CHAPTER 6

RESEARCH IN VULNERABLE POPULATIONS

6.1 Research Involving Children

The DSRB regards children as a vulnerable population and requires additional protection to be in place when children are to be included in research.

6.1.1 Definitions

ASSENT – Affirmative agreement of a minor to participate in research. The absence of expression of agreement or disagreement should not be interpreted as assent.

CHILDREN – Persons who have not attained legal age for consent to treatments or procedures involved in the research (i.e., minors), which under Singapore law is an individual under the age of 21 years. However, persons who are below the age of 21 but are or were married are considered as adults who can give legally effective consent.

DEPUTY – An individual appointed by the court under the Mental Capacity Act who is given the authority to make decisions on behalf of a person who lacks capacity.

GUARDIAN – An individual who is authorised under law to give permission on behalf of the child to general medical care.

LEGAL REPRESENTATIVE – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, where the subject or prospective subject is a minor, the legal representative refers to:

a. A deputy appointed under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of a minor to being a subject in clinical trials; or

b. If there is no deputy referred to in (a), an adult parent, or (if there is no adult parent to act as a legal representative of the minor) a guardian, of the minor.

PARENT – The child's biological or adoptive parent.

PERMISSION – The agreement of the parent(s) or guardian to the participation of their child or ward in research.

WARD – A child who is placed in the legal custody of the court or other agency, institution, or entity.

6.1.2 Categories of Research for Studies Involving Children

Children can be included in research only if the research fulfils any of the following three categories:

CATEGORY 1 – Research that does not involve more than minimal risk. In order to approve research in this category, the DSRB must determine that adequate provisions are made for

soliciting the consent or assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

CATEGORY 2 – Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subject. In order to approve research in this category, the DSRB must determine that:

a. The risk is justified by the anticipated benefit to the subject;

b. The relation of the anticipated benefit to the risk is at least as favorable to the subject as that presented by alternative approaches; and

c. Adequate provisions are made for soliciting the consent or assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

CATEGORY 3 – Research involving greater than minimal risk and no prospect of benefit to the individual subjects. In order to approve research in this category, the DSRB must determine that:

i. The risk of the research presents no more than a minor increase over minimal risk;

ii. The intervention or procedure presents experiences to the subject that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social or educational situations, and;

iii. The intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for the understanding or the amelioration of the disorder or condition; and

iv. Adequate provisions are made for soliciting the consent or assent of the children and the consent of their parents or guardians (or the legal representative as stipulated in the applicable regulations if different).

Reasonable prospect of direct benefit to a person means:

a. 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 person; and

b. The risks associated with the trial are reasonable in relation to what is known about:
    i. The medical condition of the person;
    ii. The risks and benefits of standard therapy, if any;
    iii. The risks and benefits of the proposed use of the investigational product.

6.1.3 Consent Requirements for Studies Involving Children

PARENTAL PERMISSION – Since children have not reached their full intellectual and emotional capacities and are legally unable to give a valid informed consent, involving children in research requires the permission of their parents or legal guardian. The DSRB will use the following guidelines to determine consent or assent requirements:

a. If both parents are available and willing to provide permission, the PI should obtain consent from both parents.

b. For research approved under Category 1 and 2, permission from at least one parent or guardian must be obtained.

c. For research approved under Category 3, permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

I. Clinical Research Studies Regulated under the HBRA

Human biomedical research studies involving children are subject to the requirements laid out in the HBRA. Appropriate consent must be obtained from the following persons in the following circumstances:

a. Where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the biomedical research, consent is obtained from both the minor and at least one adult parent or guardian of the minor;

b. Where the minor has sufficient understanding and intelligence to enable the minor to understand biomedical research and the DSRB has waived the requirement to obtain the consent of at least one adult parent or guardian of the minor, consent is obtained from the minor;

c. Where the minor does not have sufficient understanding and intelligence to enable the minor to understand what is proposed in the research and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs, consent is obtained from at least one parent or guardian of the minor;

d. Where the minor lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of minors to which the minor belongs, consent is obtained from:

    i. Deputy who is authorised to give consent to the biomedical research on behalf of the minor; or

    ii. At least one adult parent or guardian of the minor.

