CHAPTER 5

INFORMED CONSENT

© NHG Health

5.1 Important Considerations for the Informed Consent Process

Informed Consent Process

The DSRB requires that informed consent must be obtained from all human subjects prior to their participation in any research unless the process, or any part thereof, has been waived by the DSRB.

Informed consent is the process by which a subject or their legal representative voluntarily confirms their willingness to participate in a particular research, after having been informed and been provided with the opportunity to discuss all aspects of the research that are relevant to the subject's decision to participate. Informed consent is to be documented by means of a written, signed, a (paper or electronic) and dated ICF. Obtaining consent remotely may be considered when appropriate.

The informed consent process is necessary to ensure that subjects are fully informed before deciding whether to volunteer in research studies of any type. The person obtaining consent should verify the identity of the subject (or legally acceptable representative) and ensure no coercion or undue influence during the consent process.

The PI should ascertain to the best of his or her ability that any persons making a decision on behalf of the subject, acts in the best interest of the subject and has regard, to the subject's past and present wishes and feelings and any factors which the subject would consider if he or she were able to do so.

The most current version of the ICF approved by the IRB and regulatory authority (if applicable) should be used as a guide while describing to the subjects all the necessary information that they need to make an informed decision about participating in the study.

Conducting the Informed Consent Process

The following considerations should be kept in mind while conducting an informed consent discussion. Any exceptions must be specifically addressed and receive prior IRB approval. The PI must reinforce these considerations to all research team members who will be involved in the informed consent process.

a. Subjects must be given adequate time to consider and ask questions before making a decision whether or not to participate. This might mean letting the subject bring home the consent form and return the next day or after a few days if the subject wishes to participate.

b. Subjects should be encouraged to discuss participation in research with their family members.

c. Subjects should be approached in an environment conducive for consent discussion. For example, it would not be appropriate to approach a subject immediately before a procedure or surgery, while in labour, while under sedation and in any other situation where a subject might feel compromised.

d. Neither the investigator nor the investigator site staff should coerce or unduly influence a subject or LR to participate or to continue their participation in the research.

© NHG Health

e. Informed consent should be conducted by the PI, or a qualified member of the study staff who is listed in the IRB Application Form as the designated person(s) or study role(s) for conducting the informed consent discussion. Any change to the designated person or study role for obtaining consent should be submitted to the IRB for review and approval. The PI must ensure that the person is delegated on the study delegation log and appropriately trained to explain the benefits and risks of the study adequately and conduct the consent process appropriately without compromising on the quality of the consent.

f. For clinical trials that are regulated by HSA, only the PI or an investigator authorized by the PI, who is a qualified practitioner is allowed to obtain informed consent from the subjects. Where the clinical trial is led by a pharmacist PI, co-investigators who are qualified pharmacist may also be authorized by the PI to obtain consent. Individuals who are not qualified practitioners or qualified pharmacists are not allowed to obtain consent but may assist in the consent process for such studies.

g. Informed consent discussion should take place in person. Where it is not practicable for the researcher to obtain consent through a physical face-to-face interaction with the research subject, the researcher may consider obtaining consent remotely, including telephone calls, email correspondence and e-Consent.

h. Varied approaches (e.g., text, images, videos and other interactive methods) may be used in the informed consent process including for providing information to the subject. The characteristics of the potential research population (e.g., subjects may lack familiarity with computerized systems) and the suitability of the method of obtaining consent should be taken into consideration when developing the informed consent materials and process. When computerized systems are used to obtained informed consent, research subjects may be given the option to use a paper-based approach as an alternative.

i. Whether the informed consent process takes place in person or remotely, the investigator should assure themselves of the identity of the subject or LR in accordance with applicable regulatory requirements.

j. Informed consent should be obtained before initiation of the study i.e. before any procedures that are being performed solely for the research.

k. If the subject is unable to give informed consent, the informed consent discussion should be conducted with the subject's legal representative.

l. The informed consent discussion must be conducted in a language understandable by the subject.

m. Should a witness be required during the consent process, the study team member who conducted the informed consent discussion must inform the witness of their responsibilities of taking reasonable steps to ascertain:

    i. The identity of the individual giving the appropriate consent;
    ii. That the consent was given voluntarily without any coercion or intimidation.

© NHG Health

n. The informed consent process is not a one-time event carried out prior to enrolling research subjects but must be a continuous ongoing process. Investigators must inform subjects or the LR in a timely manner of any new information that may affect their willingness to continue participation in the study. The communication of this information and confirmation of the willingness to continue participation should be documented. The DSRB must approve the methods of notification prior to implementation. The method could included (but are not limited to):

    i. Information Letter,
    ii. Addendum to previously signed consent form to be signed by subject, or
    iii. Revised consent form to be signed by subject.

o. New information that could impact a subject's willingness to continue participation should be accessed to determined if re-consent is needed (e.g., depending on the stage of the study, consideration should be given to whether the new information is relevant only to new subjects or to existing subjects). If re-consent is needed (e.g., information on emerging safety concerns), new information should be clearly identified in the revised informed consent materials.

p. Fresh consent from the subject would be required if existing personal data collected is to be used for a different purpose after July 2014. The DSRB approval on the revised ICF will need to be obtained prior to that re-consenting.

q. Informed consent should include information on who the subject can contact for more information on the study or to voice their concerns or complaints. The PI is responsible for addressing the subject's concerns/ complaints. The PI may refer the subject to the DSRB if the subject is not satisfied with the PI's response to the concerns/ complaints.

5.1.1 Additional Witness Requirements (For HBRA regulated studies)

For studies regulated by the HBRA, appropriate consent must be taken in the presence of a prescribed witness:

a. Who is 21 years of age or older;

b. Who has mental capacity;

c. Who must not be the same individual taking the appropriate consent; and

d. Who may be a member of the team carrying out the research.

