2006) give definitions of medical practice[7] and research.[8] They also define the responsibilities of physicians conducting medical research in the case of harms, including compliance with research ethics, the obtaining of informed consent; and approval by the EC prior to its initiation.[9]

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[6] ข้อบังคับแพทยสภาว่าด้วยการรักษาจริยธรรมแห่งวิชาชีพเวชกรรม พ.ศ. 2549

[7] "วิชาชีพเวชกรรม" หมายความว่า วิชาชีพที่กระทำต่อมนุษย์เกี่ยวกับการตรวจโรค การวินิจฉัยโรค การบำบัดโรค การป้องกันโรค การผดุงครรภ์ การปรับสายตาด้วยเลนส์ สัมผัสการแทงเข็มหรือการฝังเข็ม เพื่อบำบัดโรคหรือเพื่อระงับความรู้สึก และหมายความรวมถึงการกระทำทางศัลยกรรม การใช้รังสี การฉีดยา หรือสสาร การสอดใส่วัตถุใดๆ เข้าไปในร่างกาย ทั้งนี้เพื่อการคุมกำเนิด การเสริมสวย หรือการบำรุงร่างกายด้วย

[8] "การศึกษาวิจัยและการทดลองในมนุษย์" หมายความว่าการศึกษาวิจัย และการทดลองเภสัชผลิตภัณฑ์ เครื่องมือแพทย์ การศึกษาธรรมชาติของโรค การวินิจฉัย การรักษา การส่งเสริมสุขภาพ และการป้องกันโรคที่กระทำต่อมนุษย์ รวมทั้งการศึกษาวิจัยจากเวชระเบียนและสิ่งส่งตรวจต่างๆ จากร่างกายของมนุษย์ด้วย

[9] ข้อ 47 ผู้ประกอบวิชาชีพเวชกรรมผู้ทำการศึกษาวิจัย และการทดลองในมนุษย์ต้องได้รับความยินยอมจากผู้ถูกทดลอง และต้องพร้อมที่จะป้องกันผู้ถูกทดลองจากอันตรายที่เกิดขึ้นจากการทดลองนั้น

ข้อ 48 ผู้ประกอบวิชาชีพเวชกรรมต้องปฏิบัติต่อผู้ถูกทดลองเช่นเดียวกับการปฏิบัติต่อผู้ป่วยในการประกอบวิชาชีพเวชกรรมตาม หมวด 4 โดยอนุโลม

ข้อ 49 ผู้ประกอบวิชาชีพเวชกรรมต้องรับผิดชอบต่ออันตรายหรือผลเสียหายเนื่องจากการทดลองที่บังเกิดต่อผู้ถูกทดลองอันมิใช่ความผิดของผู้ถูกทดลองเอง

ข้อ 50 ผู้ประกอบวิชาชีพเวชกรรมผู้ทำการหรือร่วมทำการศึกษาวิจัยหรือการทดลองในมนุษย์สามารถทำการวิจัยได้เฉพาะเมื่อโครงการศึกษาวิจัยหรือการทดลองดังกล่าวได้รับการพิจารณาเห็นชอบจากคณะกรรมการด้านจริยธรรมที่เกี่ยวข้องแล้วเท่านั้น

7.3 The Mental Health Act BE 2551 (AD 2008)[10] requires written informed consent and approval of the relevant EC prior to initiation of the study in mental health patients. Use of informed consent by proxy is allowed when the subject is less than 18 years old or is mentally incapacitated. The informed consent form must be in the format promulgated in the Royal Gazette.

7.4 Article 323[11] of the Criminal Code BE 2499[12] (AD 1956) stipulates

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[10] พระราชบัญญัติสุขภาพจิต พ.ศ. 2551.

มาตรา 21 การวิจัยใด ๆ ที่กระทำต่อผู้ป่วย* จะกระทำได้ต่อเมื่อได้รับความยินยอมเป็นหนังสือจากผู้ป่วย และต้องผ่านความเห็นชอบของคณะกรรมการที่ดำเนินการเกี่ยวกับจริยธรรมการวิจัยในคนของหน่วยงานที่เกี่ยวข้อง และให้นำความใน มาตรา 21 วรรคสาม มาใช้บังคับกับการให้ความยินยอม โดยอนุโลมความยินยอมตามวรรคหนึ่งผู้ป่วยจะเพิกถอนเสียเมื่อใดก็ได้

