CHAPTER 1

RESEARCH GOVERNANCE

1.1 Office of Human Research Protection Programme (OHRPP)

The formation of the OHRPP signifies NHG's commitment to protecting research through a comprehensive setup of programmes, framework, and functions. With in-house support and expertise, the OHRPP is better positioned to drive improvement and innovation that can directly benefit the research community.

While continuing to forge close partnerships with institutions and agencies within and outside NHG, the OHRPP promotes community outreach and education for the public. The OHRPP will also take the lead in advocating best practices in human research protection through merging knowledge and experience learnt from our counterparts in the west and implementing them in Asia's context.

The goals of the OHRPP are to ensure the safety and well-being of human research subjects, and to advocate their rights through:

a. Efficient and high-quality ethics review
b. Education on human research protection
c. Quality assurance and continuous improvement
d. Engagement of public and research partners

In its entirety, the OHRPP comprises 5 divisions:	
DSRB Operations & Management	All research involving NHG patients, NHG staff, NHG premises, or NHG facilities are to be reviewed and approved by the NHG DSRB prior to initiation. The DSRB's primary role is to safeguard the rights, safety, and well-being of human research participants in NHG and her institutions, as well as ensure high quality and efficient review of research applications.
Research Quality Management (RQM)	RQM provides quality assurance activities to ensure that research protocols approved by the DSRB are carried out ethically and in accordance with all applicable regulations.
Research Education (RE)	RE develops training programmes and resources, as well as conducts educational support initiatives for investigators and researchers.
Partnerships & Outreach (P&O)	P&O oversees the extension of ethics review services and oversight to external healthcare set-up and agencies, providing a common platform of ethics review and establishing common standards of research conduct in different institutions.
Research Compliance Unit (RCU)	The RCU provides administrative support to the NHG Principal Person In Charge (PIC), Research Committee (RC), Tissue Compliance Committee (TCC), Research Data Oversight Committee (RDOC) and also oversees the propagation of a Responsible Conduct of Research (RCR) culture and promotes RCR awareness within the research community. RCU also supports other committees on RI related matters and supports functions of the NHG RI to ensure research in NHG is in compliance with the HBRA.

1.2 Role and Structure of the Domain Specific Review Boards (DSRB)

The DSRB is an independent committee constituted by medical, scientific members and laypersons, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a research study by reviewing, approving, and providing continuing review of research studies and amendments, and of the methods and materials to be used in obtaining and documenting informed consent of the research subjects.

The NHG Group Chief Executive Officer appoints members to the DSRB, for NHG RI. Each domain will consist of at least 5 members, who collectively have the qualifications and experience to carry out the DSRB's stated objectives and terms of reference to review and evaluate the ethical and scientific aspects of the proposed research studies.

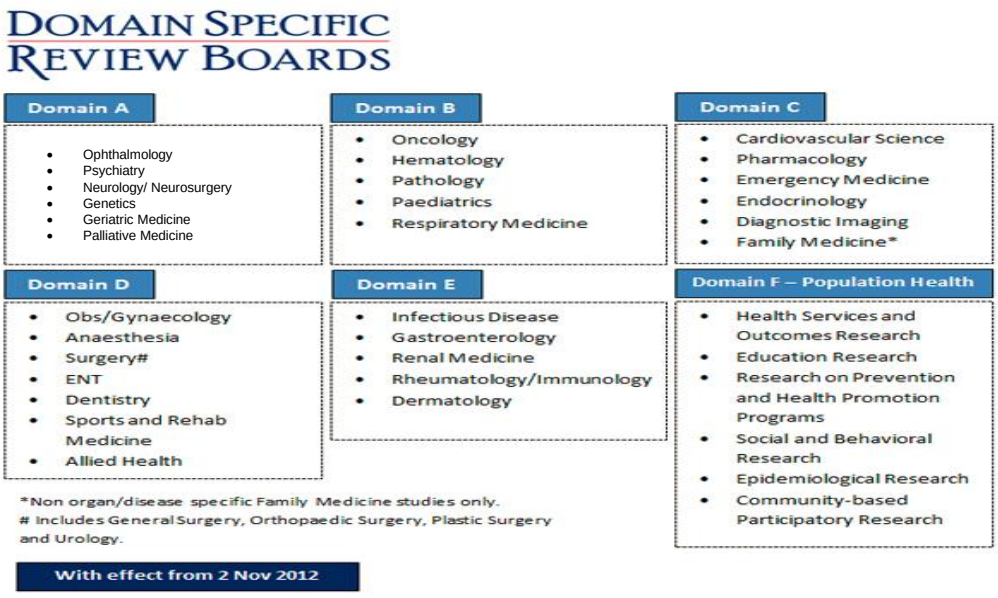
Other officials of institutions which conduct research under the oversight of NHG DSRB, may not override the decision of DSRB (or REC, where applicable). The REC is a committee comprising the DSRB chairpersons and laypersons, which collectively establishes and oversees the policies and implementation of the HRPP in NHG.