Ia. Consent for removal or use of tissue for research from minors

Where the prospective tissue donor is a minor, the appropriate consent for the removal or use of human tissue must be obtained from the following persons in the following circumstances:

a. where the minor has sufficient understanding and intelligence to enable the minor to understand what is proposed in the procedure, consent is obtained from both the minor and at least one adult parent or guardian of the minor;

b. where the minor does not have sufficient understanding and intelligence to enable the minor to understand what is proposed in the procedure and the removal of the tissue is primarily for a therapeutic or diagnostic purpose, consent is obtained from at least one adult parent or guardian of the minor;

c. where the minor lacks mental capacity and the removal of tissue is primarily for a therapeutic or diagnostic purpose, consent is obtained from:
    i. A deputy who is authorised to give consent for the removal or use of the tissue on behalf of the minor; or

    ii. At least one adult parent or guardian of the minor.

For the purpose of consent for the removal or use of tissue for research from minors, the deputy, adult parent or guardian of a minor must, in determining whether to give consent under that the above-mentioned circumstances, have regard to such matters, considerations and procedures as may be prescribed.

The DSRB may waive the requirement that the tissue be removed from a minor primarily for a therapeutic or diagnostic purpose if the board is satisfied that:

a. the removal of the tissue involves no more than minimal risks to the minor; and

b. there are reasonable grounds for believing that the proposed areas of research cannot be carried out without the use of the tissue from that class of persons, i.e., minors.

II. Clinical Trials

Clinical trials involving children are subject to the requirements laid out in the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations.

The DSRB must ascertain that the following conditions are met:

a. The child and/or the child's legal representative will be given a full and reasonable explanation of all the required elements of the informed consent; and

b. The child and/or the child's legal representative consent will be obtained.

The investigator, who must be a qualified practitioner shall obtain the consent of the child as follows:

a. In the case of a child below the age of 21 years who is or was married, the consent should be obtained from that child;

b. In the case of a child below the age of 21 years who is not and was never married (i.e., minor), the consent of the child and:

   i. The consent of the child's legal representative; and

   ii. If that legal representative is below 21 years of age, the legal representative must have sufficient understanding and intelligence to give the consent.

c. In the case of a child below the age of 21 years of age who is not and was never married (i.e., minor), but who lacks capacity to give consent to being a subject, or the child lacks sufficient understanding and intelligence to give such consent, then the consent of the child need not be obtained if:

   i. The child's legal representative consents to the child being a subject, and if the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent; and

   ii. There is a reasonable prospect that participation in the clinical trial will directly benefit that child.

IIa. Non-therapeutic clinical trials involving children or minors

For non-therapeutic clinical trials involving children/minors (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), the DSRB will ascertain that the following conditions are fulfilled:

a. The objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;

b. The trial is conducted in subjects having a disease or condition for which the investigational product being tested in the trial is intended;

c. There is some direct benefit for the group of subjects involved in the trial;

d. The foreseeable risks to the subjects involved in the trial are low;

e. The negative impact on the wellbeing of subjects involved in the trial is minimised and low.

The PI should determine if the legal representative of the child (if below 21 years of age) has sufficient understanding and intelligence to give informed consent. If the child subsequently regains capacity to consent to being a subject, the PI must ensure that, at the earliest feasible opportunity:

a. The child is given a full and reasonable explanation of the required elements of the informed consent; and

b. The child's consent to continue being a subject in the trial is obtained.

If the child refuses to consent, the PI must ensure that the child ceases to be a subject in the clinical trial.

Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

III. Other Research Studies

For other research studies not regulated under the Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations or the HBRA, and where the prospective research subject is a minor, the investigator should obtain consent from at least one adult parent or guardian of the minor. In the Singapore context,

a. When the parents are divorced, the parent who has legal custody has sole legal responsibility for the care and custody of the child. Therefore, under DHHS and FDA regulations only the permission of the parent who has legal custody is required. The parent who has legal custody is the legally acceptable representative for the child.

b. When the child is illegitimate, the mother has sole legal responsibility for the care and custody of the child. Therefore, under the DHHS and FDA regulations only the permission of the mother is required. The mother is the legally acceptable representative for the child.

c. The following individuals are legally acceptable representatives and meet the DHHS and FDA definitions of "guardian" as they have the same rights as a parent to consent on behalf of the child to general medical care:

    i. A guardian appointed under the Guardianship of Infants Act.

    ii. A person to whom the care of a child is committed under the Children and Young Persons Act.

The PI should ascertain to the best of his 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 were able to do so.

6.1.4 Waiver of Consent from Parents or Guardians

Consent from parents or guardians may not be appropriate in cases such as in research involving child abuse or neglect. The DSRB will follow the respective criteria when reviewing requests for the waiver of consent from the child's parent or guardian.

I. For human biomedical research Regulated under the HBRA

For human biomedical research studies regulated under the HBRA, the DSRB may consider a waiver of consent of at least one adult parent or guardian if the research study meets the following criteria:

a. The proposed research involves no more than minimal risk to the research subjects;

b. The waiver of parental consent will not adversely affect the rights and welfare of the research subjects; and

c. The proposed research may not practicably be carried out unless there is such a waiver, and the research proposal:

    i. Is designed for conditions or for a research subject population for which parental or guardian consent is not a reasonable requirement to protect the research subject (such as neglected or abused minors), and an appropriate mechanism for protecting the minors is substituted; or

    ii. Is of such private and sensitive nature that it is not reasonable to require permission, (such as adolescents in studies concerning treatment of sexually transmitted diseases).

II. Clinical Trials

Under the Health Products (Clinical Trials) Regulations and Medicines (Clinical Trials) Regulations, the requirement for parental consent cannot be waived in clinical trials involving minors.

III. Other Research Studies

For other research studies, the DSRB may consider a waiver of consent from parental consent if the study meets all of the following criteria:

a. The research is designed for conditions or for a subject population for which parental or guardian consent is not a reasonable requirement to protect the subject;

b. An appropriate mechanism for protecting the children who will participate as subject in the research is substituted;

c. The research is not US FDA-regulated.

For HIV or STD research that poses less than minimal risk to children, the DSRB may consider waiving consent from parent permission if the study meets both of the following criteria, in addition to the general waiver criteria set out above (e.g., HBRA consent waiver criteria):

a. Potential subjects have attained the legal age for consent for sexual activity (i.e., 16 years old).

b. The study is pertinent to children in this particular age group (i.e., 16 to 20 years old).

6.1.5 Assent by the Child

ASSENT BY THE CHILD – While a child may not have sufficient understanding and intelligence to understand what is proposed in the research, he or she may possess the ability to assent to or dissent from participation. Age-appropriate assent information should be provided and discussed with the minor as part of the consent process. Out of respect for children as developing persons, children who are unable to provide consent should be asked whether or not they wish to participate in the research particularly if the research does not involve interventions likely to be of benefit to the subjects and the children can comprehend and appreciate what it means to be a volunteer for the benefit of others. A process for consent should be considered if, during the course of the study, the minor reaches the age of legal consent, in accordance with applicable regulatory requirements. Discussion with the child regarding the study and assent process (if applicable) should be documented.

In general, the DSRB requires that consent be obtained from children who are 12 years and above, if they have sufficient understanding and intelligence to do so, together with consent from their legal representative.

For children who lack sufficient understanding and intelligence and who are 6 years and above, assent should be obtained, together with consent from their legal representative. The DSRB will determine whether all or some of the children are capable of consent or assent by considering the following:

a. The nature of research;

b. The age, status, condition of the proposed subjects; and

c. Maturity and psychological state of proposed subjects.

As a general guide, children (who are 6 years and above) should be provided with a short assent document that clearly explains discomforts and inconveniences that the child may experience if he or she agrees to participate. The document should also emphasize the voluntary nature of the research and that the child may refuse to participate without any consequences. Where possible, the child should personally write his or her name and date of assent in the assent form.

