APREG

AUSTRALIAN PAEDIATRIC RESEARCH ETHICS & GOVERNANCE NETWORK

Clinical trials, the child participant and consent:

A practical guide for investigators and sponsors

Contents:

1. Background and Purpose

APREG
The Australian Paediatric Research Ethics and Governance (**APREG**) Network was established in 2013. APREG formalised a commitment, within Australian paediatric public health organisations, to streamline the ethics and governance review of multicentre projects using the National Mutual Acceptance (**NMA**) Scheme. APREG aims to identify opportunities for collaboration and project initiatives in the ethics and governance of paediatric research.

The members of the APREG Network are The Sydney Children's Hospitals Network, Sydney; Hunter New England Local Health District, Newcastle; The Royal Children's Hospital, Melbourne; Monash Health, Melbourne; Lady Cilento Children's Hospital, Brisbane; Mater Hospital, Brisbane; Women's and Children's Health Network, Adelaide; and Princess Margaret Hospital, Perth.

Child consent to participate in medical research:

Unlike other jurisdictions around the world, the ability for a child and/or young person to consent to participate in medical research (as opposed to medical treatment[1]) is not yet described in Australian law; nor has it been tested before the courts. It is unclear whether the legislative and common law principles that apply to a child and/or young person consenting for medical *treatment* can, or should, be applied to their ability to consent to participate in medical research[2]. The National Health and Medical Research Council's (**NHMRC**) *National Statement on Ethical Conduct in Human Research* (2007) (**National Statement**) reflects this legal uncertainty. For example, section 4.2 of the National Statement suggests parental consent is required for a child to participate in a clinical trial, but remains silent on child assent.

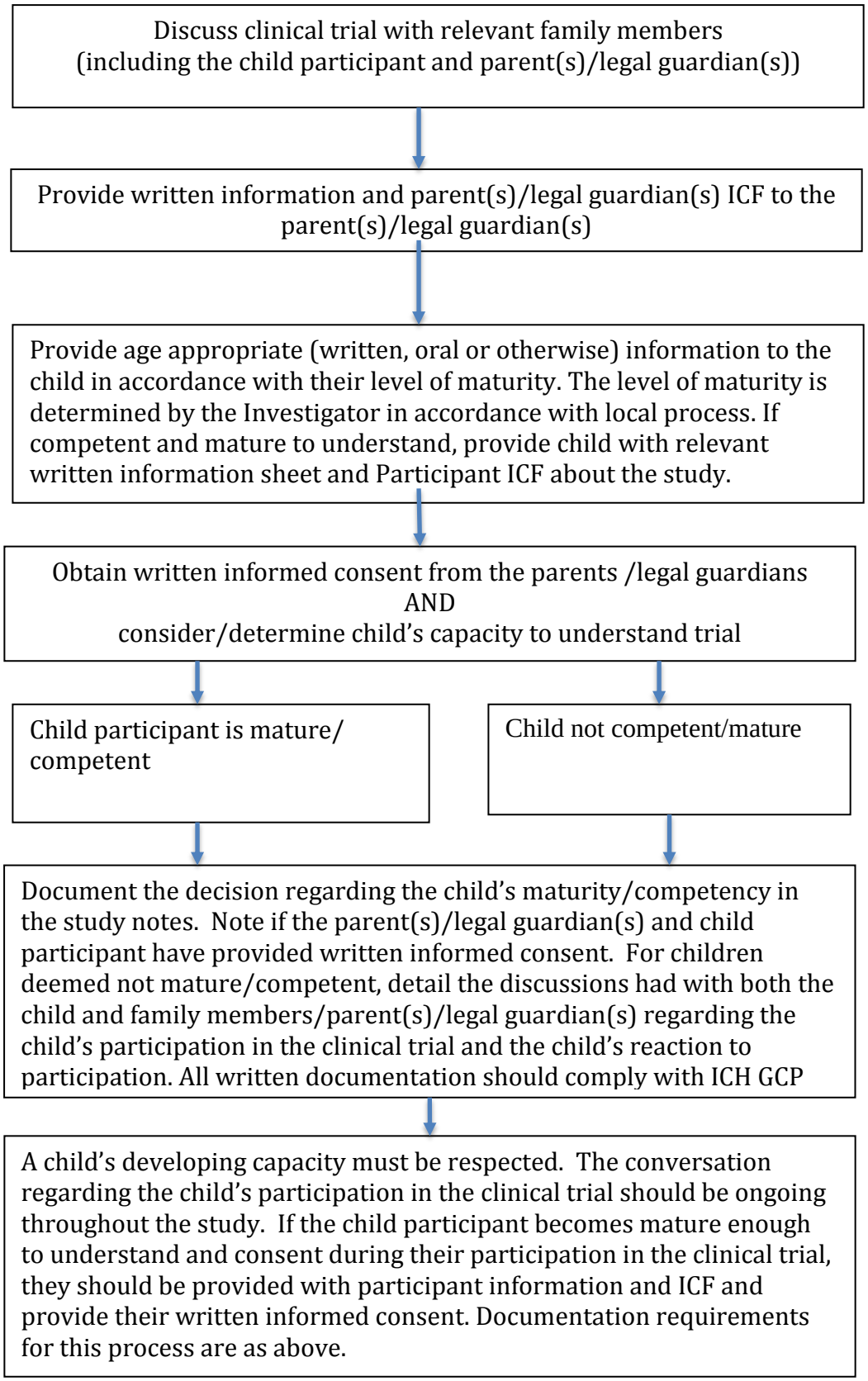
In light of the legal uncertainty, and giving due consideration to the National Statement, the purpose of this guide is to provide guidance and clarity to sponsors and researchers on the practical aspects of seeking informed consent in paediatric clinical trials. The views in this paper are considered *best practice* by the APREG members. The guide is not intended to be absolute or exhaustive, and does not constitute legal advice. APREG strongly recommends this document is read in conjunction with relevant sections of the National Statement and local legislative or policy requirements (if any).

