Operational Guidelines
for Institutional Review Boards

TABLE OF CONTENTS

1 Introduction 1
2 Definition of Human Biomedical Research 1
3 Basic Ethical Principles 2
4 Objectives of Document 3
5 Responsibilities of Institutional Review Boards 3
6 Composition of IRBs 4
7 Review of Research Project 5
8 Continuing Ethics Review and Communication 12
9 Suspension or Discontinuation of Research 12
10 Documentation and Record Keeping 13
11 Monitoring and Improvement Programme 14
12 Specific Situations 16

Glossary
References
INTRODUCTION

1.1 Human biomedical research is ethically justifiable only if it abides by acceptable moral standards within the community and is carried out in ways that respect and protect the subjects of the research. The research must conform to generally accepted scientific principles and be based on a thorough knowledge of existing scientific literature and information, adequate laboratory and, where appropriate, animal experimentation. Scientifically invalid research is unethical, in that it exposes research subjects to unwarranted risks without likely benefits. An independent ethics review committee for research projects has this checking function, where it considers, guides, and, where appropriate, approves the project.

1.2 In Singapore, the ethical principles in research today are promulgated in the form of regulatory standards, and practice guidelines, governing various aspects of clinical research, such as those contained in the Medicines (Clinical Trials) Regulations, promulgated pursuant to s.74 of the Medicines Act (Cap. 176), the Singapore Guideline for Good Clinical Practice (SG-GCP), and the Ethical Guidelines on Research Involving Human Subjects of the National Medical Ethics Committee (NMEC).

1.3 The Bioethics Advisory Committee (BAC) has, in its report on Research Involving Human Subjects: Guidelines for IRBs, made recommendations on the operational guidelines, constitution and role of institutional review boards (IRBs), in the ethics governance of human biomedical research.

DEFINITION OF HUMAN BIOMEDICAL RESEARCH

2.1 “Research” is defined as any investigation designed to develop or contribute to generalisable knowledge. This generalisable knowledge will benefit specific groups, or the whole, of the human population, rather than any specific individual.

2.2 Human biomedical research (HBR) refers to any research on human subjects that involves:
   a. intervention on, interaction with, or observation of, humans;
   b. use or manipulation of any human biological derivative (e.g. human cells, tissues and body fluids), including those which were previously acquired and stored;
   c. review, analysis and publication of previously compiled identifiable data;

for the purpose of studying, diagnosing, treating and/or preventing, any ailment, injury or adverse condition of the human mind or body.

2.3 An activity that is undertaken with the intention of improving the health of the patient may be considered “therapy”. However, the fact that some therapeutic benefit to the patient may result from an activity that is designed to develop or contribute to generalisable knowledge does not alter its status as “research”.

2.4 Where conflicts arise between research and therapy, their resolution rests on the integrity of the physician/investigator.
3 BASIC ETHICAL PRINCIPLES

3.1 All HBR must be conducted in accordance with these three (3) fundamental ethical principles:

   a. **Respect for persons**, which incorporates at least two (2) basic ethical considerations:
      i. Respect for autonomy, which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination;
      ii. Protection of persons with impaired or diminished autonomy (such as children or the mentally disabled), which requires that those who are dependent or vulnerable be afforded additional security against harm or abuse.

In the context of a diverse society such as Singapore, researchers have an especial obligation to be sensitive to religious beliefs, cultural perspectives and traditions of human subjects, both individual and collective, involved in their research.

   b. **Beneficence**, which refers to the ethical obligation to maximize benefits and to minimize harm. In the research context, it is unlikely that direct benefit will accrue to research subjects. Consequently, harm and discomfort to subjects must be minimised and the risks of research must be reasonable and justified in the light of the expected benefits. This entails a sound research design, and investigators competent both to conduct the research and to safeguard the welfare of the research subjects.

   c. **Justice**, which refers to the ethical obligation to treat each person in accordance with what is morally right and proper, and to give to each person what is due to him/her. For HBR, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized. Justice also requires that research be responsive to the health conditions or needs of vulnerable subjects. Accordingly, a researcher should:
      i. avoid imposing on any particular group of individuals who are likely to be subjects of over-researching and unfair participation in research;
      ii. ensure that the selection and recruitment of research subjects are fair; and
      iii. be non-discriminatory, and not use race, age, gender, disability or religious beliefs for the selection and recruitment of actual or future participants, except where such exclusion or inclusion of particular groups is essential to the objective of the research.

3.2 Other important ethical principles include the respect for **free and informed consent**, and protection of **privacy and confidentiality**. Especial attention must also be given to vulnerable persons, i.e. those with higher susceptibility to harms and/or with reduced ability to protect their rights and welfare, such as pregnant women, minors, prisoners and the mentally incapacitated.
4 OBJECTIVES OF DOCUMENT

4.1 The objective of the IRB Operational Guidelines (the “Guidelines”) is to provide operational guidance for IRBs and to contribute to the improvement of quality and development of consistency in the ethics review of HBR projects.

