HEALTH SCIENCES AUTHORITY

REGULATORY GUIDANCE

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CLINICAL TRIALS GUIDANCE

SAFEGUARDS AND CONSENT REQUIREMENTS IN VULNERABLE PARTICIPANTS

GN-IOCTB-06 Rev. No. 004

HSA Health Sciences Authority

PREFACE

This document is intended to provide general guidance. Although we have tried to ensure that the information contained here is accurate, we do not, however, warrant its accuracy or completeness. The Health Sciences Authority (HSA) accepts no liability for any errors or omissions in this document, or for any action / decision taken or not taken as a result of using this document. If you need specific legal or professional advice, you should consult your own legal or other relevant professional advisers.

In the event of any contradiction between the contents of this document and any written law, the latter should take precedence.

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SUMMARY OF KEY AMENDMENTS

- Aligned the overview of informed consent requirements (Section 1.3) with the ICH E6 (R3) Good Clinical Practice (GCP) Guideline

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1. INTRODUCTION

1.1. Purpose

The purpose of this document is to provide guidance to investigators and sponsors on the regulatory requirements for clinical trials involving participants who cannot provide their personal consent. The clinical trials regulations (referred to as Regulations in this guidance) defines these participants to include (i) minors, (ii) persons who lack capacity as defined in the Mental Capacity Act (MCA), and (iii) participants in clinical trials in emergency situations.

1.2. Background

The safeguards and consent requirements for this vulnerable participant population remain largely unchanged from the existing regulatory controls following the revision of the Regulations in 2016. The Regulations includes the definition of legal representative taking into consideration other applicable local laws such as the MCA, and for such clinical trials to be conducted in accordance to conditions specified in other international regulatory positions and ethical standards including the Declaration of Helsinki and ICH[1] E6 (R3) Guideline for Good Clinical Practice (GCP).

1.3. Overview of Informed Consent Requirements

Informed consent is an integral feature of the ethical conduct of a clinical trial. Trial participation should be voluntary and based on an informed consent process that ensures participants (or their legal representatives, where applicable) are well-informed.

The ICH E6 (R3) GCP guideline defines informed consent as a process by which a participant or his / her legal representative voluntarily confirms his / her willingness to participate in a clinical trial after having been informed about all

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

aspects of the clinical trial that are relevant to the participant's decision to participate.

Freely given informed consent should be obtained and documented from every participant prior to clinical trial participation. For potential participants unable to provide informed consent, their legal representatives, acting in the participants' best interest, should provide consent prior to clinical trial participation. These potential participants should be informed about the trial in a manner that facilitates their understanding.

The process and information provided should be designed to achieve the primary objective of enabling potential trial participants to evaluate the benefits, risks and burden of participating in the trial and to make an informed decision on whether or not to participate in the trial. The information provided during the informed consent process should be clear and concise so as to be understandable by potential participants or their legal representatives.

The informed consent process should take into consideration relevant aspects of the trial, such as the characteristics of the participants, the trial design, the anticipated benefits and risks of the medical intervention(s), the setting and context in which the trial is conducted (e.g., trials in emergency situations), and the potential use of technology to inform participants (or their legal representatives) and obtain informed consent.

Informed consent is documented by means of a written (paper or electronic), signed and dated informed consent form. The informed consent process requires care and patience to facilitate a reasonable degree of understanding, and it relies on three principles:

- Adequate information is provided
- Potential participant understands the information
- Consent is given voluntarily

The Principal Investigator is responsible to ensure the rights, safety, and well-being of participants. Of particular importance is obtaining informed consent according to regulatory and ethical requirements. The investigator should consider that informed consent is a process, and not just a form that potential participants must sign. Hence, the investigator and participant should have an on-going discussion about all aspects of the trial that might inform a participant's decision to take part in the study and their decision to continue their involvement.

There are however certain groups of participants who have limited capacity to make voluntary and informed decisions either because they are minors or are adult participants who lack mental capacity due to their medical conditions. Due to their inability to freely give their personal consent, the Regulations require additional conditions, as safeguards, to be fulfilled for this group of participants to be included in clinical trials. Such safeguards include obtaining proper informed consent from legal representatives and the medical assessment of decision-making capacity of the patients before enrolling such participants. This assessment and the conclusions should be recorded in the medical records.

Such participants should not be included in clinical trials if the same results can be obtained from persons capable of giving consent and the trial relates directly to the participants' clinical condition. Additionally, the participants should be included only when there are grounds the clinical trial would be of direct benefit to them, thereby outweighing the risks. When a trial does not offer the prospect of direct benefit to the patients, there should be the prospect of some benefit for the population represented by the participant. However such a clinical trial will pose only minimal risk to, and will impose minimal burden on, the minor concerned in comparison with the standard treatment of the participant's condition.

Clinical trials in rapidly evolving, life-threatening situations are necessary to advance outcomes and treatments. Clinical trials in emergency situations may concern persons with various conditions (e.g. acute trauma, stroke, heart attack). In most emergency situations, consciousness may be altered and treatment or intervention is required within a very short time. Thus, the legal representative may

not be available to provide prior informed consent and informed consent from participants is not possible. The Regulations provide for exception from prior informed consent requirement for clinical trials in emergency situations, with conditions. These conditions are prescribed in the Regulations and are described in this guidance. However, in all cases, informed consent should be sought as soon as possible after the decision to include the participants in the trial.

1.4. Scope

This guidance applies to clinical trials regulated by HSA, namely:

(i) Clinical trials of Therapeutic Products[2] and Class 2 Cell, Tissue and Gene Therapy Products (CTGTPs)[2,3] that are subject to the requirements for a Clinical Trial Authorisation (CTA) or a Clinical Trial Notification (CTN);

(ii) Clinical trials of Medicinal Products[4] that are subject to the requirements of a Clinical Trial Certificate (CTC).

[2] Therapeutic Product and CTGTP are defined in the First Schedule to the Health Products Act.

[3] Class 1 and Class 2 CTGTP are defined in the Health Products (Cell, Tissue and Gene Therapy Products) Regulations.

- Class 1 CTGTP means a CTGTP that —
  (a) is the result of only minimal manipulation of human cell or tissue;
  (b) is intended for homologous use;
  (c) is not combined or used with a therapeutic product or a medical device; and
  (d) is assigned by HSA as a Class 1 CTGTP due to a lower health risk to a user of the product.
- Class 2 CTGTP means a CTGTP other than a Class 1 CTGTP.

[4] Medicinal Product is defined in the Medicines Act.