There are currently 5 biomedical domains (A – E) on broad but related disease groupings, and a Population Health Domain (F). Each board is made up of 11-15 members and is constituted in compliance with the HBRA and GCP guidelines.

The purpose of such an arrangement is to ensure that more appropriate expertise can be concentrated within each domain to assess the scientific and ethical merits of each study submitted for ethics review.

The specialties under each domain of DSRB are shown in figure 1 below.

Figure 1: Specialties under each DSRB domain



Genetics studies should be submitted to the DSRB domains according to the relevant disease groupings or medical specialty that is intended to be studied. Non disease specific genetics studies shall continue to be submitted to DSRB A for review.

1.3 Role of Institutions, Department and Institution Representatives, Investigators and Other Study Team Members

1.3.1 Institutions

The DSRB, as well as the institutions, must approve a research proposal before it can be conducted in institutions under the oversight of NHG DSRB. The protection of human subjects in research is a collaborative effort by the Research Institution (RI), DSRB and all institutions under the oversight of NHG DSRB. While the DSRB is an independent review committee responsible for ensuring that the research proposal protects the well-being, safety and rights of the research subjects, each institution ensures that the proposal is in keeping with the relevant regulatory requirements, its overall research direction, objectives, standards, and image.

1.3.2 Department Representative (DR)

The DR plays a key role in ensuring that a research study is in keeping with the research objectives, image and standards of the relevant departments and institutions. The role of a DR is to provide an overview assessment of the significance, concept, and innovation of a research study.

The DR should also determine whether the PI is adequately trained, qualified, possesses sufficient time and resources to carry out the research study.

The DR will endorse all applications made to the DSRB. In general, the DR will be the Head of Department, Chief, Department Research Head or equivalent of the PI's and site PI's department.

In some departments, alternative persons may be appointed as DRs, provided he / she is able to adequately perform the responsibilities of a DR. Where appropriate, the Head / Chief of a Division (e.g., Division of Medicine) who oversees several departments may comment in lieu of one of his / her Head / Chief of department. Should the Head or Chief be the PI or be part of the study team, then their reporting officer should be the DR.

1.3.3 Institution Representative (IR)

The IR has been determined by each institution as the authority to approve any research study to be conducted in the institution. The role of the IR is to assess if the research is in keeping with the institution's research objectives, image, and standards.

In general, the IR's role is not to evaluate the scientific or ethical merits of the research study (although they may offer their comments), as all these will be considered by the DR, DSRB or a grant approving body (if applicable).

The IR must endorse the application before it may be reviewed by the DSRB. This authority is generally delegated to one of the following persons:

a. Director of Research (or equivalent); or

b. Chairperson of a specially appointed committee for this purpose; or

c. Chairman Medical Board.

For multi-centre studies, the IR of each of the site PIs must endorse the application to be conducted at his / her institution. The DSRB will proceed to review the application as long as the IR of the overall PI has endorsed the application. A study may not be initiated at a study site if the site PI did not obtain his / her IR's endorsement.

1.3.4 Investigators and Other Study Team Members

The PI is the overall person responsible for the proper conduct of research. In general, there is only one person who is appointed as the PI for each research study.

The PI is allowed to delegate study-related tasks to qualified/ trained members of the research study team (e.g., co-investigators or collaborators). When the tasks have been delegated, the PI must ensure that the delegation log is updated with each team member's assigned responsibilities prior to the start of the research. The PI and all study team members have the responsibility to comply with DSRB policies and applicable regulatory requirements.

For multi-centre studies within NHG and all institutions under the oversight of NHG DSRB, each institution should have a site PI who is responsible for the conduct of the study in his / her institution. One of the site PIs should be designated as the overall PI for the study, who is responsible for the coordination of investigators at different institutions participating in the multi-centre study, including but not limited to communication with the DSRB.