มาตรา 21 การบำบัดรักษาจะกระทำได้ต่อเมื่อผู้ป่วยได้รับการอธิบายเหตุผลความจำเป็นในการบำบัดรักษา รายละเอียดและประโยชน์ของการบำบัดรักษา และได้รับความยินยอมจากผู้ป่วยเว้นแต่เป็นผู้ป่วยตามมาตรา 22**

ถ้าต้องรับผู้ป่วยไว้ในสถานพยาบาลของรัฐหรือสถานบำบัดรักษา ความยินยอมตามวรรคหนึ่งต้องทำเป็นหนังสือ และลงลายมือชื่อผู้ป่วยเป็นสำคัญ

ในกรณีที่ผู้ป่วยมีอายุไม่ถึงสิบแปดปีบริบูรณ์ หรือขาดความสามารถในการตัดสินใจให้ความยินยอมรับการบำบัดรักษา ให้คู่สมรส ผู้บุพการี ผู้สืบสันดาน ผู้ปกครอง ผู้พิทักษ์ ผู้อนุบาล หรือผู้ซึ่งปกครองดูแลบุคคลนั้น แล้วแต่กรณี เป็นผู้ให้ความยินยอมตามวรรคสองแทน

หนังสือให้ความยินยอมตามวรรคสองและวรรคสาม ให้เป็นไปตามแบบที่คณะกรรมการกำหนดโดยประกาศในราชกิจจานุเบกษา

[11] มาตรา 323 ผู้ใดล่วงรู้หรือได้มาซึ่งความลับของผู้อื่น โดยเหตุที่เป็นเจ้าพนักงานผู้มีหน้าที่โดยเหตุที่ประกอบอาชีพเป็นแพทย์ เภสัชกร คนจำหน่ายยา นางผดุงครรภ์ ผู้พยาบาล นักบวช หมอความ ทนายความ หรือผู้สอบบัญชี หรือโดยเหตุที่เป็นผู้ช่วยในการประกอบอาชีพนั้น แล้วเปิดเผยความลับนั้น ในประการที่น่าจะเกิดความเสียหายแก่ผู้หนึ่งผู้ใด ต้องระวางโทษจำคุกไม่เกินหกเดือน หรือปรับไม่เกินหนึ่งพันบาท หรือทั้งจำทั้งปรับ

[12] ประมวลกฎหมายอาญา พ.ศ. 2499

the duties of certain health and some other professions to maintain confidentiality of their clients. Its Article 324[13] requires those who learn about scientific secrets and release them and cause damage will also be guilty of a criminal offence. Both offences could result in six months imprisonment and/or a one thousand baht fine.

7.5 Article 420 of the Civil Code BE 2535[14] (AD 1992) states that anyone who intentionally or carelessly carries out illegal acts causing loss of life, damage to health, freedom, property, or any rights are regarded as culpable and have to pay fines to cover those acts.

7.6 The Medical Council in its Rule of Medical Council on the Observance on Medical Ethics on Stem Cell Transplantation for Therapeutic Purposes BE 2552[15] (AD 2009) considers clinical research studies on stem cells, progenitor cells, or cells cultured from stem cells under its jurisdiction, except approved haemato-

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[13] มาตรา 324 ผู้ใด โดยเหตุที่ตนมีตำแหน่งหน้าที่วิชาชีพ หรืออาชีพอันเป็นที่ไว้วางใจ ล่วงรู้หรือได้มาซึ่งความลับของผู้อื่น เกี่ยวกับอุตสาหกรรม การค้นพบ หรือการนิมิตในวิทยาศาสตร์ เปิดเผยหรือใช้ความลับนั้นเพื่อประโยชน์ตนเองหรือผู้อื่น ต้องระวางโทษจำคุกไม่เกินหกเดือน หรือปรับไม่เกินหนึ่งพันบาท หรือทั้งจำทั้งปรับ

[14] มาตรา 420 ผู้ใดจงใจหรือประมาทเลินเล่อ ทำต่อบุคคลอื่นโดยผิดกฎหมายให้เขาเสียหายถึงแก่ชีวิตก็ดี แก่ร่างกายก็ดี อนามัยก็ดี เสรีภาพก็ดี ทรัพย์สินหรือสิทธิอย่างหนึ่งอย่าง ใดก็ดี ท่านว่าผู้นั้นทำละเมิดจำต้องใช้ค่าสินไหมทดแทนเพื่อการนั้น

[15] ข้อบังคับแพทยสภาว่าด้วยการรักษาจริยธรรมแห่งวิชาชีพเวชกรรมเรื่อง การปลูกถ่ายเซลล์ต้นกำเนิดเพื่อการรักษา พ.ศ. 2552

logical diseases which have their own regulations.[16] Clinical trials on stem cells have to be approved by the local EC and the Medical Council prior to their initiation.