If the child is unable to personally write his or her name and/or date on the assent form, the child could affix his or her thumbprint (where possible). The impartial witness (i.e., not a member of the study team) should complete the child's name and/or assent date, personally sign and date on the assent form and an explanation should be documented in the source document (e.g., assent form, medical records). A completed copy of the assent form should also be provided to the child or legal representative.

For research involving children who are 12 years old and above and who have sufficient intelligence and understanding to provide consent, provision should be made in the same

consent document that will be signed by the parents or legal representative for the signature of the child. An explanation should be documented in the source documents if they are unable to provide consent.

It is recommended that where possible, PIs and study team should engage an independent assessor to determine whether the child (aged 12 years old and above) has sufficient understanding and intelligence to provide consent.

The PI may request for waiver of consent or assent from children where applicable. A process for consent should be considered if, during the course of the research, the minor reaches the age of legal consent.

The DSRB must review and approve both the assent and consent document prior to initiation of the study.

The PI may use the NHG Health DSRB Assent Document Template to develop the child assent form.

The NHG Health DSRB Assent Document Template is available for download at the NHG Health Research Website**.**

WAIVER OF CONSENT or ASSENT BY THE CHILD - The DSRB may determine that the consent or assent of the child is not necessary (unless prohibited by the applicable regulations) when either of the following are met:

a. The children are not capable of providing consent or assent based on the age, maturity, or psychological state;

b. The capability of the children is so limited that they cannot reasonably be consulted;

c. The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research;

d. The research meets the criteria for waiver of the consent process as set out in chapter 5.11 Waiver of Informed Consent, even when the children are capable of consent or assenting.

6.1.6 Special Circumstances – Wards of Court

Additional protections need to be in place when a Category 3 research (i.e., greater than minimal risk to the subject with no prospect of direct benefit to the individual subject) involves children who are wards of court or any other institution or entity. In order to approve such studies, the DSRB must determine that the research is:

a. Related to their status as wards,

b. Conducted in schools, hospitals, institutions, or similar settings where majority of the children involved as subject are not wards.

For such research, the DSRB will require the appointment of an advocate in addition to any other individuals who are acting on behalf of the child as a guardian. The advocate must be an individual who has the background and experience to act in, and agrees to act in, the best interest of the child for the duration of the child's participation in the research. This individual must not be associated in any way (except in the role of advocate or member of the DSRB) with the research, investigator or the guardian organisation.

6.2 Research Involving Pregnant Women, Foetuses and Neonates

The DSRB regards pregnant women, human foetuses, neonates of uncertain viability, or nonviable neonates (i.e., neonates determined to be unable, after delivery, to survive to the point of independently maintaining heartbeat and respiration) as a vulnerable population and requires additional protections to be in place when pregnant women, human foetuses, neonates of uncertain viability, or nonviable neonates are included in research.

6.2.1 Definitions

DEAD FOETUS - A foetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord.

DELIVERY - Complete separation of the foetus from the woman by expulsion or extraction or any other means.

FOETUS - Foetus means the product of conception from implantation until delivery.

NEONATE – Refers to newborn.

NONVIABLE NEONATE – Refers to a neonate after delivery that, although living, is not viable

PREGNANCY - Encompasses the period of time from implantation until delivery. A woman shall be assumed to be pregnant if she exhibits any of the pertinent presumptive signs of pregnancy, such as missed menses, until the results of a pregnancy test are negative or until delivery.

VIABLE - As it pertains to the neonate, means being able, after delivery, to survive (given the benefit of available medical therapy) to the point of independently maintaining heartbeat and respiration.