4.2 The Guidelines are not intended to displace existing national documents on ethics governance, but should be viewed in tandem with them when considering the rationale for ethics governance.

4.3 The Guidelines are not intended to cover activities performed pursuant to existing legislation, e.g. quality assurance (QA) and clinical audit activities conducted pursuant to the Private Hospital and Medical Clinic (PHMC) Act. QA and clinical audit activities that fall within the definition of HBR, unless performed pursuant to existing legislation, will however require approval from an IRB prior to commencement of the activity.

4.4 The provisions in the Guidelines cover only IRBs that review HBR, and are not intended to apply to ethics committees that address issues related to clinical practice, and/or research relating to:
   a. Genetically modified organisms;
   b. Animals and their treatment; and/or
   c. Disciplines of the humanities and social sciences, such as Economics and Sociology.

5 RESPONSIBILITIES OF INSTITUTIONAL REVIEW BOARDS

5.1 The IRB is a vehicle for an institution to implement its system of ethics governance of research carried out in the institution.

5.2 The primary role of the IRB is to ensure adequate protection of potential and actual human subjects, through the review of HBR projects. The goals of research, while important, should never be permitted to override the safety and well-being of research subjects.

5.3 IRBs are to provide independent, competent, and timely ethics review of HBR projects. They must demonstrate competence and efficiency in their work.

5.4 IRBs are responsible for:
   a. ethics review and approval of HBR projects;
   b. continuing review, such as the evaluation of progress updates of research projects and adverse event reports provided by researchers, to ensure the continued validity of ethics approval of projects approved by them. IRBs should have the authority to withdraw the ethics approval of research projects where there are sufficient concerns over the safety and well-being of research subjects;
   c. reporting to their respective institutions any unusual or unexpected events arising from the research, in accordance with their standard operating procedures; and
   d. providing feedback to, and maintaining dialogue about applicable standards with, their constituent researchers.
5.5 IRBs should perform their functions according to written policies and operating procedures, maintain written records of their activities, and comply with all relevant institutional and regulatory requirements.

5.6 IRBs should have in-depth understanding of the basic ethical principles governing research, and be familiar with existing national regulations, legislative requirements and institutional policies governing the conduct of HBR.

**Institutional Conflict of Interest**

5.7 Although IRBs are appointed and supported by institutions, they owe a public and professional duty to act with total impartiality, objectivity and independence.

5.8 Should an IRB be of the view that there exist circumstances or considerations which make impossible, or might impair or adversely affect, the impartial, objective and independent discharge of its duties, the IRB should not review the research project(s) in question.

5.9 The IRB should make a special report to the board of directors of the institution on all projects in which there are actual, potential or apparent, institutional conflicts of interests.

5.10 All communications in relation to the review of such research projects should be fully documented in writing. Informal communication between the institutional officers and individual members of the IRB, in connection with the review of these research projects, is not encouraged.

6 **COMPOSITION OF IRBs**

6.1 IRBs should consist of formally appointed members who should turn over periodically to blend experience with fresh perceptions. Each term of appointment should be for at least 2 - 3 years. The composition of IRBs may vary from institution to institution depending on local circumstances.

6.2 There should be clear institutional policies on the administration of IRBs with respect to the appointment, disqualification, resignation, and replacement of IRB members. Office bearers, e.g. Chairperson, and other members of the IRB, should be appointed by their respective institution with proper terms of reference. IRB members should also be properly oriented to the role and responsibilities of IRBs and given appropriate initial and continued training, where required.

6.3 An IRB should be carefully composed such that there can be no room for any public perception that it is not independent of its institution/researchers.

6.4 Each IRB shall comprise at least five (5) members. Members should be appointed based on their personal capacity and expertise, and not in a representative capacity. As far as possible, the members of an IRB should collectively possess the expertise and understanding of the types of research commonly carried out in the institution.

6.5 The Chairperson of each IRB shall be a registered medical practitioner. Both the Chairperson and the Deputy Chairperson should be respected clinicians of the institution who possess sufficient relevant knowledge and experience in research ethics. Other members drawn from the institution should be scientifically...
competent and morally upright officers, researchers or consultants, who possess the appropriate experience and training.

6.6 To further reinforce the independence of the IRB, and to ensure that the decisions of the board are carried out in accordance with scientific thinking accepted within the community, additional external representation by specialists of favorable reputation from other institutions is encouraged.

6.7 If an IRB regularly reviews research involving a category of vulnerable subjects, such as children, pregnant women, or mentally incapacitated persons, consideration should be given to the inclusion of one or more members with the necessary expertise and experience in working with these subject groups.