7.7 The Thai Food and Drug Administration made an announcement in October 2013 about its criteria for certifying EC that meets their requirements to allow importation of IPs for human clinical research.[17]

7.8 Other guidelines that are adopted by many researchers, EC / IRB/IEC, etc. include: -

7.8.1 The Patient's Bill of Rights BE 2541[18] (AD 1998) requires that patients be fully informed before participating in or withdrawing from experiments by health professionals.[19]

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[16] "การปลูกถ่ายเซลล์ต้นกำเนิดเพื่อการรักษา" หมายความว่า การประกอบวิชาชีพเวชกรรมที่เกี่ยวกับการปลูกถ่ายเซลล์ต้นกำเนิด ซึ่งอาจเป็นเซลล์ต้นกำเนิด หรือ โพรเจนิเตอร์เซลล์ (progenitor cell) หรือเซลล์ที่เจริญมาจากการเพาะเลี้ยงเซลล์ต้นกำเนิด เพื่อการรักษาโรคในคน แต่ไม่หมายความรวมถึงการปลูกถ่ายเซลล์ต้นกำเนิดเม็ดโลหิตในการรักษาโรคโลหิตวิทยา ซึ่งเป็นไปตามข้อบังคับว่าด้วยการนั้น"

[17] ประกาศสำนักงานคณะกรรมการอาหารและยาเรื่อง หลักเกณฑ์ วิธีการ และเงื่อนไขการยอมรับคณะกรรมการพิจารณาจริยธรรมการวิจัย ในคนที่พิจารณาโครงการวิจัยทางคลินิกเกี่ยวกับยา ประกาศ ณ วันที่ 8 สิงหาคม พ.ศ. 2556 (เล่ม 130 ตอนพิเศษ 135 ง ราชกิจจานุเบกษา 14 ตุลาคม 2556 หน้า 12)

[18] ประกาศสิทธิของผู้ป่วย แพทยสภา สภาการพยาบาล สภาเภสัชกรรม ทันตแพทยสภา กระทรวงสาธารณสุขร่วมกันประกาศสิทธิผู้ป่วย ๑๖ เมษายน ๒๕๔๑

[19] ผู้ป่วยมีสิทธิที่จะได้รับทราบข้อมูลอย่างครบถ้วนในการตัดสินใจในการเข้าร่วม หรือถอนตัวจากการเป็นผู้ถูกทดลองในการทำวิจัยของผู้ประกอบการวิชาชีพด้านสุขภาพ

7.8.2 Good Clinical Practice (GCP) guidelines (1996, translated Thai version 2000) by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH GCP).

7.8.3 International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), and

7.8.4 CIOMS/WHO International Ethical Guidelines on Epidemiological Studies (2008).

7.8.5 Ethical Guidelines for Research on Human Subject in Thailand (2007) issued by the Forum for Ethical Review Committees in Thailand (FERCIT).

The Ministry of Public Health and the National Research Council of Thailand are working on drafts of the human research acts which are now in progress at the time of going to print.

8 Research Issues Requiring Special Consideration

8.1 Vulnerable Populations

8.1.1 Definition

Vulnerable persons are those who are relatively or absolutely incapable of protecting their own interests. More formally, they may have limited capacity or freedom to consent or decline to consent. They may have insufficient power, intelligence, education, resources, strength, or other needed attributes to protect their own interests.

8.1.2 Factors Affecting Vulnerability

Vulnerability may be influenced by many factors, including impaired cognitive function that will affect mental capacity,

vulnerability through disease or medically-related issues; by socioeconomic status and by situation which will affect their capacity to make free and willing decisions (see CIOMS guideline 13).

Vulnerable groups may include, e.g., children, elderly persons, persons in hierarchical order (e.g., boss and subordinates, military personnel, etc.), marginalised populations, prisoners, handicapped or mentally disabled persons, terminally ill patients, and persons who are economically or educationally disadvantaged.

