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GUIDELINES FOR HEALTH RESEARCH INVOLVING MINORS

1. INTRODUCTION

The Medical Research and Ethics Committee (MREC) recognizes the importance and need of research for development of better tools, procedures and approaches for the prevention, treatment and management of diseases and health problems affecting or beginning in minors. [1]Often it is not sufficient, scientific or ethical to carry out research with adults and apply the findings to children. This may be because:

a) The disease processes in children may differ from those in adults. Some childhood diseases have no close analogies in adults, and therefore to understand these in any detail, it is necessary to carry out research with children.
b) The physiology of children is different from that of adults, and the pharmacokinetics of many drugs will vary with the age of the child. Treatments designed specifically to meet the needs of children ensure that age-related differences in drug handling and/or effects are recognized, that the doses needed for efficacy are understood, and that any adverse effects can be avoided.
c) Many disorders can only be understood in the context of a child's growth and development. Examples include changes in the visual system following early squint, or the way the developing brain adapts to injury or damage in babies.
d) Children are not small adults. For therapy to be effective, its delivery must suit their needs. Use of adult formulations is often not suitable, e.g., many children find it easier to swallow a liquid formulation that a tablet.

In preparing this set of guidelines, the MREC has referred to the published guidelines of many other organizations and have adapted those that are deemed relevant and appropriate to health research conducted by the Ministry of Health Malaysia (MOH).

1.1 Purpose and legal context

Unless otherwise stated in Malaysian common and syariah laws, these guidelines will be followed by the MREC in the review and approval of research conducted by researchers of the MOH or other researchers using facilities of the MOH. Researchers submitting proposals for the approval of MREC are advised to understand and follow these guidelines in the planning and preparation of their study documents.

1.2 Research Involving Minors

Minors represent a vulnerable population and thus deserve special protection. Research involving minors should be conducted in an ethical manner adhering to the fundamental ethical principles of research involving human subjects[2-10]. Research should only include minors if the new information that is to be obtained cannot by

obtained by research in adults. [11]If the involvement of minors is unavoidable, the following should be considered:

- the least vulnerable among them (i.e. older children) should be selected;
- the choice of subjects should be made on the basis of the likely target of the investigational product being tested, the possibility of extrapolation, and the scientific validity of such an approach.

2. DEFINITIONS / GLOSSARY

For the purpose of these guidelines, the following definitions shall apply.

2.1 Assent

A minor's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.

2.2 Competent

[1] Having the ability, given the necessary information, to understand the nature and the consequences of the proposed procedure or treatment, and to use that information to make a valid choice in accordance with an individual's own fundamental values.

2.3 Consent

The voluntary agreement of an adult or competent individual, after having been informed of all aspects of a research that are relevant to the subject's decision to participate.

2.4 Guardian

An individual who is authorized by law to consent on behalf of a minor to participate in research.

2.5 Investigational product

A product being tested or used as a reference in a study. Includes products already with marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for an unauthorized indication, or when used to gain further information about the authorized form.

2.6 Minimal risk

[5]The probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

2.7 Minors = Child

All individuals from birth until less than the legal age of adulthood (18 years old).

2.8 Parent

A minor's biological or adopted father or mother.

2.9 Permission

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

3. RESPONSIBILITIES OF THE MREC

When considering research involving minors, where necessary, the MREC will seek advice on the relevant field of paediatric care. The MREC may approve research involving minors if the research satisfies the following conditions:

3.1 Research not involving greater than minimal risk

Such research can be approved only if there are adequate provisions to obtain the consent or permission of the parents or guardian, and assent of the minor as set forth in Part 4 below.

3.2 Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects

Such research can be approved only if:

a) the risk is justified by the anticipated benefit to the subjects;
b) the relation of the anticipated benefit to the risk is at least as favourable to the subjects as that presented by available alternative approaches; and
c) adequate provisions are made to obtain the consent or permission of the parents or guardian, and assent of the minor as set forth in Part 4 below.