If the subject is unable to read or personally sign and date on the ICF, the witness should be an impartial witness (i.e. not be a member of the study team).

Exemptions for requiring a Prescribed Witness

The presence of a prescribed witness is not required if the research -

a. Is not invasive;

© NHG Health

b. Is not interventional; and

c. Is not restricted human biomedical research.

For example, human biomedical research that comprises solely of a survey or collection of information from subjects may be treated as not invasive and not interventional*, subject to the determination of the DSRB, thus they may be exempted from the requirements for witness.

The presence of a prescribed witness is not required if the following conditions are met -

a. The research is interventional but the intervention involves no more than minimal risk to the research subject;

b. The research subject is able to read and sign the appropriate consent form; and

c. The research is not a restricted human biomedical research.

**Interventional: The HBRA defines research as interventional if it involves any activities that have physical, mental or physiological effect (whether temporary or permanent) on the body of the research subject. Examples of intervention include (but are not limited to) buccal swabs, drawing of blood for research purposes, X-ray or MRI scans. A research is not considered interventional (nor invasive) if the intervention is carried out primarily for non-research purposes (i.e. routine clinical procedure).*

5.1.2 Withdrawal from Research

When subjects withdraw from a research, the discussion between the investigator and the subject should distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.

a. An investigator may ask a subject who is withdrawing, whether the subject wishes to allow continued follow-up and further data collection subsequent to their withdrawal from the interventional portion of the study.

b. If a subject withdraws from the interventional portion of a study and consents to allow continued follow-up and further data collection, the investigator must obtain the subject's consent for this limited participation.

c. The discussion with the subject should distinguish between study-related interventions and continued follow-up of associated clinical outcome invasive chart review and address the maintenance of privacy and confidentiality of the subject's information.

The DSRB must approve the consent document for the limited participation if such a situation was not described in the original consent document.

If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not

© NHG Health

access for the purposes related to the study the subject's medical records or other confidential records requiring subject's consent. However, an investigator may review study data related to the subject, collected prior to the subject's withdrawal from the study, and may consult public records such as those establishing survival status.

© NHG Health

5.2 Developing the Informed Consent Form (ICF)

5.2.1 Required Elements of Informed Consent

The following elements must be present in the consent form:

a. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed (including all invasive procedures), and identification of any procedures which are experimental.

b. A description of any reasonably foreseeable risks, discomforts or inconveniences to the subject and when applicable, the subject's partner, to an embryo, foetus or nursing infant.

c. A description of any benefits to the subject or to others that may reasonably be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.

d. The alternative procedure(s) or course(s) of treatment that may be available to the subject and their important potential benefits and risks.

e. A statement describing the extent to which, if any, confidentiality of records identifying the subject will be maintained and that by agreeing to participate in the research, the subject/legal representative allows direct access to source records, based on the understanding that the confidentiality of the subject's medical record will be safeguarded. This access is limited for the purpose of reviewing research activities and/or reviewing or verifying data and records by the regulatory authority(ies), the sponsor's representatives (e.g., monitors or auditors), IRB, in accordance with applicable regulatory requirements.

f. An explanation as to whether any compensation is provided and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

g. An explanation of whom to contact to discuss problems and questions, obtain information and offer input to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject, and whom to contact in the event of complaints or feedback about research.

h. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may decide to stop taking the investigational product (if applicable) or discontinue participation at any time, unless the immediate discontinuation will result in a risk of harm to the subject, without penalty or loss of benefits to which the subject is otherwise entitled.

© NHG Health

5.2.2 Additional Elements of Informed Consent

When appropriate, one or more of the following elements of information shall also be provided to each subject:

a. The approximate number of subjects involved in the study. *(GCP requirement)*

b. The research's investigational product(s), and/or probability of randomisation assignment, e.g., to placebo, study, or comparator arms. *(GCP requirement)*

c. What is expected of subjects. *(GCP requirement)*

d. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo, foetus or nursing infant if the subject or subject's partner is or may become pregnant), which are currently unforeseeable.

e. Anticipated pro-rated payment, if any, for reimbursement of travel, meal or other expenses incurred due to participation in the research, which includes payment methods, amounts and schedule of payment. *(GCP requirement)*

f. Any anticipated costs/ expenses to the subject that may result from participation in the research. *(HBRA and GCP requirement)*

g. The follow-up procedures for subjects who stopped taking the investigational product, withdrew or were discontinued from the research. *(GCP requirement)*

h. Anticipated circumstances and/or reasons under which the subject's participation may be terminated by the Investigator without regard to the subject's consent. *(GCP requirement)*

i. A statement that significant new findings developed during the course of the research, which may relate to the subject's willingness to continue participation, will be provided to the subject or legal representative in a timely manner. *(GCP requirement)*

j. Whether the subject would wish to be re-identified in the case of an incidental finding^ if the proposed research expressly provides for such re-identification. *(HBRA requirement)*

   ^Incidental finding (IF) is a finding about a research subject that has potential health or reproductive importance to the research subject and is discovered in the course of conducting research but is unrelated to the purposes, objectives or variables to the study.

k. A statement that any data that have been collected until the point of withdrawal will be kept and analysed to enable a complete and comprehensive evaluation of the study. (*HBRA requirement)*

l. Whether individually-identifiable information obtained from the subject will be used for future research. *(HBRA requirement)*

© NHG Health

m. Where applicable, whether biological material taken from the research subject will be destroyed, discarded or stored for future research. *(HBRA requirement)*
n. Whether the participation of the subject involves information or tissue in individually-identifiable form. *(HBRA requirement)*

o. The circumstances, if any, under which, the research subject or the person authorised to give consent under this Part will be contacted for further consent, including but not limited to changes in the proposed research, the development of capacity by minors to make decisions and any other circumstances which could be specific to a particular research proposal. *(HBRA requirement)*

p. A statement that any biological specimen(s) collected as part of the research will not be returned to the subject as the subject has consented to gift it for the purpose of the research study and have given up his/her rights to it. However, the subject shall be allowed to request for his/her biological specimen(s) to be discarded or destroyed (e.g., upon withdrawal) if the biological specimen(s) is individually-identifiable and has not been used for the research or it has been used for research but it is practicable to discontinue further use of the biological specimen(s) for the research.