All proposed recruitment strategies and information provided to participants will be subject to the review and approval of the Reviewing Human Research Ethics Committee (HREC).

2. Definitions and Abbreviations

APREG	Australian Paediatric Research Ethics and Governance Network
CHILD	Minor / young person / person under 18 years. ('Child' will be used throughout this guide)
GCP	Good Clinical Practice
HREC	Human Research Ethics Committee
ICF	Informed Consent Form (*NB: the ICF and any written information provided to participants must be approved by the Reviewing HREC*)
ICH	International Conference on Harmonisation
INVESTIGATOR	Person responsible for the conduct of the clinical trial at the site ('Investigator' will be used throughout this guideline and, where relevant or the context requires, includes those with delegated responsibility and the Coordinating Principal Investigator for NMA studies)
National Statement	*National Statement on Ethical Conduct in Human Research* 2007
NHMRC	National Health and Medical Research Council of Australia
NMA	the National Mutual Acceptance scheme for the ethical and scientific review of human research, applicable in participating jurisdictions only (currently, New South Wales, Victoria, Queensland, South Australia and the Australian Capital Territory)
Reviewing HREC	the HREC responsible for the ethical and scientific review and approval of the clinical trial at a site or at multiple sites under NMA
RGO	Research Governance Officer
TGA	Therapeutic Goods Administration of Australia

3. Flow Chart: Obtaining consent



Guide: Obtaining consent

A child's immediate and extended family may be impacted by a child's participation in a clinical trial. The child participant may need to come to the hospital for multiple study visits, missing school and sporting activities, and require parents and carers to transport them to study visits. Children, parents/legal guardians and other family members who may be impacted by a child's participation in a clinical trial should be involved in a conversation, and reach consensus, about the child's participation in the study.

1. Who must provide written informed consent to participate in a paediatric clinical trial?

(i) Written informed consent must be obtained from the parent(s)/legal guardian(s) of the child participant

AND

(ii) Children, deemed by the investigator to have the requisite capacity and maturity to understand the nature and demands of the research, should also be asked to provide their written informed consent to participate in the research. This informed consent can either be obtained on their own ICF or by counter-signing the parent(s)/legal guardian(s) ICF.

2. What written information should be provided to the parent and child?

Parent(s)/legal guardian(s) should be provided with written information and the Parent ICF.

Children deemed by the investigator to have the requisite capacity and maturity to understand the nature and demands of the research should be provided with written information (as below) and a Participant ICF.