2. DEFINITIONS

2.1. Minor

A minor is a person who is below 21 years of age, and is not and was never married.

2.2. Legal representative for a minor

The legal representative for a minor is:

(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 participant 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.

2.3. Adult

An adult is a person who is:

(a) at least 21 years of age; or

(b) below 21 years of age, and is or was married

2.4. Person lacking capacity

A person who lacks capacity is one who lacks mental capacity in relation to a matter if, at the material time, he is unable to make a decision for himself in relation to the matter because of an impairment of, or a disturbance in the functioning of, the mind or brain. An individual is unable to make a decision for himself if he is unable to: (i) understand the information relevant to the decision; (ii) retain that information; (iii) use or weigh that information as part of the decision-making process; or (iv) communicate his decision (whether by talking, using sign language or any other means).

2.5. Legal representative for an adult lacking capacity

The legal representative for an adult lacking capacity is:

(i) 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 participant; or

(ii) where there is no donee or deputy referred to in (i), any of the following persons in descending order of priority*:

[A] a spouse of the adult;

[B] an adult child of the adult;

[C] a parent or guardian of the adult;

[D] an adult sibling of the adult; or

[E] any other adult named by the adult (i.e. when the adult did not lack capacity) as someone to consult on the issue of the adult being a participant.

*Note: For Section 2.5:

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

(b) A person referred to in Section 2.5(ii) cannot be a legal representative of the participant or prospective participant 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 participant or prospective participant being a participant;

(c) The person referred to in [B], [C], [D] or [E]:

(i) 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 sub-paragraph (a) or (b); and

(ii) 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 sub-paragraph (a) or (b)) has objected to being a participant.

2.6. Qualified Practitioner

A Qualified Practitioner is a person who is:

(a) a registered medical practitioner under the Medical Registration Act; or

(b) a registered dentist under the Dental Registration Act

2.7. Specialist

A specialist is a person registered as a specialist under section 22 of the Medical Registration Act in the branch of medicine under which the participant is to be treated.

2.8. Reasonable prospect of direct benefit

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;

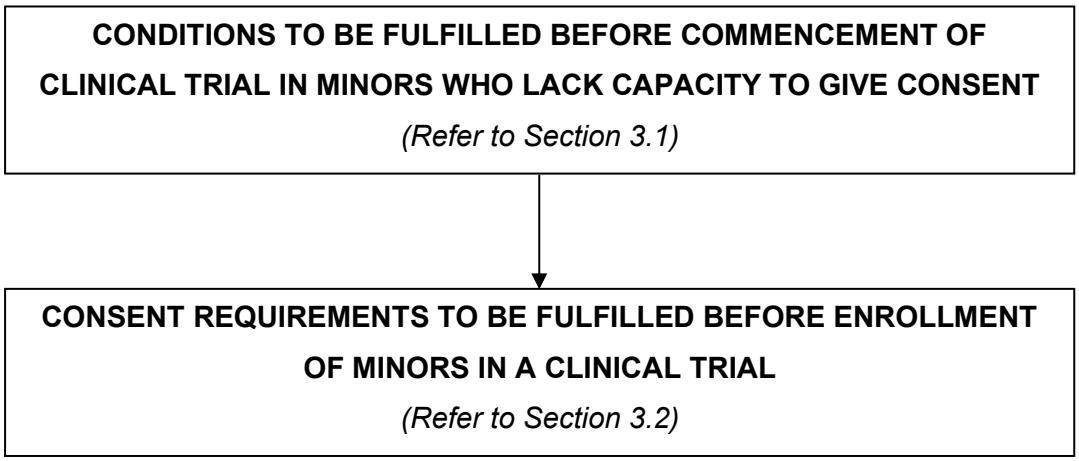
  (ii) the risks and benefits of standard therapy, if any;

  (iii) the risks and benefits of the proposed use of the therapeutic product.

3. SAFEGUARDS AND CONSENT REQUIREMENTS FOR MINORS

Refer to Figure 1 for a summary of the safeguards and consent requirements for minors.

Figure 1. Summary of the safeguards and consent requirements for clinical trials in minors



3.1. Conditions to be fulfilled before commencement of clinical trial in minors who lack capacity to give consent

3.1.1. The following conditions must be fulfilled before commencement of a clinical trial in minors who lack capacity to give consent:

(a) It is established that there is reasonable prospect that participation in the trial will directly benefit the minor (Refer to Sections 3.1.2, 3.1.3 and 3.1.7); or

(b) All of the following are met:

(i) The objectives of trial cannot be met by means of a trial in participants who can give informed consent personally **[Necessary – Refer to Figure 2]**;

(ii) The trial is conducted in participants having a disease or condition for which the product being tested in the trial is intended **[Relevant – Refer to Figure 2]**;

(iii) There is some direct benefit for the group of participants involved in the trial (Refer to Sections 3.1.2 and 3.1.4);

(iv) The foreseeable risks to the participants involved in the trial are low (Refer to Section 3.1.5); and

(v) The negative impact on the well-being of participants involved in the trial is minimised and low (Refer to Section 3.1.6).

3.1.2. Benefit

Benefit is defined as progress in treatment, diagnosis or prevention of the disease for the participants. This may be obtained through either increased efficacy or safety resulting in a better benefit-risk balance, or through the provision of an alternative to existing treatment with at least similar expected benefit-risk balance. Benefit can also be obtained through contribution to patient care, including better route of administration, decreased frequency of dosing, improvement in relation to potential medication errors or compliance, reduced treatment duration, or a clinically relevant age-appropriate formulation.

3.1.3. Prospect of direct benefit to the participant

Refer to Section 2.8 for the definition of prospect of direct benefit. Prospect of direct benefit refers to the clinical trial which is expected to play a clinically relevant role in the treatment, diagnosis or prevention of the disease for the participants. The estimation of prospect of direct benefit for the participant is based on a scientific hypothesis made at the inception of the clinical trial. Phase III randomised controlled trials would offer prospect of direct benefit. However, depending on the study design, early phase trials may also offer the prospect of direct benefit to the participant. The expected direct benefit should outweigh the risks and expected burdens.

3.1.4. Prospect of direct benefit for the group of participants involved in the trial

When a trial does not offer the prospect of direct benefit to the participant, there should be the prospect of some benefit for the population represented by the participant. However, such a clinical trial should pose only minimal risk to, and impose minimal burden on, the participant concerned in comparison with the standard treatment of the participant's condition. Benefit for the population includes increased knowledge of the medicine and/or of the condition, which is expected to result in better diagnostic tools, better prevention or better treatment strategies for the condition at stake. Examples of research falling in this category are observational studies and some pharmacokinetic studies. This benefit expected from the trial should be identified in the protocol. The magnitude of expected benefit for the population is determined by a variety of factors, such as the severity of the condition, its prevalence, the relevance of the data to be obtained, and the likelihood that the trial will succeed in producing these data.

