Alternative and waived consent in Neonatal Trials

HREC Conference 2023

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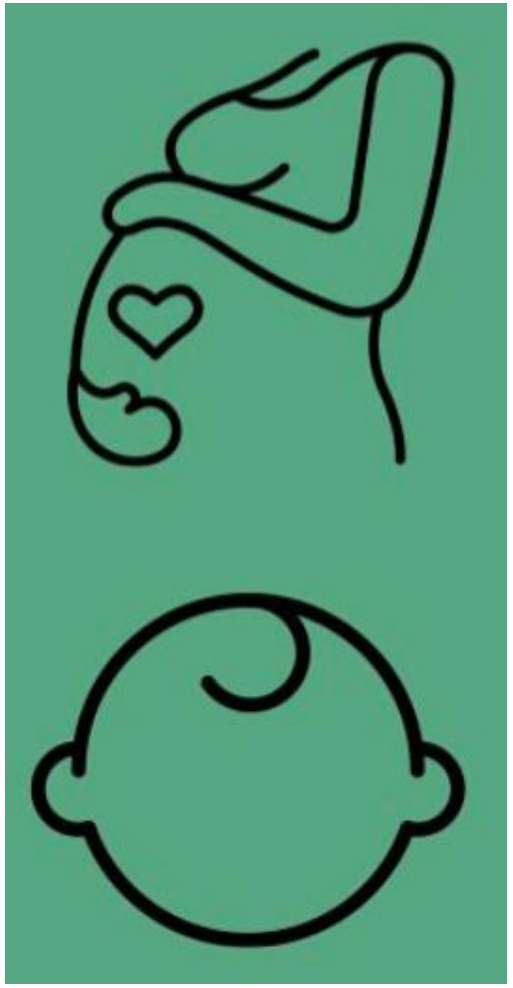
- Challenges with consenting for neonatal research
- Alternative and waived consent models in neonatology
- When is a trial low risk?
- Parental views on alternative consent modes

Challenges with consenting for neonatal research

Neonatal care in 2023

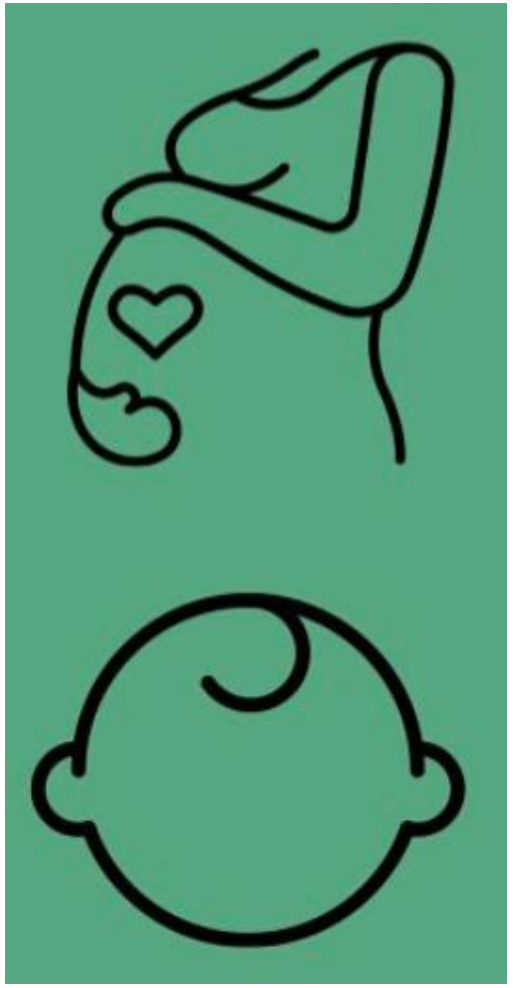
- Approx 15 million babies born preterm each year (<37 weeks), 1 million will die
- Approx 1 in 10 infants born preterm or unwell requiring admission to neonatal unit
- Many interventions need to be done urgently in the delivery room (eg: resus) or the first hours of life
- While the majority of infants do well, a high rate of mortality or long-term disability persists in the most extremely premature infants

Clinical trials in high risk or vulnerable groups



- Pregnant women and infants are often excluded from research
  - Sickest and most premature infants are often excluded from neonatal trials
  - Many emergency neonatal therapies never rigorously tested
  - majority of medications administered to infants are used outside of their terms of licence
  - “[Newborn] resuscitation has evolved based on extrapolation and assumption rather than clinical measurement.” A.D Milner. Arch Dis Child 1991

Clinical trials in high risk or vulnerable groups



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Public consultation on Section 4 of the National Statement

Why is consent in Neonatal research so tricky?