**Independent consultants**

6.8 An IRB may, at its discretion, invite independent consultants to assist in special areas in the review of a research project. These consultants serve only to provide the necessary expertise, and are not allowed to vote. These consultants may be specialists in ethical or legal aspects, specific diseases or methodologies, or they may function as representatives of communities, patients, special interest groups or major local religions. These consultants should have no conflicts of interest, in relation to the research project, arising from any personal involvement, financial interests in the outcome, or any involvement in competing research. Terms of reference for independent consultants should be established.

**Indemnity**

6.9 IRB members should be formally assured, e.g. in their letters of appointment, that the institution will provide legal protection against liabilities that may arise in the course of the conduct of their duties carried out in good faith.

7 REVIEW OF RESEARCH PROJECT

**Types of ethics review**

7.1 Institutions should determine with the IRB, the categories of research for which each type of ethics review requirement would apply. Every proposed HBR project shall undergo the type of ethics review corresponding to its risk of harm to research subjects. Where uncertain of the required extent of review, the research project should be subjected to a higher level of review.

7.2 Research involving the writing up or reporting of individual patients' cases by their own doctors (i.e. within the scope of the doctors' clinical management of the patients) would be exempted from any ethics approval, since medical practitioners are already bound by the ethical code of patient-confidentiality, and have an obligation to ensure that no harm comes to their patients.

**Full review**

7.3 All HBR projects involving interventions that pose a more than “minimal risk” to research subjects shall be subjected to a full review. “Minimal risk” refers to the probability and magnitude of harm and discomfort anticipated in the research that are not greater, in and of themselves, than those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or
tests. Research projects with special ethics concern e.g. that involve the creation of human embryonic stem cell lines also require full ethics review.

**Expedited review**

7.4 HBR projects involving minimal or remote risk to research subjects may be reviewed via an expedited track by IRBs, where appropriate.

7.5 The Chairperson alone or at least two IRB members may make decisions on research projects that qualify for expedited review. Decisions made by the members must be unanimous. Operational procedures on the expedited review of research projects, e.g. authority of IRB Chairperson, delegation of tasks to IRB members and the method of reporting and ratification of decisions to the full board, should be clearly documented.

7.6 The following may be considered for expedited review:

a. Minor and non-substantive changes to previously approved research projects;

b. The analysis of patient information without interaction with subjects. The IRB needs to be satisfied that the researchers will take appropriate measures to protect the privacy of the subjects;

c. Research involving human tissues from tissue banks. IRBs must be satisfied that the tissue is obtained from a reliable source, in which consent has been obtained for the tissues to be used for research, and that the donor’s privacy is protected; and

d. The local portion (at the level of specific institutions) of a multi-centre or multi-national research project that has already received a full review by the lead IRB.

**Exempted review**

7.7 The most important consideration is that there must be no likelihood of harm to the research subject. Decision on endorsement of exempted status may be made by the Chairman alone or unanimously by at least two IRB members. HBR projects that could qualify for exempted review would include those using publicly available databases.

7.8 Researchers shall be required to submit all such research projects to the IRB for endorsement of their status of exemption.

**Exceptional situations**

7.9 It may be ethically acceptable to abbreviate, or temporarily suspend, the usual ethics review procedures and requirements in some exceptional circumstances, provided that all other applicable legislative and regulatory requirements are satisfied. In situations where urgent research has to be carried out by an institution for the sake of national security or for the urgent protection or treatment of whole populations at risk, its IRB should consult MOH for special exemption or expedited review of the specific research project.

**Elements of Review**

7.10 The primary task of an IRB lies in the ethics review of HBR projects, with special attention given to the informed consent process, and the suitability and feasibility of the protocol. IRBs are required, in their review of protocols, to take into consideration the requirements of existing applicable laws and regulations. In addition, the following should be considered, where applicable:
7.10.1 **Scientific design and conduct of the clinical trial**

a. A research project with little or no scientific merit, where the risks of discomfort or harm to subjects are not justified by the expected benefits, is ethically unacceptable. The IRB, however, is not responsible for carrying out the scientific review of research projects. It is for researchers to provide to the IRB all relevant findings, whether positive or negative, of the review for scientific merit, and to satisfy the IRB that an objective review has been carried out.

b. The scientific review of research projects may be carried out by such committees, bodies or agencies as the IRB may, in its judgement, recognise as appropriate.

c. IRBs may rely on the scientific review carried out by the grant funding agency, on the proviso that IRBs make their own determination as to the objectivity and adequacy of the review that had been carried out. IRBs should require a more extensive or rigorous scientific review, if deemed necessary.

7.10.2 **Recruitment of research subjects**

The IRB should be satisfied that the selection of subjects is equitable, and that the means of establishing initial contact, manner of recruitment, and information to be conveyed to potential subjects (or their representatives), are acceptable.