6.2.2 Conditions for Research Involving Pregnant Women and Foetuses

Pregnant women and foetuses may be involved in research if all of the following conditions are met:

a. Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and foetuses;

b. The risk to the foetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the foetus; or, if there is no such prospect of benefit, the risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means;

c. Any risk is the least possible for achieving the objectives of the research;

d. If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the foetus, or no prospect of benefit for the woman nor the foetus when risk to the foetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, and her consent is obtained;

e. If the research holds out the prospect of direct benefit solely to the foetus, then the consent of the pregnant woman and the father is obtained, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy had resulted from rape or incest;

f. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the foetus or neonate;

g. For children who are pregnant, their consent or assent and their parents' consent are obtained;

h. No inducements, monetary or otherwise, will be offered to terminate a pregnancy;

i. Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy;

j. Individuals engaged in the research will have no part in determining the viability of a neonate.

6.2.3 Conditions for Research Involving Neonates

Neonates of uncertain viability and nonviable neonates may be involved in research only if all of the following conditions are met:

a. Where scientifically appropriate, preclinical and clinical studies have been conducted and data is provided for assessing potential risks to neonates;

b. Each individual providing consent is fully informed regarding the reasonably foreseeable impact of the research on the neonate;
c. Individuals engaged in the research will have no part in determining the viability of a neonate.

d. Additional requirements as prescribed below for neonates of uncertain viability and nonviable neonates have been met.

NEONATES OF UNCERTAIN VIABILITY – Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research unless the following <u>additional</u> conditions are met:

a. The DSRB determines that:

i. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or

ii. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate from the research.

b. The legally effective informed consent of either parent of the neonate or, if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legal representative is obtained, except that the consent of the father or his legal representative need not be obtained if the pregnancy resulted from rape or incest.

NONVIABLE NEONATES – After delivery, nonviable neonates may not be involved in research covered by this subpart unless all of the following additional conditions are met:

a. Vital functions of the neonate will not be artificially maintained;

b. The research will not terminate the heartbeat or respiration of the neonate;

c. There will be no added risk to the neonate resulting from the research;

d. The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means;

e. The legally effective informed consent of both parents of the neonate is obtained, except that the waiver and alteration provisions do not apply.

i. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy had resulted from rape or incest.

ii. The consent of a legal representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

VIABLE NEONATES – A neonate that has been determined to be viable after delivery may be included in research only to the extent permitted by, and in accordance with, the requirements stated in chapter 6.1 Research Involving Children.

6.2.4 Conditions for Research Involving the Placenta, Dead Foetus or Foetal Material After Delivery

Research involving (after delivery) the placenta, dead foetus, macerated fetal material, or cells or tissues or organs excised from a dead foetus, shall be conducted only in accordance with any regulations governing such activities.

Where information associated with the material described above is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those living individuals, those individuals will be considered as research subjects, and the conditions stated in chapter 6.2 Research involving Pregnant Women, Foetuses and Neonates (as described above and where applicable) will apply.

6.3 Research Involving Cognitively Impaired Persons

The DSRB regards cognitively impaired persons as a vulnerable population and requires additional protections to be in place when cognitively impaired persons are to be included in research.

6.3.1 Definitions

COGNITIVELY IMPAIRED – Having either a psychiatric disorder (e.g., psychosis, neurosis, personality or behaviour disorders), an organic impairment (e.g. dementia) or a developmental disorder (e.g. mental retardation) that affects cognitive or emotional functions to the extent that capacity for judgment and reasoning is significantly diminished. Others, including persons under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps, may also be compromised in their ability to make decisions in their best interests.

COMPETENCE – A legal term used to denote capacity to act on one's own behalf; the ability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Competence may fluctuate as a function of the natural course of a mental illness, response to training, effects of medication, general physical health, and other factors. Therefore, mental status should be re-evaluated periodically.

DEPUTY – An individual appointed by the court under the Mental Capacity Act who is given the authority to make decisions on behalf of a person who lacks mental capacity.

DONEE – An individual appointed by a person under the Mental Capacity Act who is given the authority to make decisions on behalf of a person when he or she loses mental capacity.

INCAPACITY – Refers to a person's mental status and means inability to understand information presented, to appreciate the consequences of acting (or not acting) on that information, and to make a choice. Often used as a synonym for incompetence.

