

Children's Health Queensland Human Research Ethics Committee

Decision Making Principles

2017

Over-arching Policy Framework

When considering applications for ethics approval of research the Human Research Ethics Committee (HREC) of the Children's Health Queensland uses the framework provided by the NHMRC *National Statement on Ethical Conduct in Human Research*. This policy framework can be accessed from the NHMRC web-site.

<http://www.nhmrc.gov.au/publications/synopses/e72syn.htm>

Additionally, the HREC operates within the governance framework of Queensland Health. The Office of Health and Medical Research has promulgated several key policy documents:-

a) QHealth Research Management Policy and Framework, 2008

<https://www.health.qld.gov.au/system-governance/policies-standards/doh-policy/>

b) Standard Operating Procedures for Ethics Committees

https://www.health.qld.gov.au/ohmr/documents/regu/hrec_sop.pdf

These are broad policy frameworks that provide information on:-

- Risk, benefit and Consent
- Ethical considerations specific to research methods
- Ethical considerations specific to participants
- Processes of research governance and ethical review.

It is not possible within these broad policy documents to cover the needs of unique groups such as children.

Paediatric Specific Decision Making Framework

The Human Research Ethics Committee (HREC) of the Children's Health Queensland has therefore developed a decision making framework specific to children that recognises:-

- The importance of research in children in developing safe and effective treatments that may benefit individuals who are subjects of the research but also the broader population of children
- Need for a careful balancing of benefits of developing new therapies for children against the risk of injury or death to a research subject
- Special vulnerability of children and the need to ensure their protection and safety in research studies.

The HREC has operated for over 40 years. During this time, its operations and decision making has continued to evolve informed by Position Statements and policy publications on paediatric research ethics from international bodies and professional Colleges and associations.

No research is ethical if it is scientifically un-sound. e.g.

- Study design not likely to answer the hypothesis
- Study has insufficient numbers (power) to answer the hypothesis.

As a consequence, studies considered by the HREC undergo joint ethical and scientific review.

In this regard, the HREC has taken note of (but is not bound by) seven principles enunciated by Emanuel et al (2000):-

- (1) **value**—enhancements of health or knowledge must be derived from the research
- (2) **scientific validity**—the research must be methodologically rigorous
- (3) **fair subject selection**—scientific objectives, not vulnerability or privilege, and the potential for and distribution of risks and benefits, should determine communities selected as study sites and the inclusion criteria for individual subjects
- (4) **favourable risk-benefit ratio**—within the context of standard clinical practice and the research protocol, risks must be minimized, potential benefits enhanced, and the potential benefits to individuals and knowledge gained for society must outweigh the risks
- (5) **independent review**—unaffiliated individuals must review the research and approve, amend, or terminate it. This relates to comparative or placebo controlled therapeutic research where an independent Safety Monitoring Committee is usually established.
- (6) **informed consent**—individuals should be informed about the research and provide their voluntary consent; and
- (7) **respect for enrolled subjects**—subjects should have their privacy protected, the opportunity to withdraw, and their well-being monitored.

Fulfilling all seven requirements is necessary and sufficient to make clinical research ethical.

What Makes Clinical Research Ethical?

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Reading Age of Parent Consent Information Packages

A significant percentage of the Australian population, perhaps 30%, have low levels of health literacy which refers to their ability to comprehend health related printed materials. It is thus important to be mindful of this when developing Parent Consent Information packages. The National Institutes of Health in the USA suggests materials be prepared at 6th Grade level. The Centre for Disease Control recommends materials be at 8th Grade level.

It is not possible to obtain understood consent if the parent / guardian cannot read the material.

Few people will volunteer that they have difficulty reading. A useful strategy for the person taking the consent is to ask if the person prefers to receive information orally or in writing. If they say orally, this requires the person taking consent to talk them through the document slowly and carefully.

Another useful strategy when doing this is to use the “teach-back” technique whereby the person is asked to repeat in their own words their understanding of what they have been told.

When the nature of the information that is thought to be required in the Consent Information Package is unavoidably complex, it is strongly recommended that a simplified, easy to read summary is provided. The use of diagrams and flow sheets in this summary may also be of assistance.

Microsoft Word© has the capacity to calculate the reading age of a document. It is highly recommended that this is used.

Separately, based on the experience of assessing many applications, the HREC has adopted a number of reference points for decision making. These include:-

- A requirement that before permitting research that involves administration of medications or related treatment interventions to children, the safety and efficacy of the treatment must have been demonstrated in a significant cohort of adult subjects. If the proposed medication or treatment is to be administered to infants, the HREC would not approve this unless the safety and efficacy has first been established in older children.¹
- In general, Phase 1 studies will not be approved in children¹. The only exception being for diseases or conditions that only occur in children.
- For trials of new vaccines, the HREC expects to see safety and efficacy data on a minimum of 500 adults before considering approval for use in children. The only exception being a vaccine for infections that only occur in children
- The HREC does not permit the use of advertisements to attract paediatric research subjects who suffer from any particular medical condition or illness
- The HREC does not permit the use of advertisements for healthy children to act as controls if the control subjects would receive any medication or treatment
- The HREC will not approve any research study that involves administration of sedation or general anaesthesia to health control subjects
- The HREC will only approve the use of sedation or anaesthesia for research subjects where this is clinically indicated as a part of their clinical treatment and consistent with Clinical Best Practice Treatment for that condition
- The HREC approves the payment of reasonable and appropriate out-of-pocket expenses for parents of children who participate in research studies. The HREC does not permit monetary or similar inducements for children to participate in research studies¹. The child's participation may be rewarded with a certificate
- A requirement for approval of a research study is that the researcher gives an undertaking that it is their intention to submit the results for presentation or publication
- The HREC requires researchers to adhere to a policy in regard to the collection of blood tests for research purposes (See attached). Aside from restricting the volume of blood collected, the general principles of the HREC in this regard are:-
 - every attempt be made to minimise discomfort to the child e.g. use of EMLA cream or a similar product
 - where practical, the collection of blood for research purposes be coordinated with the collection of blood for routine clinical purposes
- In any situation where there is a direct or potential conflict between the child's interest and the research interest, the child's interest should always prevail over that of research¹.
- No child should participate in a study unless a benefit to children in general will result¹
- Placebo controlled trials are inappropriate in paediatrics when risk would be increased by withholding a known effective treatment¹.