8.1.3 Research Involving Vulnerable Persons

General Considerations

Special justification is required for inviting vulnerable individuals to serve as research subjects and the means of protecting their rights and welfare must be strictly applied. Ethical justification for their involvement usually requires that investigators satisfy their EC/B/IEC that the research cannot be carried out equally well with less vulnerable subjects:

1) The research is intended to obtain knowledge that will lead to improved diagnosis, prevention or treatment of diseases or other health problems characteristic of, or unique to, the vulnerable class–either the actual subjects or other similarly situated members of the vulnerable class;

2) Research subjects and other members of the vulnerable class from which subjects are recruited will ordinarily be assured reasonable access to any diagnostic, preventive or therapeutic products that will become available as a consequence of the research;

3) The risks attached to interventions or procedures that do not hold out the prospect of direct health-related benefit will not exceed those associated with routine medical or psychological examination of such persons unless the EC authorises a slight increase over this level of risk;

4) And when the prospective subjects are either incompetent or otherwise substantially unable to give informed consent, their agreement may be supplemented by the permission of their LAR or other appropriate representatives.

8.2 Community Advisory Board

8.2.1 Definition

Community Advisory Board (CAB): is a common mechanism used to promote community engagement in clinical research, through a committee composed of appropriate and relevant representatives from the community, and proactive consultation or interaction between CAB members and research staff.

8.2.2 General considerations

Community consultation is a crucial step to ensuring that a research programme is effectively responding to the perceptions and needs of local communities involved in clinical trials or epidemiological studies.

While CABs are neither a specific ethical requirement nor required in every trial, they have become a de facto standard for clinical research in the HIV/AIDS (Human Immunodeficiency Virus/ Acquired Immune Deficiency Syndrome,) field, and are considered necessary for effective communication with local communities engaged in such research. In settings where the CAB model may not be applicable, research networks and international groups have encouraged systematic mechanisms for community consultation to be in place.

Guidelines

The following are the suggested minimum requirements for CABs:

8.2.3 CAB Mission and Goals

1) Every CAB should have a clearly defined mission statement, which should be developed early in the life cycle of the CAB, in collaboration between CAB members and research staff.

2) It is advisable that CABs establish goals for their work that allow for further detailing of how the CAB will achieve its mission.

8.2.4 CAB Membership Considerations

1) A CAB should have diverse representation, bringing together members with different profiles, experiences, and expertise.

2) An institution makes sure that relevant populations are well represented in the CAB. This includes representation of the groups that will be recruited for the research as well as people living with HIV/AIDS, and community leaders.

8.2.5 Institution Responsibility Considerations

1) Every institution should have designated liaison staff for its CAB, with adequate capacity to provide technical assistance to the CAB at every stage of its activity and growth.

2) The CAB should have regular interaction with research staff. It is recommended that the centre's Principal Investigator (PI) meet with the CAB on a regular basis. In case of significant occurrences in the HIV/AIDS or other relevant fields, especially those which are locally relevant, CABs should meet with the PI or other appropriate clinical staff as soon as possible for briefing and clarifications.

3) The institution should provide adequate resources in order for the CAB to function effectively; CAB-related expenses such as meeting space, supplies, transport, and training should be incorporated into the institution's budget.

8.2.6 CAB Operations

1) CABs should develop a charter or agreement to formalise their operations and structure in a consensual document.

2) Appropriate roles should be assigned to select CAB members to form a governing structure for the CAB.

3) It is recommended that CABs meet monthly during their first year of operation and as necessary after the first year, but not less than quarterly.

4) The assigned community liaison staff from the institution should work with the CAB to develop a strategic set of activities or action plans that accurately reflect the research agenda of the institution and the concerns of the surrounding community.

8.2.7 CAB Member Training

1) An initial training cycle should be offered to all CAB members, including orientation about the institution, the roles of the CAB, as well as information on, e.g., HIV/AIDS vaccine research and development, clinical research, and ethics.

2) An assessment of training needs and refresher training should be offered to CABs periodically, or whenever significant new information that may affect the research becomes available (such as the results of research happening at the site or elsewhere).

8.3 Stem Cell Research

Stem cells (SC) are immature cells that replicate themselves and have the ability to differentiate into a variety of different types of cells. SC have the potential to provide treatments for a host of debilitating diseases and prevent suffering from Alzheimer's, Parkinson's, diabetes, multiple sclerosis, heart disease, and spinal cord injury. Few other areas of science have generated as much excitement, scrutiny and controversy. Cells manufactured in large quantities outside their natural environment in the human body can become ineffective or produce significant adverse effects, such as tumours, severe immune reactions, or growth of unwanted tissue.