q. When the research involves tests such as HIV testing, that require mandatory reporting to the Ministry of Health if positive, this should be disclosed in the informed consent form, as amended/updated in the MOH mandatory reporting policy.

r. If the research involves genetic testing or DNA banking, the applicable issues in DNA banking and genetic research should be included.

s. If the research involves establishing a specimen or tissue repository, the applicable issues in specimen collection for tissue or specimen repositories should be included.

t. A statement of the intended research use of personal data, including whether biological specimen with personal data could be sent out of Singapore to an overseas collaborator.

u. The process by which the subject's data will be handled, including in the event of the withdrawal or discontinuation of participation in accordance with applicable regulatory requirements. *(GCP requirement)*

v. If the research results are published, the subject's identity will remain confidential. The research may be registered on publicly accessible and recognised databases, per applicable regulatory requirements. *(GCP requirement)*

w. That research results and information on the subject's actual treatment, if appropriate, will be made available to them should they desire it when this information is available from the sponsor. *(GCP requirement)*

x. Any other information that is, in the DSRB's judgment would add meaningfully to the protection of the rights and welfare of subjects.

© NHG Health

Consent requirements for clinical trials regulated by Health Sciences Authority (HSA) involving the collection of human tissue (as defined by HSA)

In addition to the elements required in ICH GCP, the following elements must be present in the informed consent form:

a) The provision of the tissue is voluntary and the renunciation of the trial subject's rights to use the tissue and any intellectual property rights that may be derived from the tissue;

b) Whether the trial subject would wish to be re-identified in the case of an incidental finding^ relating to the collected tissue if the research expressly provides for such re-identification;

c) Whether the tissue will be exported or removed from Singapore to a place outside Singapore.

Consent requirements for studies involving Tissue Banking activities (e.g., removal, donation, supply or use of human tissue as defined by HBRA) regulated under the HBRA Human Tissue Framework (HTF)

The HBRA HTF requirements will apply for tissue banking activities under a Tissue Bank. Examples of tissue banking activities may include, but are not limited to:

a) Collection of left over tissue from a current HBR or clinical trial for future research;

b) Collection of tissue beyond the objectives and endpoints of the protocol approved by the IRB and/or regulatory agencies e.g. HSA;

c) Collection of additional tissue beyond what is approved in the current HBR or clinical trial;

d) Supply of leftover tissue from a researcher's own HBR or clinical trial to other researcher(s) for research that is not the researcher's own IRB-approved research,

e) Use of tissue for pre-clinical studies (e.g., research conducted using human tissue before actual clinical trial starts).

In addition to the elements listed in the HBRA section 12(1), when appropriate, one or more of the following elements of information must be present in the consent form:

a. An explanation of the specific research purpose for which the tissue is intended to be used, if this information is available but if not available, the purpose for which the tissue is intended to be used may be stated as for general research.

© NHG Health

b. A statement to describe whether the tissue will be used for any purpose other than research and if so, the specific purpose for which the tissue will be used.

c. A statement that the donation of the tissue is voluntary and the renunciation of the donor's rights to the tissue and any intellectual property rights that may be derived from the use of the tissue.

d. A description of the proposed area(s) of research approved by the IRB in a case where it has waived the requirement that the removal of the tissue is primarily for a therapeutic or diagnostic purpose.

e. A statement about whether the tissue will be used in restricted human biomedical research involving human-animal combinations.

f. Whether the tissue will be exported or removed from Singapore to a place outside Singapore.

Please refer to HBRA section 12(2) for the full list of consent elements to be included when research involves such tissue banking activities.

5.2.3 General Considerations for the ICF

Whether using the sponsor generated consent form or developing a consent form for an investigator-initiated study, the PI must ensure that the following aspects should be considered when drafting ICFs:

a. All the relevant elements, as outlined above, are present in the consent form.

b. SECOND PERSON - The language of the ICF should be written in second person style so that the consent form conveys a dialogue with information being provided and that there is a choice to be made by the subject rather than presumption of the subject's consent with the use of the first-person style.

c. LANGUAGE SHOULD BE SIMPLE – The information provided in the ICF must be in a language understandable to the subject. The ICF should not include complex language that would not be understandable to the subjects. When technical and scientific terms are used, they should be adequately explained using common or lay terminology.

d. EXCULPATORY LANGUAGE – Consent forms may not contain any exculpatory language (i.e., should not contain any language that causes the subject to waive or to appear to waive any legal rights or that releases or appears to release the investigator, the institution, the sponsor, or their service providers from liability for negligence.

e. FDA-REGULATED TEST ARTICLES – For all research involving test articles regulated by the US FDA, the ICF must include a statement that the purpose of the study includes evaluation of both the safety and effectiveness of the test article. The consent document must also include a statement that the FDA will be given access to the subject's medical records.

© NHG Health

f. DOCUMENT FOOTER AND PAGE NUMBER – The version number and version date of the ICF should be clearly stated as document footer at the bottom of every page. The page number (i.e. Page X of Y) should also be clearly stated at the bottom of every page.

The PI may use the NHG Health DSRB Informed Consent Form (ICF) Template to develop the consent form.

For the ICFs or Assent Template to be used in Mutual Recognition of IRB Reviews for Collaborative Studies

Each study site should use the ICF and Assent Template provided by their own IRB.

Please go to each IRB's webpage for more details on the required minimum training requirements.