7.10.3 **Care and protection of research subjects**

The IRB should assess, amongst other factors:

a. the previous training, qualifications and professional experience of the principal investigator (PI) of the research project;

b. the plans to withdraw or withhold standard therapies for the purpose of the research project, and the justification for such action;

c. medical care to be provided to research subjects during and after the course of the research project;

d. the adequacy of medical supervision and psycho-social support for the research subjects;

e. the steps to be taken, if research subjects should choose to withdraw their participation in the research project before its completion;

f. the plans (if any) to make the investigational product available to the subjects, following the completion of the research project;

g. the financial costs to research subjects.

Researchers must inform the subjects' attending physician(s)\(^1\) about the subject's participation in research that involves any level of clinical interaction with the treatment or management of patients for medical conditions relevant to the proposed research, if the physician(s) can be identified and if the subject agrees to the physician(s) being informed\(^2\). Clear arrangements should also be made with the attending physician for the researcher to ensure proper transfer of the responsibility of medical care of the subject in the clinical area under research to the researcher.

---

\(^1\) The physician should be informed and given the opportunity to communicate his opinion and recommendation to the patient, prior to the commencement of the research.

\(^2\) Researchers are advised to be cautious and consider not enrolling subjects who do not consent to their attending physicians being informed.
Researchers must ensure that subjects are duly informed and clearly aware of any intended change in their treatment regimen. Researchers in such research studies which involve changes in clinical treatment regimen should be qualified physicians (or dentists, where appropriate) registered with the appropriate professional boards, and should be responsible for all research-related medical (or dental) decisions.

7.10.4 Protection of research subject privacy and confidentiality

Researchers should be required to put in place adequate measures to protect the privacy and confidentiality of data concerning the research subjects, in accordance with all existing laws on data privacy and confidentiality.

7.10.5 Informed consent process

a. Informed consent should be taken, not in advance, but at the time of enrolment of a subject into the research project. Subjects should be provided with adequate and clear information (including the purposes, methods, demands, risks and potential outcomes of research, and the likelihood and form of publication of research data and results), to make a free and informed decision whether or not to participate in the project. A person can refuse to participate in a research project, and not need to provide any reasons or justifications for the decision made. The decision to refuse participation, where it is made by a patient, should not affect the standard of care that the patient receives.

b. Sufficient time must be given to the prospective subjects for reflection. They must not be unduly pressured to give their consent for participation, and should be assured that the standard of care that they would receive would not be affected by their refusal to participate in the research. In cases where the attending physician is the researcher, it is desirable that the task of consent-taking be delegated to another person who has no direct link to the patient’s medical management. Where this is not possible, the IRB may allow the consent to be taken by the physician-researcher if it is satisfied with the safeguards documented in the protocol.

c. For research involving persons incompetent to give consent (e.g. emergency care research), consent must be obtained in accordance with prevailing law, e.g. from the Legally Acceptable Representative. Where such consent is not possible, the IRB should determine that the proposed research protocol adequately addresses relevant ethical concerns and meets applicable legislative and regulatory requirements. There should also be procedures in place to inform the subject and his family, at the earliest possible opportunity, of his inclusion in the study, and that they may discontinue participation at any time, without any compromise in the standard of care provided to the patient.

d. Consent for use of tissues in research should be free and informed. Donors should be entitled to choose between making a general gift which may be used for any research purpose, or a restricted gift which may be used only for research purposes specified by the donor. Where one of the primary purposes or objectives of the taking of the tissue is research, the consent form for the donation of the sample for research should be separate from the consent form for therapeutic or diagnostic purposes. These two types of informed consent should be obtained separately, by different persons, viz. the researcher to obtain
consent for research use, and the attending physician to obtain consent for therapeutic/diagnostic purposes.

e. In situations where consent or re-consent is impossible for use of legacy tissue, the IRB should require researchers to put in place measures to ensure the protection of privacy and confidentiality of donors.

7.10.6 Community/subject considerations
The IRB should consider in the review of a research project, its impact on, and relevance to, the local population, especially the communities from which the research subjects are to be drawn. Whether, and the manner in which, the results of the research project will be made available to the subjects, and the rest of the communities concerned, should also be reviewed.

7.10.7 Conflict of interest issues
In addition to the potential conflict of interest issues discussed above, the IRB should review study-related financial incentives, such as recruitment bonuses paid for reaching an accrual goal within a specified timeframe, and finder’s fees for referral of potential research subjects. The IRB should also review whether project-related payments reflect the actual market value of services or efforts involved. Non-project-related financial incentives, e.g. serving as a paid consultant or speaker on behalf of a sponsor, gifts in kind and non-monetary rewards to investigators, or their family members, should also be reviewed.