Please refer to chapter 3 The Study Team for more information on the requirements for PI.

1.4 Research Regulations and Guidelines

All research involving patients, staff, premises, or facilities of all institutions under the oversight of NHG DSRB must be reviewed and approved by NHG DSRB prior to initiation.

All research reviewed and approved by the DSRB for conduct in institutions under the oversight of the DSRB must comply with DSRB's requirements as outlined in this manual. These requirements are compiled based on local and international regulations, some of which are listed below:

a. Health Products Act and its subsidiary legislation – applicable for clinical trials of therapeutic products and Cell, Tissue and Gene Therapy Products which include chemical drugs, biologics, Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs);

b. Medicines Act and its subsidiary legislation – applicable for clinical trials of medicinal products include complementary health products (e.g., Chinese proprietary medicines);

c. Human Biomedical Research Act (2015) and its subsidiary legislations – applicable for human biomedical research studies and donation of human tissues;

d. Personal Data Protection Act and its subsidiary legislation – to regulate the collection, use and disclosure of personal data;

e. ICH GCP E6(R2) – all clinical trials are required to abide by GCP guidelines;

f. US DHHS Regulations 45 CFR 46 – applicable for research funded by US federal funds e.g., National Institutes of Health (NIH), National Cancer Institute (NCI), National Institute of Allergy and Infectious Diseases (NIAIDS), etc.;

g. US FDA Regulations 21 CFR 50 / 56 / 812 – when the research is being conducted under an Investigational New Drug (IND) Application or Investigational Device Exemption (IDE), or when the results of research are intended to be submitted to FDA;

h. Bioethics Advisory Committee report on Ethics Guidelines for Human Biomedical Research (published October 2021);

All organisational officials, researchers and research staff (including students involved in conducting research), DSRB chairpersons and members and employees of NHG's OHRPP, are required to abide by the abovementioned regulations and guidelines.

1.4.1 Definition of Research and Other Important Definitions

I. The Health Products Act

CLINICAL TRIAL - An investigation in respect of a health product that involves human subjects and that is intended to:

a. Discover or verify its clinical, pharmacological or pharmacodynamics effects;

b. Identify any adverse effect that may arise from its use;

c. Study its absorption, distribution, metabolism and excretion; or

d. Ascertain its safety or efficacy;

"Efficacy", in relation to a health product that is a device, includes the ability of the device to properly carry out its intended purposes.

II. Medicines Act

CLINICAL TRIAL - An investigation or series of investigations consisting of the administration of one or more medicinal products of a particular description by, or under the direction of:

A) A doctor or dentist to one or more of his patients; or

B) Two or more doctors or dentists, each product being administered by or under the direction of one or other of those doctors or dentists to one or more patients, where (in any such case) there is evidence that medicinal products of that description have effects which may be beneficial to the patient or patients in question and the administration of the product or products is for the purpose of ascertaining whether, or to what extent the product has, or the products have, those of any other effects, whether beneficial or harmful.

I**II. ICH GCP**

CLINICAL TRIAL – Any investigation in human subjects intended to discover or verify the clinical, pharmacological and / or other pharmacodynamics effects of an investigational product(s), and / or to identify any adverse reactions to an investigational product(s), and / or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and / or efficacy.

SUBJECT / TRIAL SUBJECT – An individual who participates in a clinical trial, either as a recipient of the investigational product(s), or as a control.

IV. Human Biomedical Research Act

HUMAN BIOMEDICAL RESEARCH -

Research that is intended to study:

a. The prevention, prognostication, diagnosis or alleviation of any disease, disorder or injury affecting the human body; or

b. The restoration, maintenance or promotion of the aesthetic appearance of human individuals through clinical procedures or techniques; or

c. The performance or endurance of human individuals,

And where the research involves –

i. Subjecting an individual to any intervention (including any willful act or omission) that has a physical, mental or physiological effect (whether temporary or permanent) on the body of the individual; or

ii. The use of any individually-identifiable biological material obtained from the human body; or

iii. The use of any individually-identifiable health information.