Due to tremendous current unmet needs to cure disease or prolong life, SCs are sometimes being prematurely promoted and/or over promoted and used without adequate evaluation. Such practices raise concerns in regulatory and medical communities. Before SCs can be used widely, qualified research must be carefully done to evaluate their efficacy and safety. There is an urgent need for clear guidelines that would allow for both response to

rapidly evolving science and shifting public opinion to ensure ethical and scientific standards.

Guidelines on SC research in various countries are still evolving. In Thailand a Guideline was published in the "Bioethical Issues and Guidelines" by the National Health Foundation and the National Centre for Genetic Engineering and Biotechnology in 2003. Continuous update on the issue is needed to catch up with the rapidly progressing science.

The Medical Council in its Rule of Medical Council on the Observance on Medical Ethics on Stem Cell Transplantation for Therapeutic Purposes BE 2552 (AD 2009) considers clinical research studies on SCs, progenitor cells, or cells cultured from SCs under its jurisdiction except for approved haematological diseases which have their own regulations. Clinical trials on stem cells have to be approved by the local EC and the Medical Council prior to its initiation.

8.3.1 Recommendations:

1) Since SC research involves complex ethical issues and public concerns, a special Stem Cell Oversight Committee (SCOC) should be established to conduct ethical review of all human pluripotent stem cell research proposals recommended for approval by relevant agencies. SCOC's members should include

experts in biology, assisted human reproduction, ethics, law, and social sciences, as well as representatives of the general public.

2) All research proposals involving human embryonic SCs and/or the grafting of human pluripotent SCs into humans or animals, falling within the scope of this Guideline, should require approval from both SCOC and the relevant EC.

3) Research involving the grafting of SC to human subjects can be done if carried out in well-designed clinical trials after the approval of the EC and SCOC and in compliance with the Medical Council's regulations on SCs.

SC donor(s) must be informed during the consent process:

• Regarding the individual (s) who may receive medical benefits from the use of the SCs or who may be recipients of the cell transplants.

• The research was not intended to provide direct medical benefits to the donor(s)

• The results of research may have commercial potential

• The donor(s) would not receive financial or any other benefits from any such commercial development

• A pregnant woman's decision to discontinue her pregnancy was made prior to any request made to her to participate in the research

• Pluripotent somatic SCs from a legally incompetent person must be obtained from a surgical, diagnostic, or other legitimate practice not including research, and have been authorised by an SCOC for use in research.

Use of stem cells or tissues from a cadaver must also be authorised by an SCOC. For imported stem cells, it must be proven that the original acquisition process of cells complied with the above.

8.4 Gene Therapy Research

Gene therapy is an experimental technique that uses genes (DNA, RNA, or nucleic acids) to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

• Replacing a mutated gene that causes disease with a healthy copy of the gene

• Inactivating, or "knocking out," a mutated gene that is functioning improperly

• Introducing a new gene into the body to help fight a disease

Although gene therapy is a promising treatment option for a number of diseases (including inherited disorders, some types of cancer, and certain viral infections), the technique is still under study to make sure that it will be safe and effective. Gene therapy is currently being tested only for the treatment of diseases that have no other cures.

8.4.1 General Considerations

1) The institution should consider establishing a technical committee dealing with gene therapy research experience. An example of this type of committee is the Recombinant DNA Advisory Committee (RAC) which makes recommendations on research involving the use of recombinant DNA and on developments in recombinant DNA technology.

2) No research participant should be enrolled until the project has been approved by this committee and the EC.

3) The informed consent document should provide, in addition to information required otherwise, the following issues

(a) A description of the gene transfer component must be included in the informed consent for the subjects and explained in non-technical language

(b) The approximate number of people who have previously received the genetic material under study

(c) Types of adverse experiences, their relative severity, and their expected frequencies

(d) Warning that, for genetic materials previously rarely or never used in humans, unforeseen risks are possible, including ones that could be severe

(e) Any possible adverse medical consequences that may occur if the subjects prematurely withdraw from the study

(f) The possibility of other investigational alternatives should also be included.

(g) Specific information about any financial costs that might occur in the long term after the study is completed and may not be covered by the investigators or the institution involved

8.5 Traditional and Herbal Medicine

8.5.1 Definition

Traditional Medicine (TM) is treatment involving the use of herbal medicines with traditional procedure-based therapies. However, successful treatment is often the consequence of both types of treatment acting synergistically. The terms are used interchangeably; along with TM are terms such as complementary/alternative/non-conventional medicine.