IRB	Minimum Training Requirements
A*STAR	Please click here for A*STAR-IRB min training requirements (accessible via A*STAR intranet only).
NHG Health DSRB	Refer to 3.2.1 Training Courses.
NTU	Please click here for NTU-IRB min training requirements.
NUS	Please click here for NUS-IRB min training requirements
SingHealth	Please click here for SingHealth min training requirements.

© NHG Health

5.3 Who can Obtain Consent

Informed consent discussion should be conducted by the PI or an appropriately trained member of the study team who is listed in the DSRB application form as the designated person or study role for conducting the informed consent discussion. The study delegation or responsibility log should also indicate all study staff delegated by the PI to take informed consent.

Any change to the designated person(s) or study team role(s) delegated to take consent should be submitted to the DSRB for review and approval. The PI must ensure that the delegated person is appropriately trained to explain the benefits and risks of the study adequately and conduct the consent process appropriately without compromising on the quality of the consent.

5.3.1 Consent for HSA Regulated Clinical Trials

For HSA-regulated clinical trials, only the PI or an investigator authorized by the PI, who is a qualified practitioner, is allowed to obtain informed consent from the subjects. Where the clinical trial is led by a pharmacist PI, co-investigators who are qualified pharmacist may also be authorized by the PI to obtain consent. Individuals who are not qualified practitioners or qualified pharmacists are not allowed to obtain consent but may be delegated to assist in the consent process for such studies.

QUALIFIED PRACTITIONER – Under the Health Products Act (Clinical Trials) and Medicines (Clinical Trials) Regulations, this refers to:

a. A registered medical practitioner under the Medical Registration Act (Cap. 174); or

b. A registered dentist under the Dental Registration Act (Cap. 76) whose name appears in the first division of the Register of Dentists maintained and kept under section 13(1)(a) of that Act.

QUALIFIED PHARMACIST – Under the Health Products (Clinical Trial) Regulations, refers to an individual who:

a. Is a registered pharmacist under the Pharmacists Registration Act (Cap. 230);

b. Holds a valid practicing certificate granted under section 23 of that Act; and

c. Is in active practice as defined in regulations 2 of the Pharmacist Registration (Practicing Certificate) Regulations 2008 (G.N.No.S 438/2008).

5.3.2 Consent for Human Biomedical Research (HBR) regulated by HBRA

For HBR regulated by HBR:

© NHG Health

a) Appropriate consent must be taken in the presence of a prescribed witness who is:

i. who is 21 years of age or older;

ii. who has mental capacity; and

iii. who must not be the same individual taking the appropriate consent.

iv. who may be a member of the team carrying out the research.

b) The presence of a prescribed witness is not required if the research is:

i. is not invasive;

ii. is not interventional; and

iii. is not restricted human biomedical research.

For example, human biomedical research that comprises solely of a survey or collection of information from subjects may be treated as not invasive and not interventional, subject to the determination of the IRB, thus they may be exempted from the requirement for witness.

c) The presence of a prescribed witness is not required if following conditions are met:

i. the research is interventional but the intervention involves no more than minimal risk to the research subject;

ii. the research subject is able to read and sign the appropriate consent form; and

iii. the research is not restricted HBR.

If the subject is unable to read or personally sign and date on the informed consent form, the witness should be an impartial witness and should not be a member of the study team.

© NHG Health

5.4 Documentation of Informed Consent

5.4.1 General Requirements for Consent Documentation

In most circumstances, the DSRB will require that informed consent is documented by the use of a written consent form approved by the DSRB and signed by the subject or the subject's legal representative.

Each subject or his or her legal representative (and witness if applicable), must personally sign and date a copy of the most current IRB approved ICF prior to enrolment or participation in any aspect of the study, unless this requirement has been waived by the IRB. The subject or his or her legal representative must be given a complete copy (paper or electronic) of the signed ICF and any other informed consent materials prior to participation. A complete copy of the original signed ICF should also be maintained in the investigator file.

The DSRB may approve procedures for documentation of informed consent that involve any of the three options listed below. The DSRB will determine which procedure is appropriate for the research study being reviewed:

a. A written ICF signed by the subject or legal representative; or

b. A written ICF appended with a short consent form, with oral presentation; or

c. In limited circumstances, a waiver of documentation of consent.

The study team member who conducted the informed consent discussion must personally sign and date the ICF. Additionally, the study team member who conducted the consent discussion should minimally record the following in the subject's source documents (e.g., medical records, if applicable).

a. Protocol reference (e.g., protocol number, protocol title);

b. Date of informed consent;

c. Informed consent process (e.g., for use of substituted consent/ impartial witness/ prescribed witness, translator, verification of the appropriate legal representative for consent, use of assent form)

d. Whether a copy of the signed ICF was given to the subject.

Documentation in the medical records is not required if the study does not involve access to medical records. However, minimally required information on the informed consent process should be documented in other source records.

Where applicable, reasonable efforts must be made to contact legal representatives in the descending order of priority in accordance with applicable regulations, and such efforts and reasons of unavailability (e.g., overseas, deceased) of prior class must be documented.

© NHG Health

As per institutional requirements, a copy of the ICF may need to be filed in the medical records, to document the subject's participation in a research study. If the ICF is not placed in the medical records due to confidentiality reasons, a statement in the medical records indicating the subject's participation in the research study should be included. If the research protocol may impact the subject's health, a statement in the medical records must include enough description of the intervention for other healthcare professionals to deal with any medical problems that may arise.

When participation in the study might impact the subject's health and/or medical care, the attending or referring doctor should be informed of the subject's participation in the study, if the subject agrees to the attending or referring doctor to be informed.

In certain situations, the DSRB may approve a request for waiver or alteration to the informed consent process. More information on this is provided in chapter 5.10 Waiver of Documentation of Consent and chapter 5.11 Waiver of Informed Consent.