Several factors may contribute to the decision to consider the clinical trial as providing a prospect of direct benefit for the participant concerned or the prospect of direct benefit to the population represented by the participant

- intention of direct benefit, that is clear from the trial design (by the presence of clinical efficacy and end-points) and duration;

- existing knowledge from (pre)clinical studies with the investigational product or comparable products in other participants;
- indications for efficacy of the investigational product for the condition under study or in the population under study;
- in case of existing knowledge on dosage, the plausibility that in a dose-escalating study the begin dose is effective.

3.1.5. Foreseeable risks are low

Risk is defined as the probability and magnitude of harm or discomfort anticipated in the clinical trial. Risk assessment may include the evaluation of the invasiveness and intrusiveness of study procedures, the risks of the investigational product or the control, the risk of withholding active treatment in some cases. The trial should pose only minimal risks to, and impose minimal burden on, the participant concerned in comparison with the risks and burden associated with the standard treatment of the participant's condition.

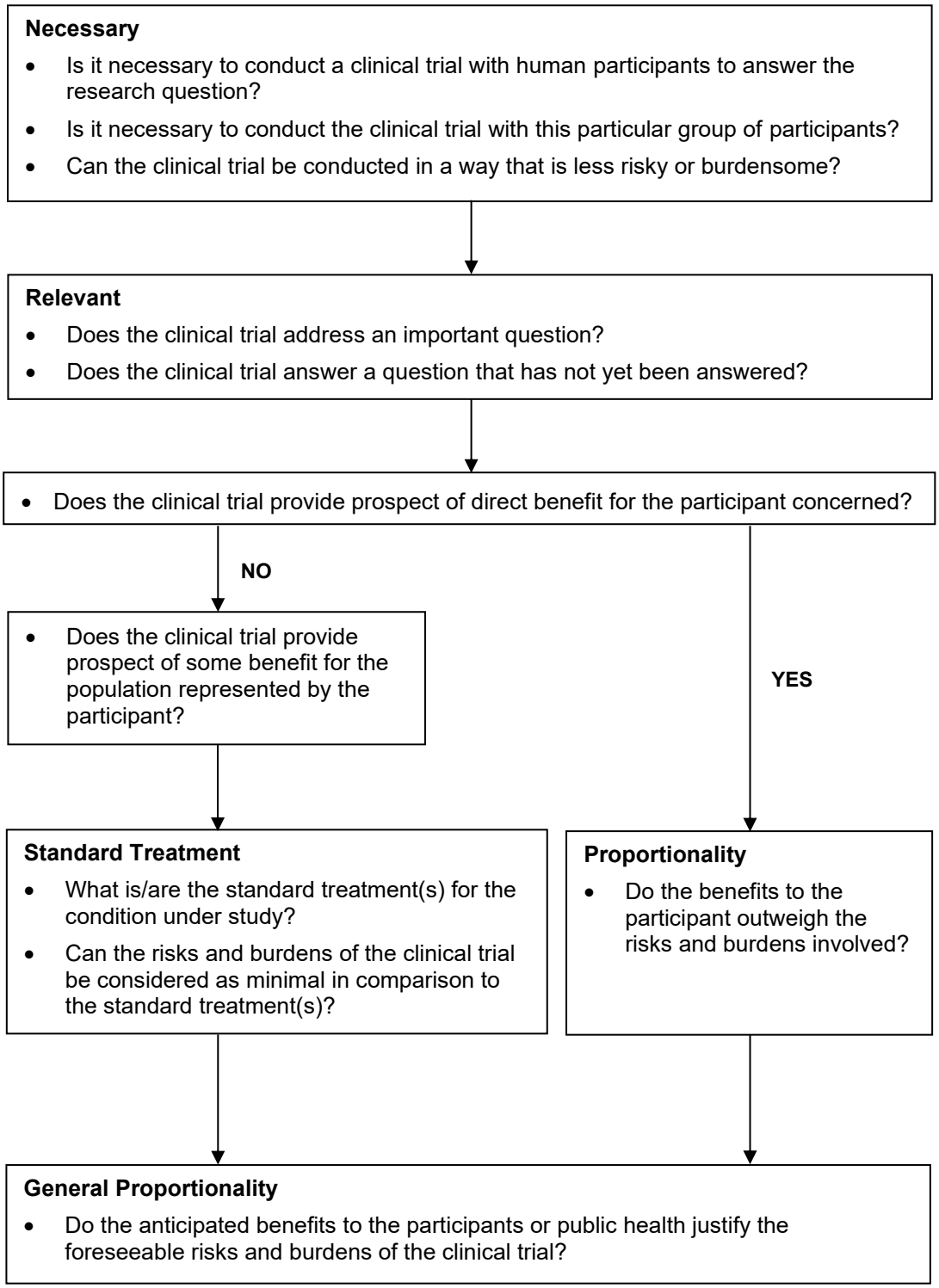
3.1.6. Negative impact on well-being of participant

The negative impact on the well-being of a participant refers to the burden that affects the participant, due to elements of the trial that cause pain, discomfort, fear, disturbances of the participant's life and personal activities, or otherwise unpleasant experiences.

3.1.7. Guide to assessing the acceptable levels of risk and burden in relation to the benefit

Refer to Figure 2 for a guide to assessing the acceptable levels of risk and burden in relation to the benefit.

Figure 2. Guide to Assessing Acceptable Levels of Risk and Burden in Relation to the Benefit



3.2. Consent requirements to be fulfilled before enrollment of minors in a clinical trial

3.2.1. The legal representative of the minor must consent to the minor being a participant in a clinical trial.

3.2.1.1. The legal representative must act in the best interests of the minor. Please refer to Section 6 of the Mental Capacity Act on the determination of what is in a person's best interests.

3.2.1.2. If the legal representative is below 21 years of age, the legal representative must have sufficient understanding and intelligence to give informed consent. The investigator should determine if the legal representative of the minor (if below 21 years of age) has sufficient understanding and intelligence to give informed consent.

3.2.2. The minor must give consent to being enrolled in a clinical trial.

3.2.2.1. The investigator should determine if the minor has sufficient understanding and intelligence to give informed consent.