INCOMPETENCE – A legal term meaning the inability to manage one's own affairs. Often used as a synonym for incapacity.

INSTITUTION – A residential facility that provides food, shelter, and professional services (including treatment, skilled nursing, intermediate or long-term care, and custodial or residential care).

LEGAL REPRESENTATIVE – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, where the subject or prospective subject is an adult who lacks capacity to consent, the legal representative refers to -

a. The donee or deputy appointed pursuant to or under the Mental Capacity Act in relation to the giving or refusing of consent on behalf of the adult to be a subject; or

b. where there is no donee or deputy referred to in paragraph a., subject to paragraph c., any of the following persons in descending order of priority:

   i. A spouse of the adult;

   ii. An adult child of the adult;

   iii. A parent or guardian of the adult;

   iv. An adult sibling of the adult;

   v. Any other adult named by the adult (when the adult did not lack capacity) as someone to consult on the issue of the adult being a subject.

c. In addition, all of the following shall apply:

   i. The order of priority applies in the absence of actual notice of any contrary indication given by the subject or prospective subject (when the subject or prospective subject did not lack capacity);

   ii. A person referred to in paragraph (b) cannot be a legal representative of the subject or prospective subject if the person is also a donee or deputy and there is an express provision in the lasting power of attorney or appointment by the court that the donee or deputy is not authorised to give consent to the adult being a subject;

   iii. A person referred to in paragraph b (ii), (iii), (iv) or (v):

      A. May be a legal representative only if all persons having a higher priority compared to that person are not available or cannot be a legal representative by reason of c (i) or (ii); and

      B. Cannot be a legal representative if any person having an equal or a higher priority compared to that person [other than a person who cannot be a legal representative by reason of c (i) or (ii)] has objected to the adult being a subject.

QUALIFIED PRACTITIONER – Under the Health Products (Clinical Trials) and Medicines (Clinical Trials) Regulations, the term Qualified Practitioner refers to an individual who is –

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.

6.3.2 Considerations for Research Involving Cognitively Impaired Persons

As a general principle, incapable persons should not be involved in research that can be conducted with capable subjects. Inclusion of cognitively impaired persons may be permitted

by HSA (for clinical trials) and DSRB if such research can provide access to an important benefit, particularly one that is not otherwise available outside of the research setting.

In addition to the general criteria for submitting research studies to the DSRB as described in chapter 4, the PI should consider the following points if the research involves cognitively impaired persons.

DEGREE OF RISK – Research that presents more than minimal risk should involve cognitively impaired persons only when the research holds prospects of direct benefit to these individuals. A minor increase over minimal risk may be permitted in research involving institutionalised individuals only where research is designed to evaluate an intervention of foreseeable benefit to their care. If a research study possesses more than minimal risk and no prospect of direct benefit to the individuals, the PI should justify to the DSRB the appropriateness of the research study.

Reasonable prospect of direct benefit to a person means:

a. 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 person; and

b. The risks associated with the trial are reasonable in relation to what is known about:
    i. The medical condition of the person;

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

    iii. The risks and benefits of the proposed use of the investigational product.

SELECTION OF SUBJECTS – Research involving persons whose autonomy is compromised by disability or restraints on their personal freedom should bear some direct relationship to their condition or circumstances. Persons who are institutionalised should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researcher.

LIMITING RISKS – Investigators should include a description of appropriate psychological or medical screening criteria to prevent or reduce adverse reactions to the therapeutic and research procedures. When appropriate, the DSRB might require other healthcare providers involved in the care of these patients to be consulted to ensure that the research will not be detrimental to on-going therapeutic regimens.

ASSESSING COMPETENCE - As a general rule, all adults, regardless of their diagnosis or condition, should be presumed to be competent to consent unless there is evidence of a serious mental disability that would impair reasoning or judgment. Even those who do have a diagnosed mental disorder may be perfectly able to understand the matter of being a research volunteer, and quite capable of consenting to or refusing participation. Mental disability alone should not disqualify a person from consenting to participate in research; rather, there should

be specific evidence of individuals' incapacity to understand and to make a choice before they are deemed unable to consent.