5.4.2 Documentation of Informed Consent for Mentally Competent Subjects Who Are Incapable of Personally Signing and Dating the Consent Form

Situations may be encountered in which mentally competent subjects are unable to personally sign and date the ICF. Examples may include:

a. Subjects with physical disabilities that prevent them from being able to write;

b. Subjects who are unable to read the ICF (e.g., illiterate or visual impairment).

It should be ascertained that these subjects demonstrate mental competence and are able to understand the informed consent discussion. Subjects should also be capable of indicating approval or disapproval to study entry, to qualify for enrolment.

Documentation of informed consent for these subjects should be performed in the following manner:

a. The subject should affix his or her thumbprint onto the ICF;

b. An impartial witness will be required to attend the consent discussion, as well as personally sign and date on the ICF;

c. The impartial witness may also write the subject's name and the date of consent on the ICF, on the subject's behalf; and

d. The person taking consent should document and clearly describe the informed consent process in the subject's source documents (e.g. medical records).

The PI may seek IRB approval for waiver of documentation of consent (e.g., verbal consent). Verbal consent process should also be documented in the source records (e.g., medical records).

Please refer to Chapter 5.10 Waiver of Documentation of Consent for more information.

© NHG Health

5.5 Subjects who are Unable to Read

When a subject or his or her legal representative is unable to read (i.e., illiterate, or unable to read due to visual impairment), an impartial witness should be present during the entire informed consent discussion. The impartial witness should not be a member of the study team. If a translator is being used, this person can serve as a witness. The person conducting the consent discussion should read and explain the consent form to the subject or the legal representative.

a. The IRB approved ICF and any other written information to be provided to the subjects should be read and explained to the subject or his or her legal representative.

b. The subject or his or her legal representative must orally consent to the subject's participation in the study.

c. If capable of doing so, the subject or his or her legal representative should personally sign and date the ICF.

d. The impartial witness should also personally sign and date the ICF. By signing the ICF, the impartial witness attests that:

   i. the information in the ICF and any other written information was accurately explained to, and apparently understood by the subject or his or her legal representative; and
   ii. the informed consent was freely given by the subject or his or her legal representative.

e. After obtaining the witness signature, the person conducting the consent discussion should:
   a. personally sign and date the ICF and

   b. give a complete copy of the signed ICF to the subject or his or her legal representative.

© NHG Health

5.6 Non-English Speaking Subjects

5.6.1 Use of Translated ICFs

The preferred method of taking consent from non-English speaking subjects (who are literate in another local or other language) is to provide the subjects with the ICF written in the language understandable to them. It is not acceptable to exclude potential subjects based on their inability to speak and understand English.

If the study involves many non-English speaking subjects, the PI should include and project the costs for translations of the DSRB approved ICFs into the study grants and contract. It is the PI's responsibility to ensure that there is provision of adequate resources to obtain proper informed consent from subjects.

A certified translation of the DSRB approved ICF into the language understandable to the subject is preferred. The fully translated ICF should be accompanied by a letter of certification from the translator or translation service and kept in the investigator file.

For investigator-initiated studies where the costs of translation is a factor of concern, a certified translation is not required; documents translated by an individual fluent in the given language are acceptable. However, a letter from the translator describing his or her qualifications to perform the translation should be provided with the translated documents and kept in the investigator file.

To document the translation process by a qualified individual, the PI may use the NHG Health DSRB Certification of Translation template.

5.6.2 Oral Presentation and Use of the Short Consent Form

In the event where the ICF has not been translated and is not available in a language understandable to the subject, an alternative for investigator-initiated studies (for all types of research), is to provide an oral presentation of informed consent information and documented using **both**:

a. The DSRB approved English language ICF serving as the written summary of the information to be orally translated and presented to the subject; and

b. A short consent form (in a language understandable to the subject) stating that the elements of informed consent have been presented orally to the subject or the subject's legal representative.

When the short consent form is used, the following requirements should be used:

a. The oral presentation and the short consent form should be in a language understandable to the subject;

b. An impartial witness is required during the informed consent process, and the impartial witness should be fluent in both English and the language understandable by the subject;

© NHG Health

c. The study team member who is obtaining consent should not be the witness to the consent;

d. The subject or subject's legal representative, the study team member obtaining consent and the impartial witness must personally sign and date on both the DSRB approved English language ICF and the short consent form;

e. The subject or subject's legal representative must be provided with a complete copy of the signed DSRB-approved English language ICF together with the short consent form.

The complete set of informed consent documents for non-English speaking subject is constituted by the following:

a. The DSRB approved English language ICF; and

b. The short consent form written in the language understandable by the subject.

The short consent form should be appended to the DSRB approved English language ICF as a single set of document. A document footer (mentioning the document version number and version date) and page number (i.e. Page X of Y) must be provided as a reference to link these two document.

The NHG Health DSRB Short Consent Form templates are available in three local languages (Mandarin, Malay and Tamil).

The NHG Health DSRB Short Consent Form Templates are available for download from the NHG Health Research Website.

5.6.3 Additional Information

Fully translated informed consent forms, and all language versions of the Short Consent Form appended to the English language informed consent form are not required to be submitted to the DSRB for acknowledgement or approval prior to the use of these documents. However, the PI:

- Should ensure the accuracy of the translations and ensure that correct versions of the translated documents are used.

- Should track all versions of the translated consent forms (i.e., fully translated or Short Consent Form) to be used in the investigator file.

- Is encouraged to use a log to track the translated study documents in the investigator file.

The ICF Tracking Log Template is available for download from the NHG Health Research Website.

© NHG Health

5.7 When a Legal Representative Is Required

LEGAL REPRESENTATIVE - Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, this refers to a person who is authorised under the law and having capacity to consent on behalf of an individual (who is a subject or a prospective subject) to his / her participation in the clinical trial. A person who has such capacity is a person who does not lack capacity to so consent within the meaning of section 4 of the Mental Capacity Act.