3.3 Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition

Such research may involve children as subjects only if:

a) the risk represents a minor increase over minimal risk;
b) the intervention or procedure presents experience to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
c) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding of amelioration of the subjects' disorder or condition; and
d) adequate provisions are made to obtain the consent or permission of the parents or guardian, and assent of the minor as set forth in Part 4 below.

3.4 Research on healthy minors

In principle, healthy minors should not be enrolled as participants in research. However it is recognized that in some situations, studies need to be performed in minors who are healthy at the time of the trial. Prevention trials or paediatric vaccine trials, including immunogenicity studies, will fall into this category but should only include the target population likely to benefit. Whenever possible, the older age group should be considered for inclusion before the younger ones. Proof of concept should first be obtained in relevant animal models and/or in adults, whenever possible. Studies such as pharmacokinetic studies, which cannot be performed in adults, should be done in the intended population as far as possible.

4. REQUIREMENTS FOR CONSENT OR PERMISSION BY PARENTS OR GUARDIANS AND FOR ASSENT BY MINORS

Soliciting assent of minors gives them an opportunity to express their opinions and concerns surrounding participation in research. Even if minors do not have the maturity or experience to give fully informed consent to research participation, they can express a desire to be included or excluded. Assent requires that participants have a basic understanding of the research process and are informed about what they are expected to do. It implies that the minors understand what will be done to them and have been given the opportunity to express their preferences regarding participation.

4.1 Minors aged less than 7 years

i) The consent of parents, guardians or other legally acceptable representative, must be obtained for research involving minors aged less than 7 years. Assent of this group of minors is not required as they are deemed incapable of comprehending the research process, do not possess the elements that are required to make ethical decisions such as possession of personal values and goals, the ability to communicate, and the ability to reason or choose.

4.2 Minors aged 7 to less than 18 years

i) Assent must be obtained for research involving minors aged 7 to less than 18 years. Investigators must first obtained the permission of the parents or guardians for the participation of the minor in the research, and to solicit assent from the minor. Dissent of the minor must be respected even if the parent or guardian agrees to the participation of the minor except where 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; justification for this overrider must be documented in the study protocol and approved by the MREC.

ii) The permission of the parent, guardian or other legally authorized representative is sufficient for the involvement of the minor in research if the mental capacity or physical capability of the minor is so limited (such as in a state of coma or brain

damage) that the minor is reasonably unable to assent to participation. This must be documented in the study protocol and approved by the MREC.

4.3 Emancipated Minors

Exceptions to Parts 4.1 and 4.2 above are certain minors who are deemed "emancipated" and treated as adults for all purposes. Definitions of emancipated minors include those who are (1) self-supporting and/or not living at home; (2) married; (3) pregnant or a parent; (4) in the military; or (5) declared to be emancipated by a court. Emancipated minors can consent to participation in research without the permission or consent of the parent or guardian.

4.4 Consent or permission of one or both parents

i) The consent or permission of one parent is sufficient for the types of research covered by Parts 3.1 and 3.2.

ii) Where the research is covered by Parts 3.3 and 3.4, consent and permission is to 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 minor. Where opinions are strongly divided and consent or permission of both parents cannot be reached, it would be advisable to exclude the minor from the study unless a treatment option is only available as part of that programme. In such a case, every effort should be made to overcome the disagreement without a decision having to be referred to the courts.

4.5 Consent of parents who are less than 18 years old

For the purpose of Parts 4.1 and 4.2 above, if the parents are less than 18 years of age, they will only be able to give valid consent on behalf of their child if they are competent to make the decision in question.