DOCUMENTING CAPACITY – For all research, regardless of study population, the person who obtains the subject's consent must determine that the person has sufficient capacity to give consent. This is documented by the signature in the ICF of the person obtaining consent. The investigator may use the NHG Health DSRB Sample Language for Documentation of Capacity template for this purpose.

In research that involves cognitively impaired persons, investigators should consider the need for an independent assessment of capacity. For participation in clinical trials, an independent assessment of capacity should be made by a doctor (who is a qualified medical practitioner).

The DSRB may set qualifications for the person making assessment, such as requiring a psychiatrist or geriatrician to make this assessment. The independent assessment should be documented by a formal note that is dated and signed.

The NHG Health DSRB Sample Language for Documentation of Capacity Template is available for download at the NHG Health Research Website**.**

6.3.3 Consent for Research Involving Cognitively Impaired Persons

Informed consent is required for research studies involving cognitively impaired persons, unless waived under the conditions specified in chapter 5.11 Waiver of Informed Consent or under the following applicable criteria.

I. Clinical Trials (Regulated under the Health Products Act or Medicines Act)

The consent of adults who lack capacity shall not be required if:

a. The investigator who is a qualified practitioner, and another qualified practitioner who is a registered medical practitioner, who is not conducting the clinical trial certify in writing that –

    i. The person lacks capacity to consent to being a subject; and

    ii. It is not likely that the person will regain capacity within the window period;

b. Consent has been obtained from –

    i. That person's legal representative (as per the order of priority described in section 6.3.1); and

    ii. If the legal representative is below 21 years of age, has sufficient understanding and intelligence to give the consent (the investigator should ascertain this); and

iii. It is established that there is a reasonable prospect that participation in the clinical trial will directly benefit that person.

Ia. Non-therapeutic clinical trials involving adults lacking capacity

For non-therapeutic clinical trials involving adults lacking capacity (i.e., a trial in which there is no anticipated direct clinical benefit to the subject), the DSRB will ascertain that the following conditions are fulfilled:

a. the objectives of the trial cannot be met by means of a trial in subjects who can give consent personally;

b. the trial is conducted in subjects having a disease or condition for which the investigational product being tested in the trial is intended;

c. there is some direct benefit for the group of subjects involved in the trial;

d. the foreseeable risks to the subjects involved in the trial are low;

e. the negative impact on the wellbeing of subjects involved in the trial is minimised and low.

The PI should determine if the legal representative of the person (if below 21 years of age) has sufficient understanding and intelligence to give informed consent.

If the adult subsequently regains capacity to consent to being a subject, the PI must ensure that, at the earliest feasible opportunity:

a. The person is given a full and reasonable explanation of the required elements of the informed consent; and

b. The person's consent to continue being a subject in the trial is obtained.

If the person refuses to consent, the PI must ensure that the person ceases to be a subject in the clinical trial.

Subjects in these trials should be particularly closely monitored and withdrawn if they appear to be unduly distressed.

II. For human biomedical research (Regulated under the HBRA)

Where the prospective research subject is an adult who lacks mental capacity and there are reasonable grounds for believing that biomedical research of comparable effectiveness cannot be carried out without the participation of the class of persons to which the adult belongs, the appropriate consent for the adult must be obtained from the following persons in the following circumstances:

a. Where there is a donee or deputy who is authorised to give consent to the biomedical research on behalf of the adult, consent is obtained from the donee or deputy;

b. Where there is no donee or deputy who is authorised to give consent to the biomedical research on behalf of the adult, consent is obtained from any of the following persons in the order of priority stated, when persons in prior classes are not available, and in the absence of actual notice of contrary indications by the adult, 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;

    iv. An adult brother or sister;

    v. Any other person named by the adult as someone to be consulted on the matter in question or on matters of that kind.

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

IIa. Consent for removal or use of tissue for research involving adults who lack mental capacity

Where the prospective tissue is from an adult who lacks mental capacity to consent to the removal or use of any human tissue, and the removal of human tissue from that adult is primarily for a therapeutic or diagnostic purpose, the appropriate consent must be obtained according to the HBRA requirements for Consent for research involving adults who lack mental capacity above.