Children not yet mature or competent to provide written informed consent should receive age appropriate information about the proposed clinical trial. This information should highlight in particular any risk and/or benefits of their participation in the study. The information provided can be in written or other form, as may be determined by the investigator and approved by the Reviewing HREC (see also below).

3. Should the written information provided to the child participant differ from the written information provided to the parent(s)/legal guardian(s)?

This answer assumes that the investigator has determined that the child has the requisite capacity and maturity to consent.

If you are seeking the informed consent of a child, the information provided to the child must be sufficiently detailed in order for informed consent to occur. Generally, this information should mirror the information provided to the parent(s)/legal guardian(s).

Where an investigator determines that a child does not have the requisite competency or maturity to provide informed consent, the child should be provided with age appropriate information. A written information sheet is a useful tool to assist communications between the investigators and the child regarding the study., Other tools such as short videos, presentations, pictures, and/or story books are means by which investigators can help explain the study to the child.

Any information provided to participants and their families must first be approved by the Reviewing HREC.

4. What age must you provide written information to the child about the clinical trial?

APREG recognises the developing maturity and capacity of a child and does not provide guidance concerning a minimum age of when a participant information sheet or ICF should be provided to the child participant. This should be determined by the investigator on a case by case basis, and will vary with the type of clinical trial and level of maturity of the child participant.

5. What else should be documented during the consent process?

On completion of the informed consent process, a note should be written into the participant's medical record and/or study file by the person who performed the consent process. At a minimum this should confirm:

a. the date that the consent process took place;
b. who took consent;
c. who was consented;
d. that the person(s) involved in the discussion, and in particular those providing informed consent, have understood and were given the opportunity to ask questions (i.e. the parent only or the parent and child participant). Ideally, the notes would include documentation of any questions asked and the answers provided; and
e. that a copy of the signed ICF has been provided to the parents/legal guardians and participant (where applicable).

Investigators should also include in this note discussions conducted with the child and the decision made by the investigator regarding the child's capacity to provide informed consent. A record of any conversation about the study with the "immature" child should also be documented in detail.
All documentation for a clinical trial should be completed in accordance with the principles embedded in the ICH GCP guideline as a minimum standard.

6. What is meant by 'continuing consent'?

The informed consent process does not cease once an ICF has been signed. The practice of providing information is an ongoing process throughout a research study. If, during the course of a study, new information becomes available that may be relevant then that information must be presented to the participant and

their parents/legal guardians in an appropriate manner (e.g. in writing) and at the earliest possible opportunity. The parents/legal guardians and participant (where applicable) should be asked to re-consent by signing the revised ICF.

If a child becomes mature and competent to provide consent during their participation in a clinical trial, the investigator should take the opportunity to revisit the informed consent discussion and seek the participant's written informed consent.

This is particularly relevant to longitudinal studies, where it is likely that a participant will reach the age of majority during the term of the research. In such circumstances, researchers should proactively document:

(i) How and when the consent process will be re-visited.
(ii) What the involvement of the parent/legal guardian will be;
(iii) How the transition from parent/legal guardian consent to participant consent will be managed.

All study documentation must be approved by the Reviewing HREC and Site Authorisation provided, before it is given to participants or their parent(s)/legal guardian(s).

7. What ICFs should be submitted to the reviewing HREC for paediatric clinical trials?

(i) Parent/Legal Guardian ICF which may have provision for the child to co-sign.
(ii) Participant information statement and optional ICF for those children deemed to have requisite capacity and maturity to consent.
NOTE: Researchers should demonstrate respect for parent(s)/legal guardian(s) and participants by using age appropriate language, generally a reading age of 12 years old.
(iii) Participant information (without an informed consent form) can be provided for younger (immature) children to assist the discussion process.

4. Frequently Asked Questions

Q1: Do APREG members' sites and HRECs require assent forms?

If a child does not have the requisite capacity and maturity at the time of consent they should still be provided with information and an opportunity to express their view about their participation.

Assent is an appropriate term to describe a child's agreement to participate in a research study where that child does not have the requisite capacity to provide informed consent. However, the term "assent" has no legal standing in Australia and is not recognised in the National Statement. APREG does not recognise the term assent and assent forms are not required.