3.2.2.2. If the minor lacks capacity to give informed consent, or the minor lacks sufficient understanding and intelligence to give informed consent, informed consent from the minor is not required if the conditions outlined in Section 3.1.1 are met.

3.3. Supporting documentation

A copy of the following documentation should be maintained on file, where applicable, for enrollment of minors into a clinical trial:

(a) Deputy of minor*: Certified Court Order Letter; or

(b) Parent of minor: Birth certificate of the minor; or

(c) Legal Guardian of minor: Certified Court Order Letter.

*Note: For Deputy of Minor:

(i) The investigator should ascertain whether the Deputy has been appointed under the MCA to decide whether the minor may participate in a clinical trial. This can be verified from the Certified Court Order Letter for the Deputy.

(ii) If the investigator is unable to obtain any supporting documentation from the Deputy, the investigator may submit a written request (on hospital letterhead) for an online search via the e-services option on the Office of Public Guardian website.

3.4. Re-consent of the minor if he/she gains capacity to consent during the clinical trial

If the minor subsequently gains capacity to consent to being a participant during the clinical trial, the Principal Investigator must ensure that, at the earliest feasible opportunity:

(a) The minor is given a full and reasonable explanation of the required elements of the informed consent; and

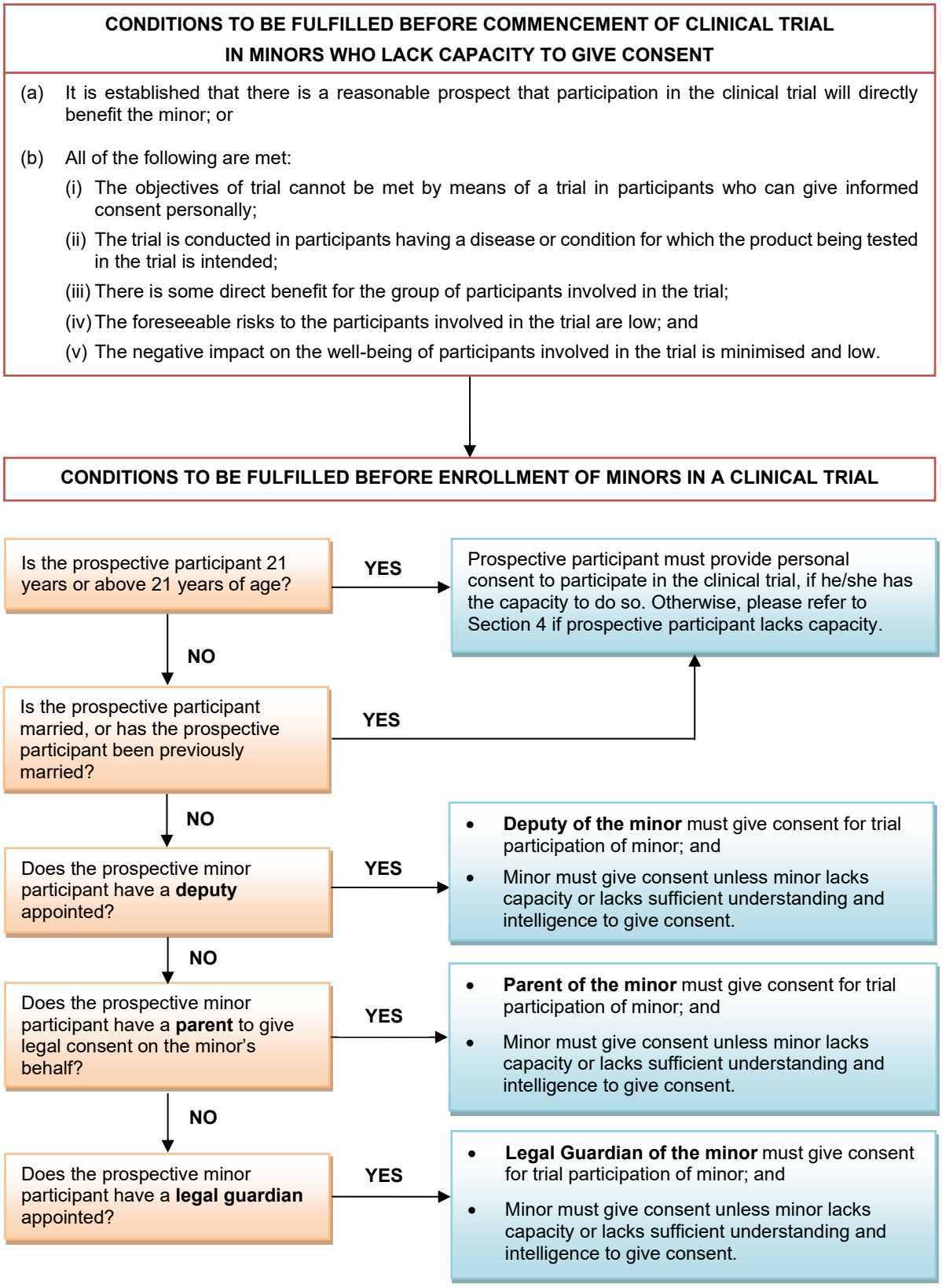
(b) The minor's consent to continue being a participant in the trial is obtained.

If the minor refuses to consent, the Principal Investigator must ensure that the minor ceases to be a participant in the clinical trial.

3.5. Flowchart

Refer to Figure 3 for a flowchart on safeguards and consent requirements in minors.

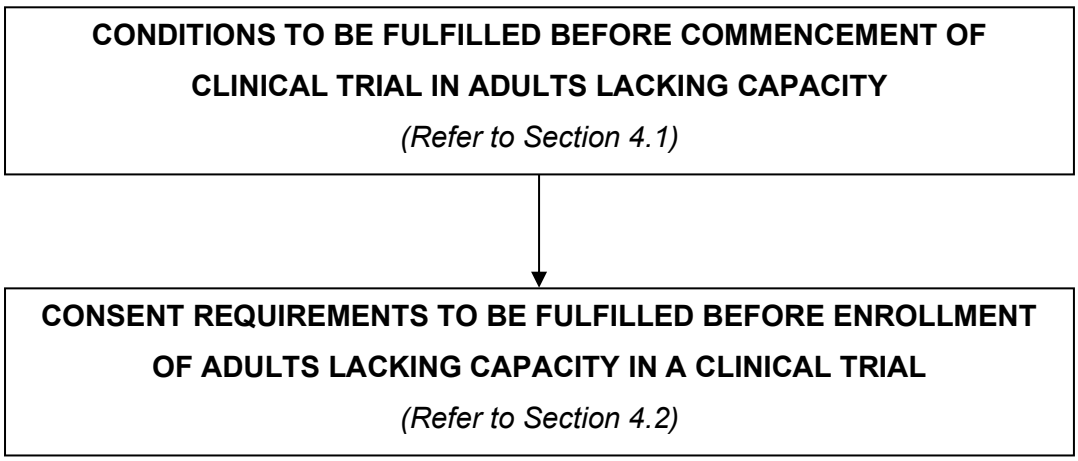
Figure 3. Flowchart on safeguards and consent requirements in minors



4. SAFEGUARDS AND CONSENT IN ADULTS LACKING CAPACITY

Refer to Figure 4 for a summary of the safeguards and consent requirements for adults lacking capacity.