LEGALLY ACCEPTABLE REPRESENTATIVE - Under the ICH GCP guidelines, the term is defined as an individual or juridical or other body authorised under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial. When a legally acceptable representative provides consent on behalf of a prospective subject, activities related to the consenting process (and re-consent, if applicable) and, where relevant, activities associated with the withdrawal of consent are applcoeicable to the subject's legally acceptable representative.

LEGALLY AUTHORISED REPRESENTATIVE - Under DHHS regulations, this means an individual or judicial or other body authorised under applicable law to consent on behalf of a prospective to the subject's participation in the procedure(s) involved in the research.

For the purposes of research under the purview of DSRB, the terms legal representative, legally acceptable representative and legally authorised representative as defined above, are synonymous and may be used interchangeably.

A legal representative may give consent on behalf of the subject for participation in a research only when the individual is not capable of giving legally effective informed consent, such as in any of the following circumstances:

a. A child as defined in Chapter 6.1;

b. An individual who is cognitively impaired; or

c. An individual who is unconscious.

Please refer to the following topics under Chapter 6 for specific consent requirements in vulnerable populations:

- *Chapter 6.1 Research Involving Children*
- *Chapter 6.2 Research Involving Pregnant Women, Foetuses and Neonates*
- *Chapter 6.3 Research Involving Cognitively Impaired Persons*
- *Chapter 6.4 Research Involving Prisoners*

© NHG Health

5.8 Consent for Research in Emergency Situations

For research conducted in emergency situations, when prior consent of the subject is not possible, the consent of the subject's legal representative (if he or she is present) should be obtained.

Where prior consent of the subject is not possible, and where the subject's legal representative is not available within the window period in which the treatment must be administered, additional measures are required to protect the rights, safety and well-being of the subject being enrolled, as well as to ensure compliance with the applicable regulatory requirements.

5.8.1 HBRA Regulated Clinical Research Studies Conducted in Emergency Situations

Under the HBRA, emergency research is deemed as human biomedical research where life-threatening emergency situations may arise such that appropriate consent may not be obtained before the research subject is subjected to any intervention, or after any individually-identifiable biological material is obtained from his or her body, or any of his or her individually-identifiable health information is used.

At the point of enrolment of each subject, provision is made for any person as follows (I) and (II) or combination of such persons,

I. A medical practitioner who is registered under the Medical Registration Act (Cap.174) as a specialist in the specialty relating to the research and who is not involved in the research as a researcher or supervisor;

II. A person approved by the Director by name, or holding the office or designation or falling within the description approved by the Director.

to certify to the best of that person's or combination of person's knowledge that the following listed below (a) and (e) have been complied with -

a. The research subjects are in a life-threatening situation;

b. There is no professionally accepted standard of treatment or the available treatments are unproven;

c. The collection of valid scientific evidence is necessary to determine the safety and effectiveness of a particular intervention or treatment;

d. Participation in the proposed research holds out the prospect of direct benefit to the research subject;

e. Obtaining appropriate consent is not feasible because:
   i. The subject will not have capacity within the time available to give their appropriate consent as a result of their medical condition or situation; and,

   ii. The subject's legal representative is not available.

© NHG Health

Following enrolment, the written certification for each subject should be retained on file for verification.

Provision must also be made for one of the following, whichever occurs first:

a. The subject is to be informed as soon as is practicable after he or she regains capacity of his or her participation in the research and given an opportunity to withdraw from further participation in the research; or

b. The subject's legal representative to be informed as soon as is practicable of the subject's participation in the research and to be given an opportunity to request that the subject be withdrawn from further participation in the research.

The PI should ensure that the subject or the subject's legal representative is informed about the research as soon as is practicable and must obtain informed consent for continued participation in the research.

Where the subject has been enrolled into a study, and where the subject or legal representative or any family member objects to the subject's continued participation in the study, the subject should be immediately discontinued.

5.8.2 Clinical Trials Conducted in Emergency Situations (regulated by the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations)

Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, a clinical trial in an emergency situation is deemed as a clinical trial which determines the safety or efficacy of the investigational product being tested in the trial on subjects where:

a. The subjects are facing a life-threatening situation that necessitates intervention;

b. The subjects are unable to consent to being subjects in the trial as a result of their medical condition; and

c. It is not feasible to request consents from the legal representatives of the subjects within the window period.

WINDOW PERIOD – The time period after onset of the event, based on available scientific evidence, within which the investigational product must be used or administered to have its potential clinical effect.

I. Documentation Required Prior to Initiating the Clinical Trial

Prior to initiating the study, the PI must provide the DSRB and HSA with documentation to indicate that this is a clinical trial of emergency situation. This documentation should be signed off by the PI who is a qualified practitioner and who is conducting the clinical trial, and 2 specialists in writing that:

© NHG Health

a. The clinical trial needs to be conducted on potential subjects who are facing a life-threatening situation, to determine the safety or efficacy of the investigational product;

b. Available treatments or procedures are unproven or unsatisfactory;

c. There is a reasonable prospect that participation in the clinical trial will directly benefit the potential subject because:

   i. The potential subjects are facing a life-threatening situation that necessitates intervention;

   ii. The appropriate non-clinical and clinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the proposed use of the investigational product to provide a direct benefit to the potential subjects; and

   iii. The risks associated with the clinical trial are reasonable in relation to what is known about:

      A. The medical condition of the potential subject;

      B. The risks and benefits of standard therapy, if any; and

      C. The risks and benefits of the proposed use of the investigational product;

d. The potential subjects are unable to consent to being subjects as a result of their medication condition;

e. It is not feasible to obtain consent from the legal representative of the potential subjects within the window period;

f. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical trial; and

g. The clinical trial cannot be practicably carried out if prior consent from the subject or his legal representative must be obtained.