- Expected benefit must exceed recognisable risks¹
- If a child under the medical care of another doctor is recruited into a therapeutic trial it is strongly encouraged that the child or young person's treating doctor is informed of the child's participation and the study contact person in the event of problems arising
- It is highly desirable that the child or young person's treating doctor not be involved in taking informed consent for participation in a research study. This is because of the power imbalance inherent in the doctor – patient relationship
- It is mandatory that researchers disclose any conflict of interest to the HREC
 - Examples include paid consultancies, share-holding, patent ownership etc
- If the researcher is receiving payment from a third party for participation in the study, it is mandatory that this information be included in the Consent Information documents:
 - If the payment is used to support research infrastructure and other unfunded projects within the Department or by the researcher a statement to this effect should be included
 - If the researcher will obtain direct personal benefit from the payment, it is mandatory that this is disclosed in the Consent Information Package

While many of these reference points for decision making have evolved over the time the HREC has operated, many of these principles are now supported by recently published international guidelines, particularly the European Union Guideline *Ethical Considerations for Clinical Trials Performed in Children (2006)*¹

Guidance on Informed Consent

It is a requirement that the beginning of any informed consent information package contain a statement to the effect that "This is a research study and participation is optional. It is ok to say no."

In any invitational statement in the Informed Consent package, the Committee has a strong preference for "You / your child are being asked / requested to participate" rather than "You are being invited to participate"

Blood Sampling Guideline

The HREC provides the following guideline for investigators to consider when designing a protocol that involves drawing blood from subjects. This guideline is based on a guideline in use at *The Children's Hospital, Boston*.

- Up to 5% of the whole blood volume may be removed over an 8 week period, on a single occasion or in divided portions, from human subjects in good health and with a hematocrit of not less than the low normal value for age.

The table below shows values for mean blood volume based on age.
(Geigy Scientific Tables, 7th Ed.)

Age	Mean blood volume per weight (mL/kg)
Newborn, 15-30 minutes of age	76.5
Newborn, 24 hours	83.3
Children, 3 months	87
Children, 6 months	86
Children, 1 year	80
Children, 6 years	80
Children, 10 years	75
Children, 15 years	71

$$\text{Weight (kg)} \times \frac{\text{Mean blood volume (mL)}}{\text{weight (kg)}} \times 0.05 = 5\% \text{ of whole blood volume}$$

Example:

- Determine *Mean blood volume per weight* based on age of child
e.g. A 3 month old child will have a *Mean blood volume per weight* of 87 mL/kg
- Multiply the *Mean blood volume per weight* times the child's weight
e.g. For a 3 kg child, multiply 87mL/kg x 3 kg = 261mL (261mL is the child's total blood volume)
- Multiply the child's total blood volume by 5% (0.05) to obtain *5% of the total blood volume*
e.g. 261mL x 0.05 = 13.05 mL

Thus, 13.05 mL is the total amount of blood which may be removed from a 3 month old child who weighs 3kg.

- Additional volumes of blood may be removed in subsequent 8 week periods using the same criteria, as long as the subject remains in good health and maintains a hematocrit level of not less than the low normal value for age.
- If blood samples for research purposes are to be obtained at the same time a clinical sample is drawn, or if it is expected that additional clinical samples will be taken during the 8 week period, the total amount of blood (research and clinical) should not exceed 5% of whole blood volume, unless specifically approved by the HREC. For this reason, investigators must know and take into consideration clinically indicated blood drawing requirements for potential subjects.

6. The amount of blood drawn should be limited to that needed to meet the goals of the particular study.
7. Whenever the volume of blood to be removed will exceed 1% of whole blood volume of the subject, hematocrit should be checked in advance to determine that it is not less than the low normal value for age. The frequency of monitoring hematocrit levels should be commensurate with the volume of blood to be removed, and the estimated vulnerability of the subject to blood loss.
8. If a subject may not be in good health, and in particular may have a cardiovascular, pulmonary or hematopoietic problem, the volume of blood to be removed should be adjusted accordingly.
9. If the study protocol necessitates that the volume of blood to be removed exceeds the above criteria recommended for subjects in good health, or that the volume cannot be reduced in consideration of poor health or low hematocrit level, the CCI will consider approving the project only if the added risk can be justified by the expected direct benefit to the subjects.
10. Whenever possible, blood should be taken at the same time that a clinically indicated blood draw is performed.
11. The estimated volume and frequency of blood to be removed, risks associated with blood removal, and the measures to be taken to minimize those risks should be included in the research consent form.
12. Measures to minimize the risk of a potential reaction to a blood draw should be taken. Use of EMLA cream is recommended to minimize pain (optional).

Document history

Version	Date	Changed by	Nature of amendment
1	8/10/14	Amanda Smith	Original.
2	9/7/15	Amanda Smith	Minor administrative amendments.
3	14/1/16	Amanda Smith	Minor administrative amendments.
4	5/4/17	Alan Isles	Addition of information.