Figure 4. Summary of the safeguards and consent requirements for clinical trials in adults lacking capacity



4.1. Conditions to be fulfilled before commencement of clinical trial in adults lacking capacity

4.1.1. The following conditions must be fulfilled before commencement of a clinical trial in adults lacking capacity:

(a) It is established that there is reasonable prospect that participation in the trial will directly benefit the adult (Refer to Sections 3.1.2 and 3.1.3); or

(b) All of the following are met:

(i) The objectives of trial cannot be met by means of a trial in participants who can give informed consent personally **[Necessary – Refer to Figure 2]**;

(ii) The trial is conducted in participants having a disease or condition for which the product being tested in the trial is intended **[Relevant – Refer to Figure 2]**;

(iii) There is some direct benefit for the group of participants involved in the trial (Refer to Sections 3.1.2 and 3.1.4);

(iv) The foreseeable risks to the participants involved in the trial are low (Refer to Section 3.1.5); and

(v) The negative impact on the well-being of participants involved in the trial is minimised and low (Refer to Section 3.1.6).

4.2. Consent requirements to be fulfilled prior to enrollment of an adult lacking capacity in a clinical trial

4.2.1. An investigator (who is a qualified practitioner) and another qualified practitioner (who is a registered medical practitioner and not conducting the clinical trial) must certify in writing that:

(a) The adult lacks capacity to consent to being a participant in the trial; and

(b) It is not likely that the adult will regain capacity within the window period.

4.2.1.1. The documentation of capacity should be performed before informed consent is obtained from the legal representative of the participant lacking capacity.

4.2.1.2. The documentation of capacity should either be documented in the participant's medical records or in the participant's informed consent form.

4.2.2. The legal representative for the adult lacking capacity must provide informed consent prior to enrollment of the adult lacking capacity in a clinical trial. The legal representative must act in the best interests of the adult. Please refer to Section 6 of the Mental Capacity Act for further details about best interests of a participant.

4.2.2.1. If the legal representative is below 21 years of age, the legal representative should have sufficient understanding and intelligence to provide informed consent.

4.3. Supporting documentation

A copy of the following documentation should be maintained on file, where applicable, for enrollment of adult participants lacking capacity into a clinical trial:

(a) Donee of adult participant*: Certified Lasting Power of Attorney (LPA) Form; or

(b) Deputy of adult participant*: Certified Court Order Letter; or

(c) Spouse / Adult Child / Parent / Guardian / Adult Sibling / Any other adult: Documentation of relationship to adult participant lacking capacity in the participant's medical records.

*Note: For Donee / Deputy of Adult Lacking Capacity:

(i) The investigator should ascertain whether the Donee or Deputy has been authorised to decide whether the adult participant lacking capacity may participate in a clinical trial. This can be verified from the Certified LPA Form (for Donee) or the Certified Court Order Letter (Deputy).

(ii) If the investigator is unable to obtain any supporting documentation from the Donee or Deputy, the investigator may submit a written request (on hospital letterhead) for an online search via the e-services option on the Office of Public Guardian website.

4.4. Re-consent of an adult lacking capacity if he/she regains capacity to provide informed consent during the clinical trial

The adult participant lacking capacity must re-consent if he/she regains capacity to provide informed consent during the clinical trial. The investigator, at the earliest feasible opportunity, must provide a full explanation of the clinical trial; and seek the adult's consent to continue participation in the clinical trial.

In the event that the adult refuses to consent, the investigator must ensure that the adult participant ceases to be used as a participant in the clinical trial.

4.5. Flowchart

Refer to Figure 5 for a flowchart on safeguards and consent requirements in adults lacking capacity.

Figure 5. Flowchart on safeguards and consent requirements in adults lacking capacity