II. Documentation Required At the Point of Enrolment

At the point of enrolment of each subject, an investigator of the trial who is a specialist and one specialist who is not conducting the trial must certify in writing before enrolling the subject in the trial that:

a. The subject is facing a life-threatening situation which necessitates intervention;

b. The subject is unable to give consent as a result of his or her medical condition;

c. It is not feasible to obtain consent from the subject or to contact subject's legal representative within the window period in which the study treatment must be administered; and

© NHG Health

d. Neither the subject, nor his or her legal representative, nor any member of the subject's family, has informed any investigator of any objection to the subject's participation in the clinical trial.

The written certifications made prior to trial initiation and at the point of enrolment of each subject should be retained on file for verification.

III. Documentation Required After Enrolment of Each Subject

If the consent of the subject in the clinical trial in an emergency situation cannot be obtained because of his or her medical condition, and it is not feasible to obtain consent from the legal representative of the subject within the window period; then the PI must ensure that, at the earliest feasible opportunity (including during the window period):

a. All reasonable efforts are made to contact any member of the subject's family; and

b. The member of the subject's family is given a full and reasonable explanation of the required elements in the informed consent; and

c. The member of the subject's family does not object for the subject to be or continue being a subject in the trial.

Once the consent is obtained from the subject, the decision by the legal representative or family member ceases to apply. If the subject is unable to consent and consent is obtained from the legal representative, the decision by the family member ceases to apply.

Where the subject has been enrolled into a trial, and where the subject or legal representative or any family member objects to the subject's continued participation in the trial, the subject should be immediately discontinued.

© NHG Health

5.9 Consent on the Removal or Use of Human Tissue or Health Information for Research in Deceased Persons

When the prospective research subject or tissue donor is a deceased person, appropriate consent must be obtained:

a. For the use of the deceased person's individually identifiable —

   i. Biological material;

   ii. Body or any part of the body; or

   iii. Health information; or

b. For the removal or use of human tissue for research from the deceased person, appropriate consent must be obtained from any of the following persons in the order of priority stated, when persons in prior classes are not available at the time of death, and in the absence of actual notice of contrary indications by the deceased person, or actual notice of opposition of a member of the same class or a prior class:

   i. The spouse;

   ii. An adult son or daughter;

   iii. Either parent or a guardian of the deceased person at the time of the person's death;

   iv. An adult brother or sister;

   v. The administrator or executor of the estate of the deceased person;

   vi. Any other person authorised or under obligation to dispose of the body of the deceased person.

© NHG Health

5.10 Waiver of Documentation of Consent

The DSRB may waive the requirement for the PI to obtain a signed ICF for some or all subjects if the DSRB finds that:

EITHER

a. All the following are true:

   i. The only record linking the subject and the research would be the consent document;

   ii. The principal risk would be potential harm resulting from a breach of confidentiality;

   iii. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the participant's wishes will govern;

   iv. The research is not subject to FDA regulations.

OR

b. All the following are true:

   i. The research presents no more than minimal risk of harm to subject, and

   ii. The research involves no procedures for which written consent is normally required outside of the research context.

For FDA–regulated studies, the waiver of documentation of consent may be granted only if criteria (b) is met.

5.10.1 Verbal and Implied Consent

Verbal Consent - In cases where the documentation requirement is waived, the DSRB may require the PI to submit for review, a written description of the information that will be provided to the subject.

This can be in the form of a written statement regarding the research, which involves the use of an information sheet that includes most or all of the elements of an ICF but does not require the subject's signature. The PI must submit the written statement to DSRB for review and approval. The DSRB may require the Investigator to enquire with the subject if the investigator may record that subjects have given verbal consent in the study record (e.g., Enrollment log).

If providing a written statement is not feasible (for example, subject contact is made by phone only), the DSRB may ask to see a script of what will be said to prospective subjects to evaluate the consent process.

Implied Consent – DSRB may also approve for studies to use implied consent. For example, PI conducts a survey where the survey materials clearly state that by responding to the questions and returning the survey back, the recipients will be considered to have agreed to

© NHG Health

participate in the research. By sending back the completed survey, the recipient has implied that he or she consents to participate in the research study but has not signed on an informed consent document.

5.10.2 Examples on Waiver of Documentation of Consent

Examples of studies where a waiver of documentation of consent may be approved:

a. When the identities of subjects will be completely anonymous and there is minimal risk involved in the study. The signed informed consent would be the only record linking the participant to the study; therefore it would be the only identifier in the study.

b. A study in which the only document linking the subject to the research is the consent form, and the principal risk of harm is breach of confidentiality.

c. When the study involves only a telephone interview.

The scenario given below illustrates how the criteria for a waiver of documentation of consent may be applied to a research study.

Scenario:
A researcher plans to evaluate the effectiveness of a smoking cessation programme with women who are receiving prenatal care at the local health clinic. During a prenatal visit, any women who are already participating in the smoking cessation programme will be asked to complete a written questionnaire about the program. The one-time written questionnaire includes questions about how well the women are complying with the program and how they feel about their progress. There is no identifying information about the subjects on the questionnaire and whether the subjects complete the questionnaire has no effect on the care they may receive at the clinic.

How the above example satisfies the criteria for waiver of documentation of consent:

a. Minimal risk: The anonymous questionnaire fits the definition of minimal risk, and the only potential harm comes from the breach of confidentiality.
b. Linkage: The consent document is the only record linking the subject and the research activity.
c. Implied consent: By the virtue of completing the questionnaire, the subjects have consented to participate in the research.

Acknowledgements

- Institutional Review Board: Management and Function, 3rd edition, E. Bankert, B.G. Gordon, E. A. Hurley, S.P. Shirver (2022) Jones & Bartlett Learning Company: Chapter 6-5 Waiver of Documentation of Consent.