Research that involves:

a. Human embryos or human gametes; or

b. Cytoplasmic hybrid embryos; or

c. The introduction of any human-animal combination embryo into an animal or a human; or

d. The introduction of human stem cells (including induced pluripotent stem cells) or human neural cells into an animal at any stage of development (including a pre-natal animal foetus or animal embryo); or

e. Any entity created as a result of any process referred to in paragraph (c) or (d).

RESEARCH INSTITUTION - A body of persons, whether corporate or unincorporate or other organisation, or ministry or department of the Government who or which —

a. Engages, directly or indirectly (either through contractual or other arrangements), one or more researchers to conduct human biomedical research in Singapore; and

b. Exercises supervision and control over human biomedical research conducted in Singapore by the researchers the institution has engaged.

INTERVENTION includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

INTERACTION includes communication or interpersonal contact between investigator and subject.

PRIVATE INFORMATION includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

V. US DHHS Regulations

RESEARCH - is a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.

HUMAN SUBJECT or participant is a living individual about whom an investigator conducting research:

i. Obtains data information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens
ii. Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens.

INTERVENTION - includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

INTERACTION - includes communication or interpersonal contact between investigator and subject.

PRIVATE INFORMATION - includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record).

Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

Engaged – an institution becomes "engaged in a particular non-exempt human subjects research when its employees or agents for the purposes of the research project obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research.

Employee or Agent - An institution's employees or agents refer to individuals who: (1) act on behalf of the institution; (2) exercise institutional authority or responsibility; or (3) perform institutionally designated activities. "Employees and agents" can include staff, students, contractors, and volunteers, among others, regardless of whether the individual is receiving compensation.

VI. US FDA Regulations

CLINICAL INVESTIGATION is any experiment that involves a test article and one or more human participants and that is one of the following:

a. Subject to requirements for prior submission to FDA; or
b. Not subject to requirements for prior submission to FDA, but the results of which are intended to be submitted later to or held for inspection by FDA as part of an application for a research or marketing permit.

HUMAN SUBJECT means an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. For studies involving investigational devices (i.e., requiring an IDE), human subject is defined as a human who participates in an

investigation either as individual or on whom or on whose specimen an investigational device is used or as a control. A subject may be either a healthy individual or a patient.

TEST ARTICLE means any drug for human use, biological product for human use, medical device for human use, human food additive, colour additive, electronic product, or any other article subject to FDA regulation.

VII. BAC Report on Ethics Guidelines for Human Biomedical Research (Published October 2021)

HUMAN BIOMEDICAL RESEARCH refers to any research done for the ultimate purpose of studying, diagnosing, treating or preventing, any disease, injury, disorder, or condition of the human mind or body, and which entails the involvement of humans, human biological materials or information derived from humans or human biological materials. Also included is research on human physiological processes.

PERSONAL INFORMATION is any identifiable information about an individual, living or dead. It not only includes personal particulars, but also details of medical conditions, as well as information disclosed or derived in the process of healthcare management. In the research context, it will include any information collected, used or generated as part of the research process.

HUMAN GENETIC RESEARCH is the study of genes, their functions, how they are associated with health and disease, and how genetic and environmental factors influence health. This research may involve subjects directly and specifically, or it may involve stored tissue samples or personal information from medical records or other databases. It may involve the study of a specific gene, multiple genes, gene-environment interactions, or the entire genome in seeking to establish associations between genomic variants and diseases or specific traits.

1.4.2 Principles of Ethical Research

Ethical research is research that:

a. Upholds the core ethical principles of respect for persons, beneficence and justice.

b. Protects rights, safety and well-being of human subjects.

c. Complies with all applicable regulations and guidelines.

DSRB's research policies are based on local and international ethical guidelines, some of which are listed below:

a. Belmont Report;

b. Declaration of Helsinki;

c. Human Biomedical Research Act 2015

d. The Nuremberg Code

I. The Belmont Report

The Belmont Report describes three core ethical principles for human research:

a. Respect for persons – recognition of the personal dignity and autonomy of individuals and special protection of these persons with diminished autonomy, e.g., the need to obtain informed consent.

b. Beneficence – entails an obligation to protect persons from harm by maximizing anticipated benefits and minimising possible risks of harm, e.g., the need to engage in a risk / benefit analysis and to minimise risks. Justice – requires that the benefits and burdens of research be distributed fairly, e.g., the need to have a reasonable inclusion and exclusion criteria.