TM has a long history of integrated knowledge, skills and practices which are based on the beliefs, theories, and experiences implanted/settled in various cultures, both explainable or unexplainable, consisting of health promotion, disease prevention, diagnosis, and health modification affecting physical and mental illnesses.

Herbal Medicine (HM) is a plant-derived material or preparation with therapeutic or other human health benefits which contains either raw or processed ingredients from one or more plants. In some traditions, materials of inorganic or animal origin may also be present.

HM includes herbs (root, stem, leaf, flower, fruit, or seed), herbal materials (fresh juices, gums, fixed oils, essential oils, resins, etc.), herbal preparations (extraction, fractionation, or made by steeping or heating herbal materials in alcoholic beverages and/or honey, etc.), and finished herbal products (one herb or mixture).

Active ingredients of a whole herbal medicine, if unidentifiable, are considered as one active ingredient.

8.5.2 Basic Principles

Research and development should guarantee the "safety and efficacy" as well as quality control of the traditional procedure-based therapies and HM. The efficacy of TM should be evaluated

in an integrated manner of both treatment types. As TM relies on a holistic approach, knowledge and experience obtained through the long history of established practices should be respected.

8.5.3 Research Involving Traditional and Herbal Medicine

General Considerations

1) Research and Evaluation of Traditional Procedure-Based Therapies:

Traditional procedure-based therapies are relatively safe, if they are performed properly by well-trained practitioners. Therapies should be performed within accepted parameters, and the indications for a therapy should be evidence-based when possible. The evaluation of adverse effects should be considered a priority area for systematic evaluation of the safety of these therapies. Clinical trials and other research methodologies are extremely important in the evaluation of the efficacy of traditional procedure-based therapies.

2) Research and Evaluation of Herbal Medicines:

(a) Botanical verification and quality considerations are necessary in assuring the quality, safety, and efficacy of herbal medicine. Details on specifications and quality control of the herbal medicine used are required. Chemistry Manufacturing Control (CMC) of HM to be evaluated mimics that for a traditionally-used

formulation. Evaluation of HM does not require purification to known or single chemical constituents. Good Manufacturing Practice (GMP) standards are needed prior to phase III trials

(b) Non-clinical considerations for HM:

• For HM with a well-documented history of traditional use, efficacy and safety information in existing animal data, searched from literature sources is recommended. If information is insubstantial it is necessary to perform additional non-clinical studies

• If well-known HMs are formulated into a new mixture, it may alter the chemical, toxicological and pharmacological profiles, and proof of safety and efficacy is required. Additional non-clinical studies may be needed

• For HMs without a long history of use or which have not been previously researched, the standard methods of non-clinical toxicological studies, including acute toxicity testing and long-term toxicity testing, should follow the WHO's research guidelines for evaluating the safety and efficacy of herbal medicines (see bibliography)

• Pharmacokinetics studies are technically difficult to conduct. Also, the dosing regimen can be deduced from traditional methodology. Therefore, non-clinical PK is not absolutely required.

(c) Clinical considerations for HM:

• Phase I studies are designed to determine safety associated with increasing doses in normal volunteers. Phase I studies are generally unnecessary for herbal traditional medicines. Traditional dose regimens of herbal medicines convey reasonable confidence that these regimens can safely be administered to a small number of carefully monitored clinical subjects in phase II trials.

• Phase II studies: it is important to verify tolerance in phase II trial patients. Both the literature review and the provisions in the protocol to be performed should focus on complete review of the clinical safety parameters, e.g. neurological, skin, musculoskeletal, gastrointestinal, liver, kidney, endocrine system and metabolism (sodium/potassium, calcium), cardiovascular, hematopoietic, etc.

• Phase III studies should be undertaken only after dose-ranging phase II data are available. Inappropriate rejection of intervention, "because phase II studies did not precede a phase III trial, and a suboptimal dose was used in the phase III trial", is common for HM. The chosen dosing regimen is likely to be the optimal regimen with respect to safety and efficacy.

(d) Ethical considerations in clinical trials with HM:

• Apply fundamental ethical principles; all research involving human subjects should be conducted in accordance with ethical principles contained in the Declaration of Helsinki, three basic ethical principles (the Belmont Report), laws, and regulations of the country, whichever represents the greater protection for subjects.

• A well trained, ethical investigator is the best assurance of patient safety in research. Skilled clinicians should be chosen as investigators to assure prompt recognition and appropriate treatment of any observed adverse events or worsening of a pre-existing condition.

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