7.10.8 Reimbursement and compensation
IRBs should be satisfied that the amount and method for payment and reimbursement to research subjects would not present problems of undue inducement or influence on the research subjects. The IRB should ensure that the informed consent process/document does not contain any words that would absolve a researcher from responsibility in case of accidental injury, or that would imply that subjects waive their rights to seek compensation for injuries resulting from their participation in the research project. Research subjects should be informed of whether there are any provisions for compensation for injuries arising from their participation in the research, as well as whether there are any insurance and indemnity arrangements made for the research.

7.10.9 Adequacy of a data and safety monitoring plan
a. Interventional HBR projects involving more than minimal risk to the safety of subjects would require a data and safety monitoring plan (DSMP), reviewed and approved as part of the research protocol during ethics review by the IRB. IRBs should be satisfied with the adequacy of the DSMP proposed by the researcher, in relation to the level of risk of the research project, before they approve of the research project.

b. The DSMP is not intended to cover all possible details of each monitoring element, but should describe processes planned to deal with those elements, such that the IRB would be convinced that a robust plan is in place to protect the safety and well-being of research subjects, as well as the validity and integrity of the data.
c. The DSMP should minimally include:
   i. Assessment of level of risk of the research project;
   ii. Identification of an appropriate person or group of persons responsible for monitoring;
   iii. Procedures the monitor(s) will follow;
   iv. The information to be monitored;
   v. Requirements of adverse event reporting.

d. Safety monitoring may be performed by various individuals or groups:
   i. Where risks are moderate, IRBs may require the involvement of a medical monitor (an individual specifically assigned to review adverse events in real time), or an institutional committee set up by the institution with members external to the study team.
   ii. Where risks are high, IRBs may require a data and safety monitoring board (DSMB) to be constituted, where appropriate.

7.11 IRBs should provide a fair hearing to those involved. Where there exist any doubts or difficulties with particular aspects of protocols, IRBs should clarify them in writing with the researchers.

Meeting requirements

7.12 IRBs should have formal face-to-face meetings regularly. Tele-conferencing and video-conferencing would be allowed only in exceptional circumstances (e.g. quarantine). The criteria for allowing tele-conferencing and video-conferencing, and the standard procedures for doing so, should have been provided for in the standard operating procedures of the IRB. The dates of these meetings should be scheduled and announced in advance. Decisions should not be routinely made via circulation of documents. The meeting requirements should include the following:

a. Meetings should be planned in consideration of the workload;

b. IRB members should be given enough time in advance of the meeting to review the relevant documents. IRBs may also require the submission of a lay summary of the research protocol, where this may aid the lay members of the IRB in their review. This summary should set out the salient features of the research project. In certain cases, it may also be useful to have a lay summary of the scientific review;

c. Different models of ethics review may be established by the IRB. For example, the IRB could either require all members, or appoint one or more primary and secondary reviewers, to review the complete research project documentation. The appointed reviewers would then report to the IRB and lead the discussion. Members who only review summary information must also have access to complete research project documentation.

d. The researchers and/or sponsor may be invited to present the project or elaborate on specific issues. Independent consultants may be invited to the meeting to provide expert opinion, or to provide written comments, subject to applicable confidentiality agreements;

e. Decisions should only be made at meetings where a quorum is present. A quorum of at least five (5) members is required, and must, at minimum, include the following:
   i. The Chairperson (or the Deputy Chairperson);
   ii. One (1) lay member who is external to the institution;
   iii. One (1) medical practitioner who is external to the institution.
Only members who participate in the review may participate in the decision. No proxy votes (written or telephone) are allowed;

f. The relevant elements of review mentioned above (see 7.9) should be considered before a decision is made. The ethics review by an IRB should be based on fully detailed research protocols or, where applicable, the most up-to-date progress reports. The protocols and progress reports upon which ethics review are based should be drawn up specifically for the review;

g. There should be at least a two-third majority of the quorum before any research project requiring a full review may be approved. However, IRBs are encouraged to reach a decision by general agreement. Particular attention should be paid if there are any IRB members who suspect that the safety and well-being of research subjects may be compromised. Minority views are to be addressed and documented, where appropriate;

h. The decisions of the IRB should be provided in written form. Where appropriate, a fair and frank account of how these decisions are made should be provided;

i. Meetings should be minuted with an approval procedure for the minutes. The views of all present at the meeting should be clearly considered and recorded. The proceedings of IRB discussion should be kept confidential (except when required by appropriate authorities) because of the complexity and sensitivity of issues;

j. The IRB has the right to approve or reject proposed research projects. The IRB can also request modifications to the protocol, or withdraw approval, of an ongoing research project. In cases of conditional approvals, clear suggestions for protocol modifications, and the procedure for having the protocol re-reviewed should be specified.