Q2: What if a parent and child's view regarding participation in the clinical trial conflict?

It is, in our experience, a rare occasion where the parent(s)/legal guardian(s) and child disagree about the decision to participate in a clinical trial. A child's decision not to participate must be respected. If the decision of participation cannot be agreed upon, further advice may be sought from the Reviewing HREC.

It is optimal that all family members contribute to the discussion about their child's participation as this will ultimately lead to greater study compliance.

Q3: What if the parent of the child participant is under 18 years?

Generally, a parent can consent for their own child's participation in a study irrespective of that parent's age, unless a court order is in place to state otherwise.

Q4: Who signs the informed consent form when a child's parents are separated?

It is best practice wherever possible to involve both parents in the decision making. However, generally only one parent's signature is required on the ICF.

The *Family Law Act 1975* (Cth) provides that a parent with a parenting order can consent to medical treatment on behalf of their child. Currently, consent for medical research generally follows these principles. If there is no parenting order in place either parent/ legal guardian can consent. There are penalties for parents who do not comply with an existing parenting order.

Q5: Does evidence of guardianship have to be produced at the time of consent?

No. If the child's parents are separated, the person conducting the consent process may ask if a parenting order is in place and if so reaffirm that the order must be followed. If an investigator is concerned about the validity of a parents' claim, or a claim of guardianship, they may request that the parent (or guardian) provides evidence to confirm their claim. An appropriate note should be placed on study records to confirm that evidence was provided.

Whilst determined on a case-by-case basis, where the investigator is aware of any conflict between parent(s)/legal guardian(s)/separated parents, unless there is clear evidence that the clinical trial will benefit the child it is generally best to *not* enrol the child in the clinical trial.

Q6: Can investigators request exemption from parental consent?

Yes. Section 4.2.8 of the National Statement allows the Reviewing HREC to approve a study where only the child (young person) consents. The Reviewing HREC must be satisfied the child/young person is mature enough to understand and consent

In all other circumstances, parental consent must be obtained for all children under 18 years.

Q7: How can I determine if a participant or their parent(s)/legal guardian(s) has understood what their participation will involve?

The informed consent process should be full, open and honest. It should be pitched at the level appropriate for the person/people you are talking to. Ideally, it would involve a two-way conversation between the investigator and the participant/parent(s)/legal guardian(s). For example, for a randomised control clinical trial involving a placebo, the investigator could ask questions such as '*do you understand that you/your child may get a placebo?*' / '*do you think that you/your child will definitely be getting the [active] medicine?*' / '*what do you understand about randomisation?*'. The information statement should be used as a reference point for these conversations.

5. References

1. UK Medicines for Human Use (Clinical Trials) Regulations 2004. A minor is defined as a child of less than 16 years of age. A person with 'Parental Responsibility', or a legally authorised representative, is required to provide consent on behalf of a 'minor,' even if s/he has evidential capacity, and the assent of the 'minor' should also be sought. Consent must be obtained from those over 16 years, and from participants reaching the age of 16 years during the course of a study.
2. Kirraley Bowles, *Age of Consent to Medical Treatment*, Find Law Australia, www.findlaw.com.au 27.10.2014

Resources

- Assent Task Force, Children's Oncology Group, *Guidelines for Involving Children in the decision-making about Research Participation*.
- Charles Thompson, MD, Pfizer Inc, New York, NY; Sharon Smith, MD, Connecticut Children's Medical Center, Hartford, CT; Philip Sjostedt, BPharm, The Medicine Group, New Hope, PA; Donald P. Lombardi, Institute for Pediatric Innovation, Cambridge, MA; Members of the iCAN Network, ***Assent in Pediatric Clinical Trials: An International Children's Advisory Network (iCAN) Survey***
- NHMRC National Statement on Ethical Conduct in Human Research (2007) (Updated May 2015)
- http://www.familycourt.gov.au/wps/wcm/connect/fcoaweb/reports-and-publications/publications/court-orders/parenting-orders-obligations-consequences-and-who-can-help 9 November 2015.
- Regulation (eu) no 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing directive 2001/20/ec (text with eea relevance)
- The Sydney Children's Hospitals Network Consent Procedures (2015)

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