1.5 Does My Study Require DSRB Approval?

1.5.1 Examples of Research Activities that Require DSRB Approval

Activities that involve systematic investigation and are designed to develop or contribute to generalisable knowledge are considered research and will require review and approval by NHG DSRB. This includes clinical trials, epidemiological research, retrospective medical records review research, and genetic research.

CASE SERIES – A series of 3 or more subjects qualifies as a research project and hence should be submitted for review and approval by the DSRB prior to initiation.

DATABASE STUDIES – Databases that are created with the intention of using the stored data for future research should be registered as a Standing Database (SDB). Databases which are created as part of a previous IRB approved research study that has since been completed, may be set up to store data for possible research. Such databases should be registered as a SDB upon completion of the research study.

Individual research projects extracting data from SDBs will require DSRB review and approval.

Please refer to chapter 8 Standing Database for more information on standing database.

HUMAN TISSUE BANK / REPOSITORIES – Operation of human tissue repositories and related data are subjected to oversight of the respective Research Institution (as defined in the HBRA).

Tissue Bank (TB) review boards will review and approve protocols specifying the conditions under which tissues and related data may be accepted and shared and ensuring adequate provisions to protect the privacy of donors and maintain the confidentiality of data. DSRB supports the review of TB related submissions to ensure that the recruitment and consent process of donors complies with ethics requirements and HBRA.

QUALITY ASSESSMENT / QUALITY IMPROVEMENT (QA / QI) – The following checklist in table 1 may be used to determine if a QA / QI study requires DSRB review. Where the response to all questions in the QA / QI checklist is “No”, and where there is no intention to share the information with others (i.e., contributing to generalizable knowledge) at the onset of the study, the QA / QI study will not be subject to DSRB review.

Table 1: Checklist to determine if a QA / QI study requires DSRB review.

Where the response to all these questions is "No", the QA/QI study is unlikely to require an IRB review. If you require a formal IRB letter of waiver from review, fill in and submit the DSRB exempt application form for review. Where the response to any of these questions is "Yes", the QA / QI study may need an IRB review. Complete the appropriate application form on ECOS and submit for DSRB review.			
S/N	**Questions**	**Yes**	**No**
1.	Does the proposed quality assurance activity require additional consent from subjects, beyond what is already obtained for clinical practice?		
2.	Does the proposed quality assurance activity pose any risks for subjects beyond those of their routine care?		
3.	Does the proposed quality assurance activity impose a burden on subjects beyond that experienced in their routine care?		
4.	Is the proposed quality assurance activity to be conducted by a person who does not normally have access to the subjects' records for clinical care?		
5.	Does the proposed quality assurance activity risk breaching the confidentiality of any individuals' personal information, beyond that experienced in the provision of routine care?		
6.	Does the proposed quality assurance activity involve any clinically significant departure from the routine clinical care provided to the subjects?		
7.	Does the proposed quality assurance activity involve randomization?		
8.	Does the proposed quality assurance activity involve the use of a control group or a placebo?		
9.	Does the proposed quality assurance activity seek to gather information about the participant beyond that collected in routine clinical care?		
10.	Does the proposed quality assurance activity potentially infringe the rights, privacy or professional reputation of health care providers or the institution(s)?		

1.5.2 Examples of Research-Like Activities that May Not Require DSRB Approval

Case Reports – Do not involve systematic investigation; however, the intent is to contribute to generalisable knowledge. Case reports on one or two subjects are not considered as human subject research. (Studies involving three or more subjects are considered case series and will require DSRB approval. Please refer to the description of case series in the above section.)

Outbreak Investigations – Outbreak investigations are important activities that benefit public health. Subjecting these to research standards might compromise these activities. As such, outbreak investigations are not considered to be research and do not require DSRB review. However, any interventional studies conducted during an outbreak would require review and

approval by the DSRB and / or other clinical Committees. The DSRB will make an effort to expedite the review and approval process for such protocols.

Disease Management – Disease management projects that do not require the subjects to undergo additional burdens or risks do not require review and approval by the DSRB.

Infection Control – Investigations carried out as part of an infection control program are not considered as research and these do not require review by the DSRB.

Quality Assessment (QA) / Quality Improvement (QI) – Please refer to the description of QA / QI studies in section 1.5.1 above. Where the response to all questions in the QA / QI checklist is “No”, the QA / QI study will not be subject to DSRB review.