If there is an express provision in the lasting power of attorney that the donee is not authorised to give consent to human biomedical research, the removal or use of tissue on behalf of the adult lacking mental capacity, that donee is not authorised to give consent.

III. Other Research Studies

For other research studies not regulated under the Health Products (Clinical Trials) Regulations, Medicines (Clinical Trials) Regulations or the Human Biomedical Research Act, and where the prospective research subject is an adult who lacks capacity, the investigator should obtain consent from the following persons in descending order of priority:

a. The spouse;

b. The adult son or daughter;

c. Either parent or a guardian;

d. An adult brother or sister;

e. Any other person named by the adult as someone to be consulted on the matter in question or on matters of that kind.

The DSRB may require the PI to obtain assent from prospective subjects' (i.e. the willingness and, to the extent possible, knowledge participation of those unable to give legally valid consent). The PI must obtain approval from DSRB for a simple assent form for use in such conditions.

For subjects who are unconscious and where it is not feasible to take consent from subjects or their legal representatives within the window period during which the research treatment must be administered, the consent requirements for clinical trials in emergency situations will apply.

Please refer to chapter 5.8 Consent for Research in Emergency Situations for more information.

6.3.4 Additional Consent Requirements

The PI should ascertain to the best of his 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 subjects would consider if he were able to do so.

The DSRB should consider whether to require investigators to solicit prospective subjects' assent (i.e., the willingness and, to the extent possible, knowledgeable participation of those unable to give legally valid consent).

Where appropriate, investigators must inform subjects of any important new information that may affect their willingness to continue participation. The DSRB must approve the method of notification prior to implementation. The method may include an information letter, an addendum to the previously signed ICF to be signed by subject or a revised ICF to be signed by the subject.

6.3.5 Incompetent Subjects who are Institutionalised

PERSONS WHO ARE INSTITUTIONALISED – When the research poses more than minimal risk and has no prospect of direct benefit to the individuals:

a. Persons formally adjudged incompetent who have a court appointed guardian may consent on their behalf.

b. Officials of the institution in which incompetent patients reside (even if they are the patient's legal guardian) are not generally considered appropriate, since their supervisory duties may give rise to conflicting interests and loyalties.

c. Family members or others financially responsible for patient may also be subject to conflicting interests because of financial pressures, emotional distancing, or other ambivalent feelings common in such circumstances.

6.4 Research Involving Prisoners

The DSRB regards prisoners as a vulnerable population and requires additional protections to be in place when prisoners are to be included in research.

PRISONER – An individual involuntarily confined in a penal institution, including persons: (1) sentenced under a criminal or civil statute; (2) detained pending arraignment, trial, or sentencing; and (3) detained in other facilities (e.g., for drug detoxification or treatment of alcoholism) under statutes or commitment procedures providing such alternatives to criminal prosecution or incarceration in a penal institution.

6.4.1 Considerations for Research Involving Prisoners

Research involving prisoners should bear some direct relationship to their condition or circumstances. Prisoners should not be chosen for studies that bear no relation to their situation just because it would be convenient for the researchers. The two main issues surrounding the participation of prisoners in research are:

a. Whether prisoners have a real choice regarding their participation on research or whether their situation prohibits them from exercise of free choice; and

b. Whether confidentiality of participation and of data can be adequately maintained.

Prisoners should neither bear an unfair share of the burden of participating in research, nor should they be excluded from its benefits, to the extent that voluntary participation is possible.

Only certain kinds of research may involve prisoners as subjects:

a. Studies (involving no more than minimal risk or inconvenience) of the possible causes, effects, and processes of incarceration and criminal behaviour;

b. Studies (involving no more than minimal risk or inconvenience) of prisons as institutional structures or of prisoners as incarcerated persons;

c. Research on particular conditions affecting prisoners as a class; and

d. Research involving a therapy likely to benefit the prisoner subjects.