**Conflict of interest**

7.13 IRBs and members of IRBs should take special care to avoid any conflict of interest, whether actual, potential or perceived. Conflicts of interest exist in the form of affiliation, participation, financial interests, or competition, in the research being considered, which may adversely affect the impartiality, objectivity and independence of the IRB members.

7.14 In the event that a member of the IRB has a conflict of interest in the research project under review, that member should recuse himself or herself from any consideration of that project by the IRB, and refrain from offering an opinion to the board on that project.

7.15 IRBs must remind members of these policies at the outset of each meeting and incorporate this reminder in the minutes of the meeting. The IRB minutes should also specifically reflect recusals as they occur during meetings.

**Processing time**

7.16 IRBs should provide researcher(s) with an initial outcome of its review of the proposed research project in a timely manner.
CONTINUING ETHICS REVIEW AND COMMUNICATION

Continuing review

8.1 IRBs should perform regular continuing review, such as the evaluation of progress updates of research projects, adverse event reports provided by researchers, to ensure the continued validity of ethics approval of projects approved by them. This evaluation should also include feedback/complaints received on the respective research protocol from the institutional entity appointed to receive such feedback. Continuing review should be performed at least once per year for each project, until the termination of the project. Final reports should be submitted within three months of completion of project. The frequency and type of monitoring determined by an IRB should reflect the degree of risk to the research subjects.

Progress updates of research projects

8.2 IRBs should require the Principal Investigator (PI) to submit written summaries of the progress of the research to the IRB annually, or more frequently, as requested. The PI should include in the report, any significant new developments that may affect the safety or wellbeing of the research subject, risk-benefits of the research, and the continued ethical acceptability of the project.

Summary reports of serious adverse events

8.3 All unexpected serious adverse events (SAEs) related to the research need to be reported immediately to the IRB. The immediate reports should be followed promptly by detailed written reports whereby the PI is required to interpret the event and describe any precautions taken to prevent recurrence. Expected SAEs, such as those that the protocol has identified as not requiring immediate reporting, should be submitted as regular summary reports as required by IRBs.

8.4 Researchers shall be required by IRBs to report all unexpected deaths arising from the research immediately to MOH, followed by detailed, written reports.

Changes to protocol

8.5 IRBs should require the PI to inform them and seek their written approval for any deviations from the terms of approval of the project before they can be implemented, except when they are necessary to mitigate immediate hazards to subjects, or when the changes involve only logistical or administrative aspects of the project, in which case, IRBs should be informed within seven (7) days.

Communication with researchers

8.6 IRBs should clearly communicate the monitoring and reporting requirements to PIs. IRBs should also maintain a dialogue, and provide feedback, on application standards with their constituent researchers.

SUSPENSION OR DISCONTINUATION OF RESEARCH

9.1 Where an IRB is satisfied that circumstances have arisen such that a research project is not being, or cannot be, conducted in accordance with the approved protocol and that, as a result, the safety and well-being of the study subjects are not, or will not, be protected, the IRB should withdraw its approval and inform the PI and the institution(s) of such withdrawal. Approval from the IRB should remain
withheld till such time when adequate, appropriate changes have been made to satisfy the IRB’s requirements.

9.2 Any withdrawal of approval should be accompanied by a statement, expressing the reasons for the IRB’s action, and relayed promptly to the PI, appropriate institutional officials and the relevant regulatory authority.

9.3 Researchers shall not continue the research project if ethics approval has been withdrawn, and shall comply with conditions imposed by the IRB required for re-approval of the project.

9.4 In the case of premature suspension/termination of a research project by a PI or sponsor, the PI should promptly inform the IRB of, and provide a detailed written explanation for, the suspension/termination. The IRB could require a summary of the results of the project that have been collected to be communicated to the IRB.

10 DOCUMENTATION AND RECORD KEEPING

10.1 All documentation, whether in paper or electronic form, should be kept in accordance with existing legislation and requirements, as well as institutional standards.

10.2 All documentation and communication of an IRB should be dated, filed, and archived according to standard written procedures for the IRB. The IRB should also maintain and update information on its list of IRB Chair and members.

10.3 All IRBs should maintain a record of all research protocols received, including title of project, identity of the PI, decisions made for each review, with dates and actions taken by the IRB for its continuing ethics review. An IRB should retain on file a copy of each research protocol and application for IRB review, including any information sheets, consent forms and relevant correspondence, in the form in which they were reviewed.