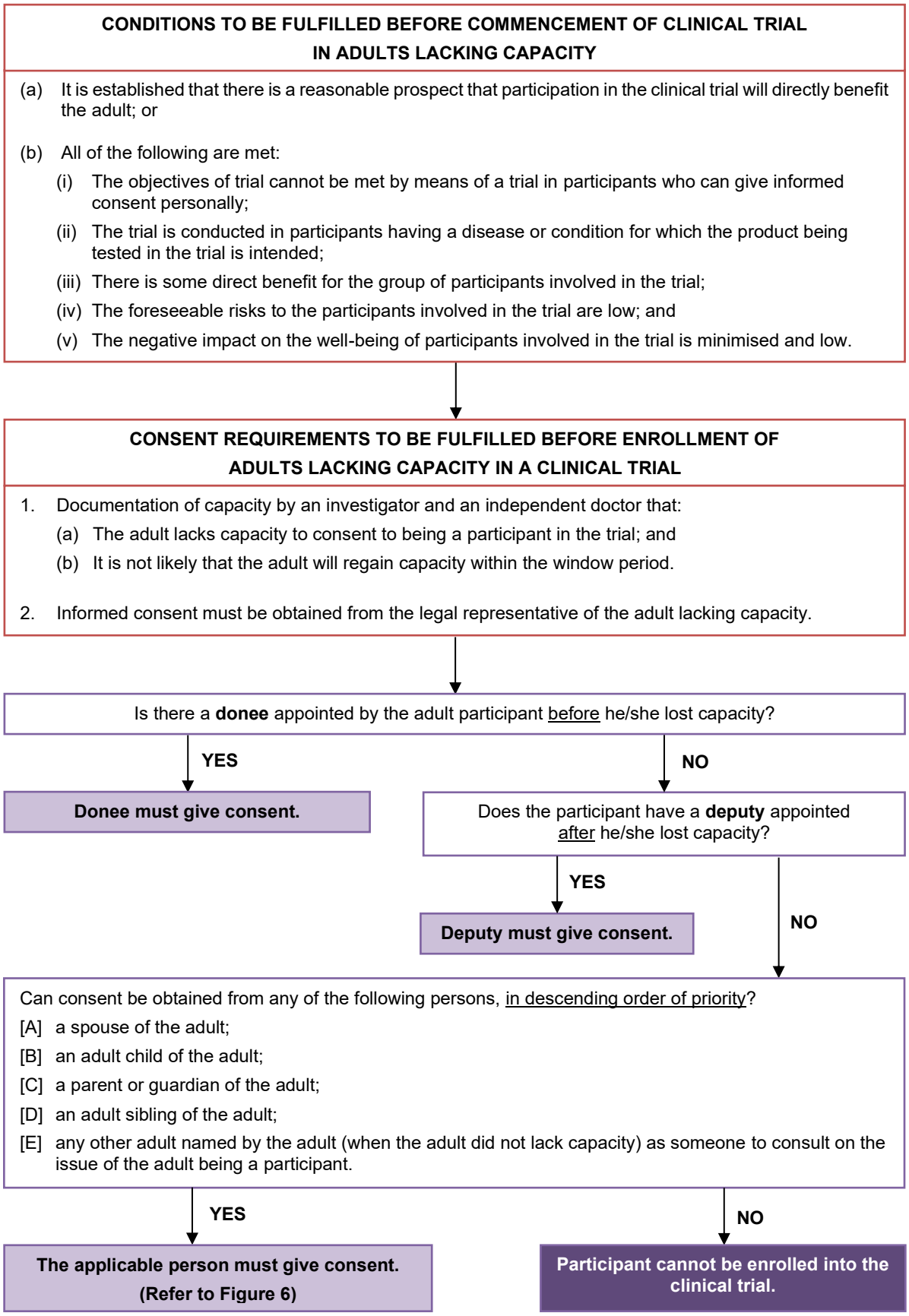
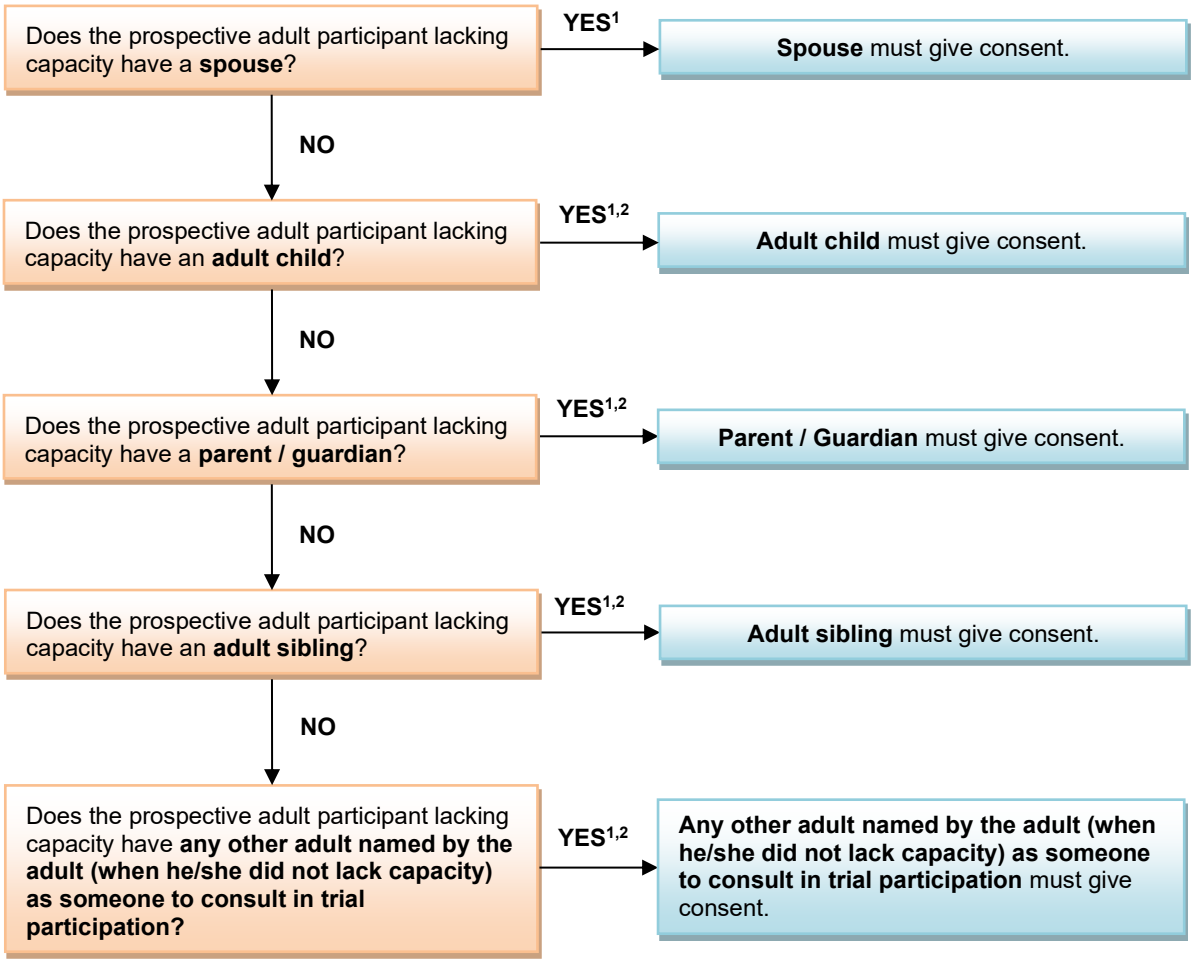


Figure 6. Hierarchy of informed consent in adults lacking capacity



[1] The person can provide consent for trial participation for the prospective adult participant lacking capacity UNLESS:

(a) There is a notice of any contrary indication given by the participant or the prospective participant (when the participant / prospective participant did not lack capacity); and

(b) 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 participant or prospective participant in the clinical trial.

[2] The person can be a legal representative for an adult lacking capacity if:

(a) All the persons of higher priority compared to that person are not available or cannot be a legal representative for certain reasons[1];

(b) If a person having an equal or higher priority compared to that person (other than a person who cannot be a legal representative for certain reasons[1]) has no objections to the trial participation of the adult lacking capacity.