© NHG Health

5.11 Waiver of Informed Consent

The DSRB may approve a consent procedure that alters or excludes some or all of the elements of informed consent, or waive the requirement to obtain informed consent, if the following are met:

a. For studies which are regulated by the HBRA, and collecting individually-identifiable health information obtained or complied before 1 November 2017:

   i. the research cannot reasonably be carried out without the use of the health information in an individually-identifiable form;

   ii. the use of the individually-identifiable health information involves no more than minimal risk to the research subject;

   iii. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject; and

   iv. the process of obtaining consent from the person, to which the individually-identifiable health information relates, will involve a disproportionate amount of effort and resources relative to the research requirements.

b. For studies which are regulated by the HBRA, and collecting individually-identifiable human biological material obtained before 1 November 2017:

   i. the research cannot reasonably be carried out without the use of the human biological material in an individually-identifiable form;

   ii. the use of the individually-identifiable human biological material involves no more than minimal risk to the research subject;

   iii. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject; and

   iv. reasonable effort has been made to re-contact the person to which the individually-identifiable human biological material relates for the purpose of obtaining his/ her consent.

c. For studies which are regulated by the HBRA, and collecting individually-identifiable health information or human biological material obtained or compiled on or after 1 November 2017;

   i. the research cannot reasonably be carried out without the use of the human biological material or health information in an individually-identifiable form;

© NHG Health

ii. the process of obtaining consent from the person, to which the individually-identifiable human biological material or health information relates, will involve a disproportionate amount of effort and resources relative to the research requirements;

iii. the use of the individually-identifiable human biological material or health information, as the case may be, involves no more than minimal risk to the research subject or donor;

iv. the waiver concerned will not otherwise adversely affect the rights and welfare of the research subject or donor; and

v. the human biomedical research or health information research would reasonably be considered to contribute to the greater public good.

Please refer to the Human Biomedical Research Act 2015 (Amendment of Third, Fourth and Fifth Schedules) Order 2017, Amendment of Fifth Schedule for more information.

d. For all other studies which are not regulated by the HBRA:

i. the research involves no more than minimal risk to the subjects;

ii. the waiver or alteration will not adversely affect the rights and welfare of the subjects;

iii. whenever appropriate, the subjects will be provided with additional pertinent information after participation;

iv. the research could not practicably be carried out without the waiver or alteration; and

v. the research is not subject to FDA regulations.

5.11.2 Examples on Waiver of Consent

Scenario 1:

Investigators will review the medical records of all patients who have undergone abdominal surgery in the past two years and correlate the data with blood chemistry values kept by pathology. Researchers are collecting limited data that will be assigned a random code number and the link is known only to the researchers. Results of the research will not affect clinical care of the individuals, since they have left the hospital.

How the above example satisfies the criteria for waiver of informed consent:

a. Minimal risk: Evaluating non-sensitive data from patient records fits the definition of minimal risk.

b. Will not adversely affect rights and welfare of subjects: Surgery and associated blood chemistry values are clinically indicated, and therefore would be taken regardless of the

© NHG Health

research. The study result would not affect any clinical decisions related to the individual's care.

c. Whenever appropriate, subjects will be provided with additional pertinent information after participation: Not appropriate in this case, since results of research would have no effect on the subjects. There are no anticipated benefits to the subjects that would change what has already occurred.

Scenario 2:

A researcher plans to review the medical records using the same procedures in the previous example. However, in this research, the hypothesis is that there is a correlation between a particular drug intervention and development of neurology problems several years later.

As with the previous example, the DSRB may find that a waiver of informed consent is appropriate for the same reasons (part a, b and c) as outlined in the example. However, there is one important difference.

Providing Additional Pertinent Information

In this example, the DSRB may determine that it would be appropriate to provide these subjects with additional information about the results of the study. For the DSRB to make this determination, the DSRB may require the researcher to submit the results of the research, along with an assessment of whether subjects should be provided additional pertinent information, to the DSRB for review. The DSRB may require the researcher to outline a process that would include how the information about the research results would be communicated to the subjects, what the results might mean and what to do if there are any questions.

Acknowledgements

- Institutional Review Board: Management and Function, R. Amdur and E. Bankert, Chap. 6-6, "Research without Consent or Documentation Thereof," M. M. Elliott.

© NHG Health

5.12 Special Requirements in Consent Taking for Restricted HBRA Regulated Research

For restricted research, appropriate consent must be obtained from the research subject who has capacity to give consent in person and must not be obtained from another person who is authorized under the subject's or donor's behalf.

5.12.1 Appropriate consent of the donor of oocyte or embryo

The appropriate consent of the donor of any oocyte or embryo for the purpose of restricted research –

a. Must be obtained from the donor in person and only if the donor has capacity to give consent; and

b. Must not be obtained from another person who is authorised to give consent on the subject's behalf.

Every research institution and every PI must ensure that consent from the donor of any oocyte or embryo for the purpose of restricted research must be separately and independently obtained from any consent for assisted reproduction treatment or any other therapeutic purpose. So long as the consent from the donor of any oocyte or embryo for the purpose of restricted research is separately and independently obtained from any consent for assisted reproduction treatment or any other therapeutic purpose, the consent from the donor need not be taken on different days.

The potential donor of any oocyte must confirm in writing at the time that her consent is taken that she had been informed of the full implications of the donation and that she does not require her oocyte for future reproductive use.

The potential donor of any embryo and her husband at the time of the assisted reproduction treatment must both confirm in writing at the time that the consent is taken that:

a. They have each been informed of the full implications of the donation; and

b. They do not require the embryo for future reproductive use.

The research institution and the PI must ensure that:

a. Only surplus embryos created in assisted reproduction treatment may be used for research; and

b. The consent of both the potential donor of the surplus embryo and her husband at the time of that assisted reproduction treatment had been obtained.

The consent from the donor of any oocyte or embryo for the purpose of restricted research must be obtained only after a period of 8 days after the day all the relevant information necessary for the informed consent had been given to the donor.

© NHG Health