4.6 Waiver of consent or permission of parents or guardians, and assent of minor

A waiver of consent, permission or assent as required in Parts 4.1, 4.2 and 4.3 above, can be approved by the MREC for the following situations; the reason and justification for the waiver must be properly documented in the study protocols.

i) The research protocol is designed for conditions or for a subject population for which parental or guardian consent or agreement is not a reasonable requirement to protect the subjects (for example, neglected or abused children). An alternate mechanism must be provided to protect the minors who will participate as subjects in the research. The choice of an appropriate mechanism will depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research subjects, and their age, maturity, status, and condition.

ii) Research involving minors in an emergency situation may be needed when treatment is available only as part of a research programme. Research involving minors in emergency situations should be carried out only where research of comparable effectiveness cannot be carried out on persons in non-emergency situations. The MREC must be satisfied that obtaining of consent, permission or assent is not practical or feasible for the study. The parents, guardians and minor must be informed about the research as soon as possible afterwards and their consent, permission or assent for future involvement sought. It must be made clear that the subject can withdraw from the study at any time.

ii) A waiver may be approved for research that:
   a) involves the collection or use of existing data, documents, records, pathological specimens, or diagnostics if these sources are taken in the course of health care or publicly available;
   b) is designed to answer an important question and will be impractical if the requirement of informed consent is to be imposed (note: refusal or reluctance of individuals to agree to participate is not evidence of impracticability sufficient to warrant waiving informed consent); or
   c) is designed to investigate, evaluate or examine public service programmes;

   provided the research satisfies all of the following:
   a) involves no more than minimal risk to the minors;
   b) will not adversely affect the rights, interests and welfare of the minors; and
   c) privacy and confidentiality or anonymity of the minors are assured in such a manner that they cannot be identified, directly or through identifiers linked to them.

5. ASSENT PROCESS

i) Obtaining assent is a cooperative process between children and researchers involving disclosure and discussion of the research project[12]. It is not about getting the minor "to sign on the dotted line"; rather it is about making sure they understand the trials and what it means to participate. Assent requires that minors have a basic understanding of the research process and are informed about what they are expected to do[13]. Minors require an opportunity to express their concerns and discuss their perceptions to ensure that they attach accurate meanings to the research experience. The assent discussion should be conducted by a study member who has working experience with minors.

ii) When the MREC determines that assent is required, it will also determine when and how assent is to be obtained and documented.

iii) Explanation and discussion of a study with a minor and obtaining the minor's assent should be conducted in the presence of the parents or guardians except for situation stated in Part 4.6 i).

iv) Special attention will be given to ensure that the process of assent discussion and decision does not take place under duress, nor should the process lead to distress on the part of the (potential) minor. Adequate time for discussion and reflection must be assured whenever possible.

v) While the assent of minors less than 7 years old is not required as stated in Part 4.1, nevertheless whenever appropriate, the minor should participate in the consent process together with the parents or guardians. Involving minors in discussions and the decision-making process respects their emerging maturity.

vi) Minors may indicate assent orally or sign an assent form. As a general rule, the subject should sign an assent form. When assent has been obtained orally, investigators are responsible for providing documentation or proof of assent.

vii) Where the minor is illiterate, or physically unable to talk or write, the assent form should be explained to the minor in a manner that the minor can comprehend. The assent form should document the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate in the study. An impartial third party should witness the entire assent process and sign the assent form.

6. ASSENT FORMAT

i) Separate documents are required for obtaining the consent / permission of parents / guardians and for assent of minors.

ii) The assent discussion and information sheet should contain at least a disclosure of the following in concrete and age-appropriate terms:
   a) that participation is voluntary;
   b) an explanation that what the minor is being asked to agree to is research rather than medical care per se;
   c) the purpose of the research;
   d) what they will be asked to do;
   e) what procedures they will undergo;
   f) basic risks and benefits to the minor as well as others;
   g) the minor has the right to leave the trial at any time and for any reason, without penalty or consequences; and
   h) that any information gathered will be kept confidential.

7. CONFIDENTIALITY OF INFROMATION

Where allowed by the study, information or data collected should be made available to the minor, parents or guardians. The minor may indicate dissent to disclose certain information (such as sexual experience, drug use, etc) to the parents or guardians, and the dissent must be respected.

8. REFERENCES

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