5. SAFEGUARDS AND CONSENT FOR CLINICAL TRIALS IN EMERGENCY SITUATIONS

5.1. Clinical trial in an emergency situation

A clinical trial in an emergency situation is a clinical trial to determine the safety or efficacy of the investigational product being tested in the trial on participants where:

(a) the participants are facing a life-threatening situation that necessitates intervention;

(b) the participants are unable to consent to being participants 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 participants within the window period.

5.1.1. Window period

The window period refers to 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. The sponsor should use pathophysiologic data and animal data to determine the window period; specify the window period in the protocol; and explain the window period in relation to the amount of time to be devoted to seeking informed consent.

5.2. Conditions to be fulfilled before commencement of a clinical trial in emergency situation

5.2.1. The clinical trial is subject to the requirements for a Clinical Trial Authorisation (CTA), Clinical Trial Notification (CTN) or Clinical Trial Certificate (CTC);

5.2.2. The Institutional Review Board (IRB) has reviewed and approved the circumstances in which consent need not be obtained; and the procedures for obtaining consent and/or informing family members at the earliest feasible opportunity, in the trial; and

5.2.3. The Principal Investigator and 2 independent specialists must certify in writing that:

(a) the trial needs to be conducted on potential participants who are facing a life-threatening situation to determine the safety or efficacy of an investigational product;

(b) available treatments or procedures are unproven (refer to Section 5.2.3.1) or unsatisfactory (refer to Section 5.2.3.2);

(c) there is a reasonable prospect that participation in the trial will directly benefit the potential participants because —

(i) the potential participants 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 therapeutic product to provide a direct benefit to the potential participants; and

(iii) the risks associated with the trial are reasonable in relation to what is known about —

(A) the medical condition of the potential participants;

(B) the risks and benefits of standard therapy, if any; and

(C) the risks and benefits of the proposed use of the therapeutic product;

(d) the potential participants are unable to consent to being participants as a result of their medical condition;

(e) it is not feasible to obtain consent from the legal representatives of the potential participants within the window period;

(f) there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the trial; and

(g) the trial cannot practicably be carried out if the consents referred to in regulation 16 must be obtained.

5.2.3.1. **Available treatments are unproven**

"Unproven" means that there is no substantial evidence that a treatment is effective for the condition of interest. This may reflect the absence of any data or the absence of studies of acceptable quality. The term "unproven therapy" includes:

(a) Treatment that is considered "standard of care" but which has never been subjected to rigorous scientific testing or submitted to HSA or other regulatory agencies (e.g. FDA, EMA) for approval;

(b) Treatment for which there are no or insufficient clinical or pre-clinical data to support safety or efficacy of the product;

(c) Treatment for which existing studies and data are insufficient to serve as the basis of approval even if the data were submitted to HSA or other regulatory agencies (e.g. FDA, EMA);

(d) A product that is not approved for, nor does the labelling for the product contain, the specific indication under study; and

(e) An available product or therapy that is not labelled for use in a specific patient population (e.g., paediatric use).

5.2.3.2. **Unsatisfactory**

"Unsatisfactory" includes situations in which the available product or therapy is effective, but there are other drawbacks to its use, such as:

(a) Safety issues (e.g., high incidence of adverse effects; exacerbation of an adverse effect for the relevant participant population);

(b) Efficacy issues, including:

- Poor survival rate;
- The treatment is only partially effective;
- The treatment fails to prevent a significant permanent disability;
- Established efficacy is low;

(c) The time for the treatment to be effective is too long (e.g., time to cessation of seizures);

(d) The treatment has limitations related to the setting in which it is needed (e.g., should be administered in the field but needs

refrigeration; is not portable; may be difficult to use (must be administered intravenously, requires surgical intervention).

5.3. Conditions to be fulfilled prior to enrollment of a participant into a clinical trial in emergency situation

If consent cannot be obtained from the prospective participant or prospective participant's legal representative, and no family member has objected to the prospective participant's trial participation (if feasible), the prospective participant may be enrolled in the clinical trial if an Investigator (who is a specialist) and 1 independent specialist must certify in writing that:

(a) the person is facing a life-threatening situation which necessitates intervention;
(b) the person is unable to consent as a result of the person's medical condition;
(c) it is not feasible to obtain consent from the legal representative of the person within the window period; and
(d) neither the person nor the legal representative of the person nor any member of the person's family has informed the principal investigator of any objection to the person being a participant in the clinical trial.

The certification should either be documented in the participant's medical records or source records.

5.4. Re-consent of a participant if he/she regains capacity to consent during the clinical trial

If anytime during the clinical trial in an emergency situation, the participant regains capacity to give consent, the investigator must, at the earliest feasible opportunity, must provide a full explanation of the clinical trial; and seek the participant's consent to continue participation in the clinical trial.

If consent cannot be obtained from the participant to continue participation in the clinical trial due to his / her medical condition, the investigator, at the earliest feasible opportunity, must make reasonable efforts to contact the participant's legal

representative to provide a full explanation of the clinical trial; and seek the participant's legal representative's consent for the participant to continue participation in the clinical trial. The legal representative must act in the best interests of the adult participant. Please refer to Section 6 of the Mental Capacity Act for further details about best interests of a participant.

If consent cannot be obtained from the participant's legal representative, the investigator, at the earliest feasible opportunity, must make reasonable efforts to contact the participant's family member to provide a full explanation of the clinical trial; and seek the participant's family member's consent for the participant to continue participation in the clinical trial.

All reasonable efforts to contact the participant's legal representative or family member (where applicable) should be documented in the participant's medical records.

If the participant / participant's legal representative / participant's family member objects to the participant to continue participation in the clinical trial, the Principal Investigator must cease using the participant in the clinical trial.

5.5. Flowchart

Figure 7 summarises the safeguards and consent requirements for clinical trials in emergency situations.