10.4 Clear operating procedures should be established, documented and made widely and easily available for important processes, which include, but are not limited to:

a. Application procedure and requirements, including other materials to be submitted by the applicant, conflicts of interest to be declared;

b. Frequency of meetings, requirements for quorum, preparation of agendas, distribution of papers prior to meetings, and minutes;

c. Timely consideration of research projects and notification of decisions;

d. Distribution of research protocols to members for the ethics review process;

e. Review procedure and methods of decision-making;

f. Monitoring activities, including reporting of adverse events;

g. Feedback loop and handling of complaints;

h. Advice to discontinue a research project;

i. Charges and payment, if any, for services for external reviews;

j. Confidentiality of content of protocols and of committee proceedings;

k. Any other procedures or requirements necessary for the initial submission of research projects for review, and subsequent reporting.
IRB decision-making

10.5 In the review of a research protocol, the views of the IRB should be documented in writing, clearly identifying the study, the documents reviewed, and the dates for the following:
   a. Approval;
   b. Modifications required prior to its approval;
   c. Non-approval;
   d. Withdrawal of any prior approval.

10.6 All communications in relation to the review of the research project, activities and other proceedings of the IRB, should be fully documented in writing, including:
   a. documents reviewed by members, including correspondence with other parties, and whether the opinion of another IRB was considered;
   b. whether approval was by expedited review;
   c. minority views that were discussed;
   d. outcome of discussion;
   e. terms and conditions, if any, of approval of any project;
   f. a record of all concerns and feedback received regarding the conduct of approved research projects;
   g. action(s) taken by the IRB to monitor the conduct of the research.

Data confidentiality

10.7 The procedure for accessing and retrieving documents of the IRB must be clearly documented to safeguard against unauthorised access to the documents of the IRB.

Archiving

10.8 IRB should also keep a list of essential documents for an appropriate number of years in accordance with existing standards of the institution and regulatory requirements, following the discontinuation or completion of a study. These include:
   a. The constitution of the IRB;
   b. The curriculum vitae of all IRB members;
   c. A record of income and expenses of the IRB, including allowances and reimbursements made to the secretariat and IRB members;
   d. Published guidelines for the submission of applications, as established by the IRB;
   e. Agendas and minutes of meetings of the IRB.

10.9 The duration of archiving shall be in accordance with applicable regulatory requirements. It should be clearly established in the standard operating procedures of the IRB, with modifications made for each protocol in consideration of inputs from the researcher, if deemed necessary, and be proportionate to the risk, and likelihood of appearance, of adverse events which may take a longer time to surface.

11 MONITORING AND IMPROVEMENT PROGRAMME

11.1 A monitoring and improvement programme should be put in place by each institution for its IRB(s) to systematically review and evaluate the working processes involved in the ethics review of research projects. This will improve the overall standards of ethics review and human subject protection.
11.2 The functions of the monitoring and improvement programme may be performed by one or more bodies appointed by the institution, e.g. in-house, or external. Where the IRB is so appointed, it will take on the programme, which could focus on the following components:

11.2.1 Monitoring of feedback from research subjects
The IRB could act as the key institutional agency that receives, acts upon, and reports to the relevant authorities on concerns and feedback expressed by the research subjects. The IRB and its appointing institution should formalise and make known arrangements that allow research subjects a one-stop direct access to the IRB, or an appropriate senior officer of the institution. In this way, research subjects can have access to independent officers in order to give feedback on the research or to express their concerns. Feedback may be submitted verbally, or in writing, and be anonymous. IRBs and their institutions should have systems in place to provide protection against the disclosure of the identity of the person providing the feedback.

11.2.2 Investigation of complaints about approved research projects
The IRB may investigate complaints relating to research projects that it has approved. The findings of, and recommendations following, each investigation should be submitted to the institution. A complaint which cannot be resolved at the level of the IRB should be escalated to the appointing institution. Where necessary, approval of the research project in question should be withheld, pending the outcome of investigations.

11.2.3 Compliance monitoring
The IRB should put in place a robust system for monitoring the conduct of research projects for compliance with the IRB-approved protocols, institutional standards or regulatory requirements. Monitoring may be effected through site visits to selected clinical investigator sites, review of documentation, and/or interviews with relevant personnel. Aspects which may be monitored include:
- Consent document, including the informed consent process;
- Subject enrolment, including recruitment criteria of subject;
- Data integrity;
- Documentation;
- Safety reporting.

11.2.4 Others
An example is comparative benchmarking of standard operating procedures with existing national standards and Good Clinical Practice (GCP) Guidelines.

11.3 There should be at least one monitoring and improvement programme coordinator who has oversight of the various functions performed under the programme of each institution.

11.4 The operational procedures related to the functions of the monitoring and improvement programme, and the roles and responsibilities of its coordinator(s), should be clearly stipulated by the appointing institution.
12 SPECIFIC SITUATIONS

Multi-centre research

12.1 Any research that involves more than one institution, whether by the same or different researchers, should be considered multi-centre research.

12.2 In such research, a “lead” IRB could be designated from among the IRBs of participating institutions. The lead IRB will conduct a full ethics review, coordinate the research project, and keep other participating IRBs informed of any decisions and amendments made during the whole research period.