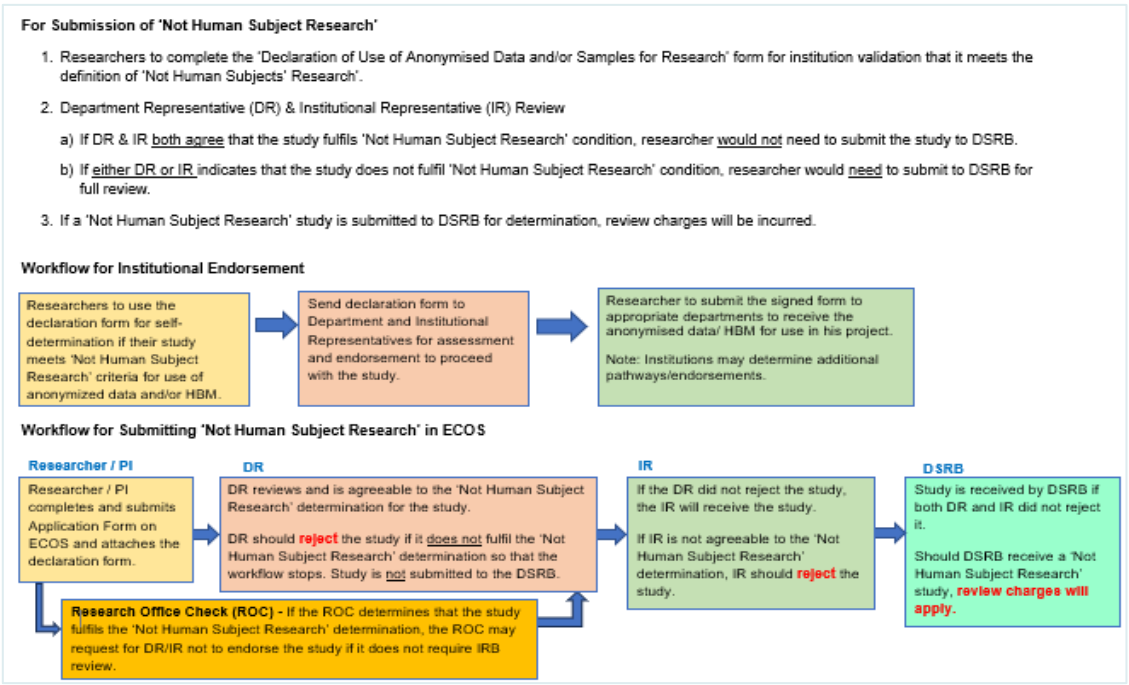
Studies Involving Anonymised Data and/or Human Biological Materials (Not Human Subject Research) – Studies involving **anonymised data / human biological materials (HBM)** will not require review by DSRB as these studies do not meet the definition of human subject research (for the definition of human subject, refer to 1.4.1), if there is no use of identifiable private information or identifiable biospecimens, and no interactions or interventions with human participants in the study.

If submitted to DSRB, the study will receive a ‘Not Human Subject Research’ outcome.

Researchers may use the ‘Declaration of Use of Anonymised Data and/or Samples for Research’ form to evaluate whether their research involving anonymised data / HBM qualifies as ‘Not Human Subject Research’ and subsequently seek endorsement from their DR and IR to proceed with their research. Researchers should retain the endorsed form as proof of institutional review.

Institutions may request researchers to submit their research applications on ECOS when there is ambiguity whether the study meets the ‘Not Human Subject Research’ criteria. The approach for submission of ‘Not Human Subject Research’ is as shown in figure 2 below.

Figure 2: Submission for ‘Not Human Subject Research’.



1.5.3 Determination of Research Status

There are many research-like activities that are conducted as part of quality assessment and improvement, infection control, disease management etc., that may not meet the definition of research and hence do not need DSRB review and approval. Further, new innovative therapies used by many doctors during their clinical management of patients may not necessarily meet the definition of research as well. Given the vague boundary between research and non-research, the PI must ascertain which regulations are applicable and then apply the definitions for research as described above.

When in doubt whether an activity requires DSRB review and approval, the PI may contact the DSRB secretariat and provide a summary of the proposal for a preliminary assessment. Alternatively, the PI may submit an application for the DSRB to review. The DSRB will issue a notification to the PI if the DSRB determines that the proposal does not meet the definition of research.