Figure 7. Safeguards and Consent Requirements for clinical trials in emergency situations (Part 1)

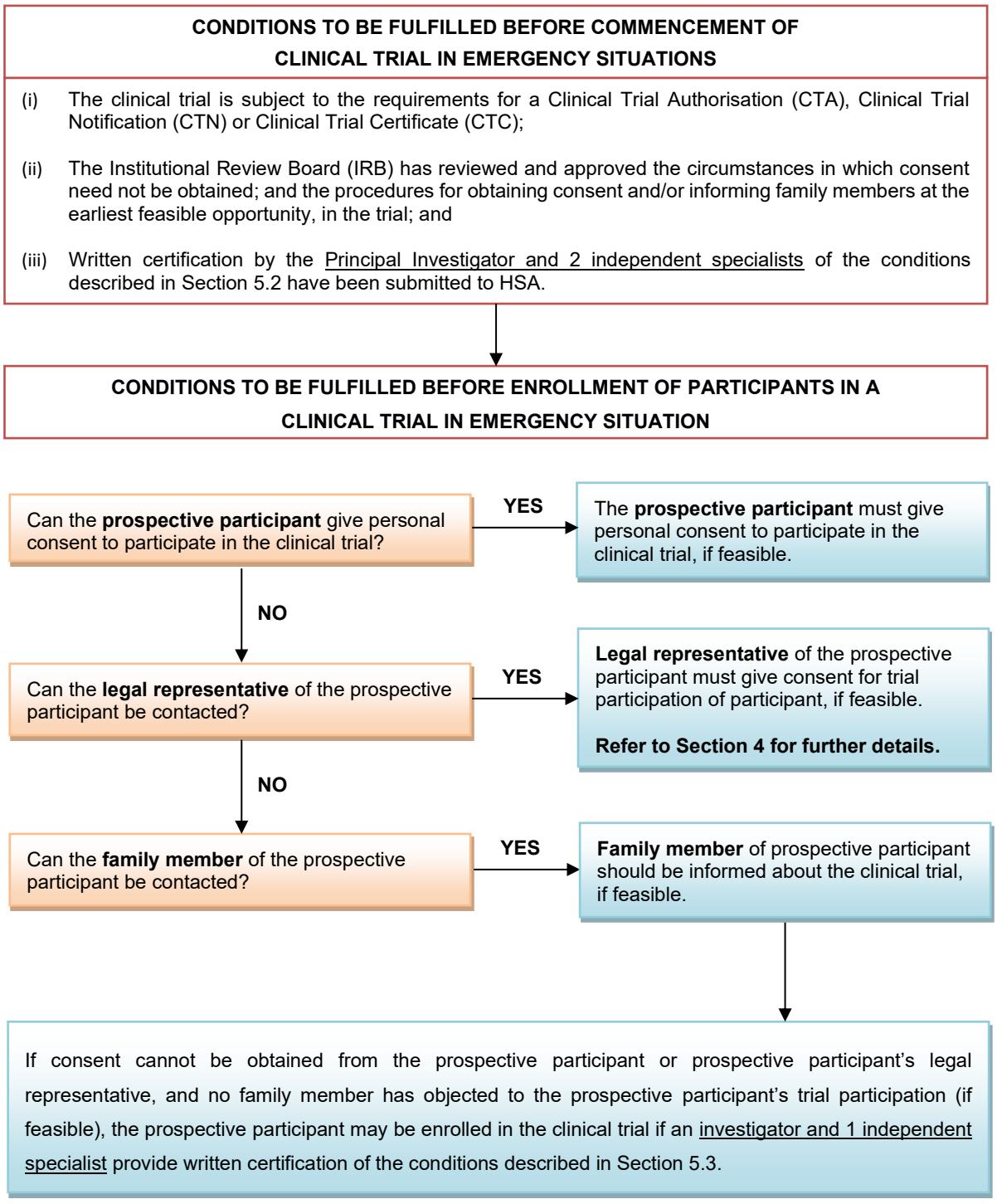
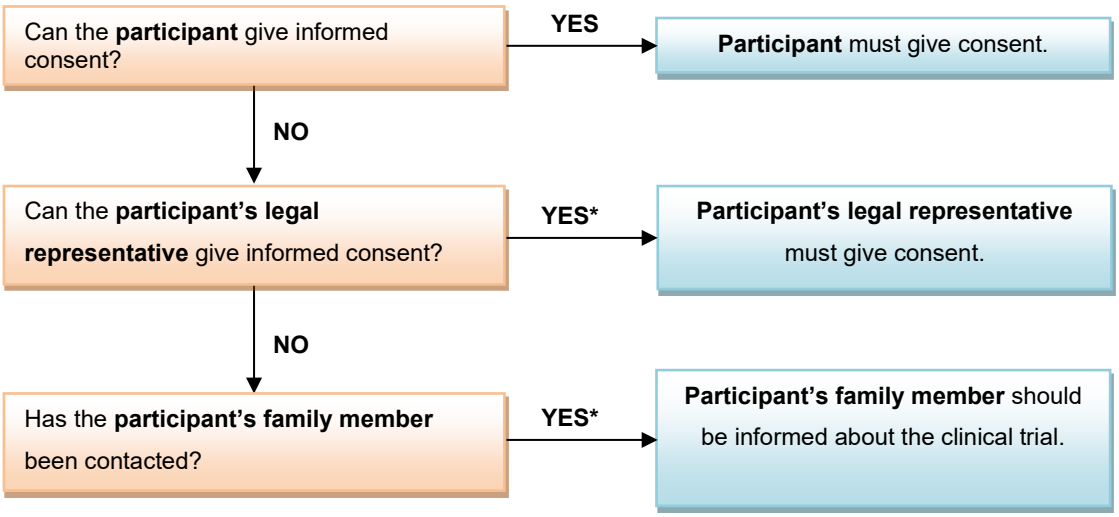


Figure 7. Safeguards and Consent Requirements for clinical trials in emergency situations (Part 2)

AFTER ENROLLMENT OF A PARTICIPANT IN A CLINICAL TRIAL IN EMERGENCY SITUATION

- The Principal Investigator must ensure that informed consent is obtained from the participant when he/she regains capacity, at the earliest feasible opportunity.
- If the participant is unable to consent, the Principal Investigator must make reasonable effort to contact the participant's legal representative, to ensure that informed consent is obtained from the participant's legal representative at the earliest feasible opportunity.
- If informed consent cannot be obtained from the participant or his/her legal representative, the Principal Investigator must make reasonable effort to contact a member of the participant's family to inform the family member about the clinical trial at the earliest feasible opportunity.



*** Despite the consent from the participant's legal representative or no objection from the family member, the Principal Investigator must continue to make reasonable effort to obtain consent from the participant or the participant's legal representative, as the case may be.**

6. REFERENCES

(i) Health Products (Clinical Trials) Regulations

(ii) Medicines (Clinical Trials) Regulations

(iii) Mental Capacity Act

(iv) Belmont Report

(v) The Patient's Consent, Prof Martin Bobrow, Bioethics Advisory Committee Singapore

(vi) European Commission's consultation document on "Ethical considerations for clinical trials on medicinal products conducted with minors", June 2016

(vii) FDA Guidance on Exception from Informed Consent Requirements for Emergency Research, March 2011

HEALTH SCIENCES AUTHORITY

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Applied Sciences Group

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