12.3 The choice of the lead IRB should be dictated by considerations such as the principal institution of affiliation of the PI, the location where the greater part of the research is carried out, the expertise of the constituted IRB, or the institution expected to have the largest number of subjects.

12.4 The primary ethics assessment could be made by the lead IRB, which should also be responsible for ensuring that a proper scientific review has been carried out. Written documentation of its decision should be sent to the IRBs of the other institutions or organisations involved, which may then choose to conduct expedited review, while reserving their rights to give further consideration to ethical and administrative aspects of the research that are specific to their own institutions or organisations.

12.5 In the submission of the research protocols, researchers should identify to their respective IRBs, the designated lead IRB responsible for the primary ethics review. Researchers are also expected to disclose to the lead IRB, any decisions made by their IRBs regarding the research. IRBs should:
   a. Coordinate their review of multi-centre research projects, and communicate any concerns that they may have, with other IRBs reviewing the project; and
   b. Determine how the conduct of multi-centre research should be supervised and define the respective roles of each institution/organisation and its respective IRB.

Multi-national research

12.6 The local portion(s) of a multi-national research project should be subject to review by the local IRB(s). Similarly, a “lead” local IRB may be designated where more than one local IRB is involved.

12.7 Local research collaborators should, as far as possible, provide their local IRBs with full documentation of ethics review applications made to the lead IRB, together with copies of all relevant queries and rulings of the lead IRB. If applications have been, or are proposed to be, submitted to other IRBs in other jurisdictions, information on these applications and their outcome should be provided to the local IRB as well.

12.8 The local IRB may then elect to grant expedited review of the project after reviewing the documentation, and the reasons for the decision of the lead IRB. In general, local IRBs should consider a full ethics review if a substantial portion of the research project is to be carried out in Singapore. Similarly, if a major part of
the research project is to be carried out in another country, the local IRBs should ask for evidence of ethics approval by the IRBs involved in that country.

12.9 The mutual recognition procedures outlined in this section do not absolve an IRB from responsibility even if the ethics review has been performed, and approval given, by another IRB.
The definitions provided within this glossary apply to terms as they are used in these Guidelines. The terms may have different meanings in other contexts.

**data and safety monitoring board (DSMB)**
A DSMB is an independent group of individuals with pertinent expertise that reviews, on a regular basis, accumulating data from an ongoing research project. The DSMB advises the sponsor, institution, or other appointing entity, regarding the continuing safety of current subjects and those yet to be recruited, and the validity of continuing the project.

**data and safety monitoring plan (DSMP)**
The DSMP is a general description of the overall framework for the study's data and safety monitoring to ensure the safety of research subjects, and the validity and integrity of the data, in interventional human biomedical research projects. Where applicable, the DSMP must be reviewed and approved by the IRB prior to the initiation of the project.

**external (members / representation)**
This refers to individuals who are not members of, or otherwise associated with, the appointing institution of the IRB.

**external review**
Reviews performed by an IRB of research projects not within the purview of the appointing institution of the IRB.

**institutional committee**
A committee set up by the institution with members independent of the study team to provide a relatively more independent review of safety data.

**institutional review board (IRB)**
An independent body (review board or committee, whether institutional, regional, or national) constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a research project, and to provide public assurance of that protection by, among other means, reviewing and approving/providing favourable opinion on the research or trial protocol, the suitability of the investigator(s), facilities, and the methods and materials to be used in obtaining and documenting informed consent of the trial subjects.

**interventional**
That which involves the administration of any drug, device, entity or any treatment which involves a concomitant risk of physical or mental injury or harm, however remote or minor.

**lay members / representation**
Lay members refer to those with primary concerns in the non-scientific area. The intent of including these members who had little or no scientific or medical training or experience is to provide a lay or community perspective. Therefore, nurses, pharmacists and other biomedical health professionals would not be regarded to have "primary concerns in the non-scientific area."
**medical monitor**
An individual specifically assigned to review adverse events in real time for research studies and with no other assigned responsibilities.

**principal investigator (PI)**
The leader of a research team who undertakes ultimate scientific and ethical responsibility of the research and team members. There may only be one PI for each project, including multi-centre research.

**protocol**
A document that describes the objective(s), design, methodology, statistical considerations, and organisation of a research study. The protocol usually also gives the background and rationale for the study, but these could be provided in other protocol referenced documents.

**serious adverse event (SAE)**
Any untoward medical occurrence due to participation in the research project that:
- results in death;
- is life-threatening;
- requires inpatient hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability / incapacity; or
- is a congenital anomaly / birth defect

**sponsor**
An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a research study.
REFERENCES


Singapore Guideline for Good Clinical Practice.


National Health and Medical Research Council. *National Statement on Ethical Conduct in Research Involving Humans*. 1999