Research in emergency setting (including delivery room)

Issues of opportunity, feasibility and ethical appropriateness:

- Lack of time
- Parental absence
- Diminished parental decision-making ability: labour, pain, medication, anxiety, distress
- Therefore parental presence ≠ ability to participate in an informed consent discussion

Challenges with prospective consent in emergency research

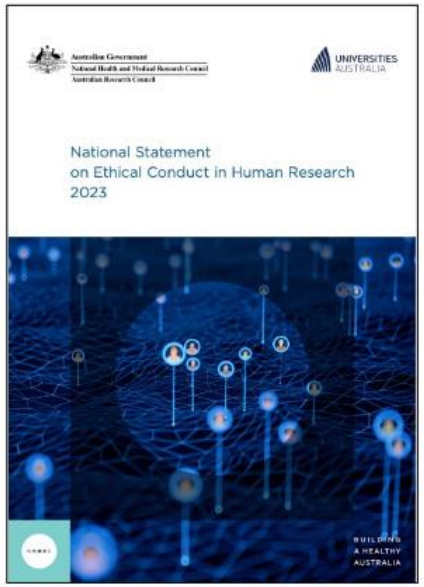
- Slow recruitment and recruitment failure common
  - TO2RPEDO study → abandoned at 15% recruitment

- Biased patient recruitment
  - Mothers missed are younger, less educated, less antenatal care and less protective medication for the fetus before delivery
  - Babies missed more preterm, smaller, less ANS, lower apgars, more resus, higher mortality and morbidity
  - Eg: APTS, SUPPORT, HEAL
  - Study results are often not applicable to the smaller and sicker babies who are most in need of the study intervention → wasted research

How can be overcome consent challenges?

Enhance existing prospective consent methods

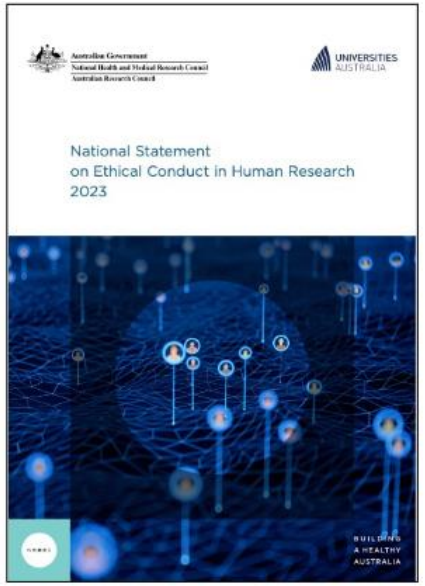
- Educate researchers
- Simplify consent forms



Consider appropriateness of alternative approaches:

- consent waiver +/- prospective assent
  +/- retrospective/deferred consent for ongoing participation
- opt-out consent

Opt-out consent



Permissible in Australia since 2014

- Research information provided widely
- Participation presumed unless action taken to decline
- Otherwise: once participants eligible – they are enrolled

- Low risk studies
- Data collected must be non-identifiable
- Scale / significance means that using explicit consent ≠ practical / feasible

Opt-out consent

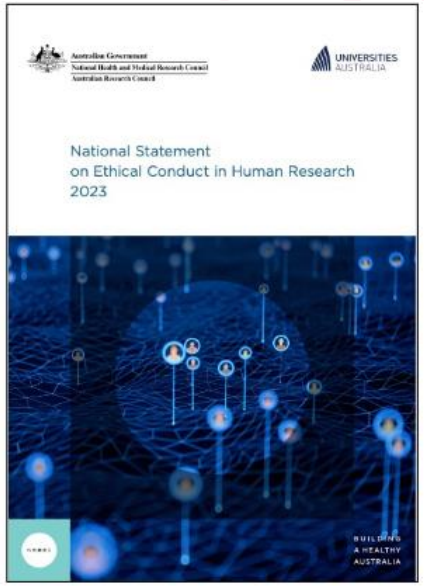
- If research is compromised when participation rate is not near complete
- Reasonable attempts to provide appropriate information and procedure to decline/withdraw
- Reasonable time period between provision of information before research begins for opportunity to decline (ie: not for true emergencies)
- Mechanism provided to obtain further information and decline

Opt-out consent

- Public research interest outweighs public interest in privacy protection
- Collected data managed according to security standards
- Not prohibited by law

Waiver of consent

- ‘When neither explicit consent nor an opt-out approach are appropriate, the requirement for consent may sometimes be justifiably waived’
- ‘When granted a waiver of consent, participants will characteristically not know that they are involved in the research…’
- Waiver for:
    1. study treatments only (deferred/retrospective consent)
    2. Study treatment + data collection (full waiver)



Waiver of consent requirements

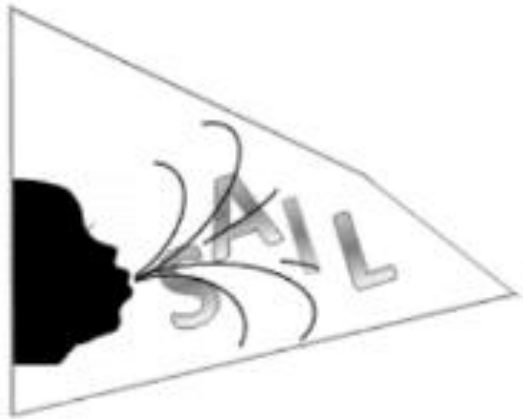
- Research no more than ‘low risk’
- Benefits of research justify risk of harm associated with not seeking consent
- Impractical to obtain consent
- No known/likely reason for thinking that participants would not consent

- Sufficient data protection/privacy/confidentiality
- If results significant to participant welfare - information made available
- Not prohibited by law

When is a trial ‘low risk’?

- Level of risk depends on what kind of research is being done:
  - Non-therapeutic research → minimal/no risk to participant
  - Therapeutic research
    - Novel treatments → additional risk above routine clinical care
    - Comparative effectiveness trials (pragmatic clinical trials) → minimal additional risk above routine care[1]

Waived consent for study treatment



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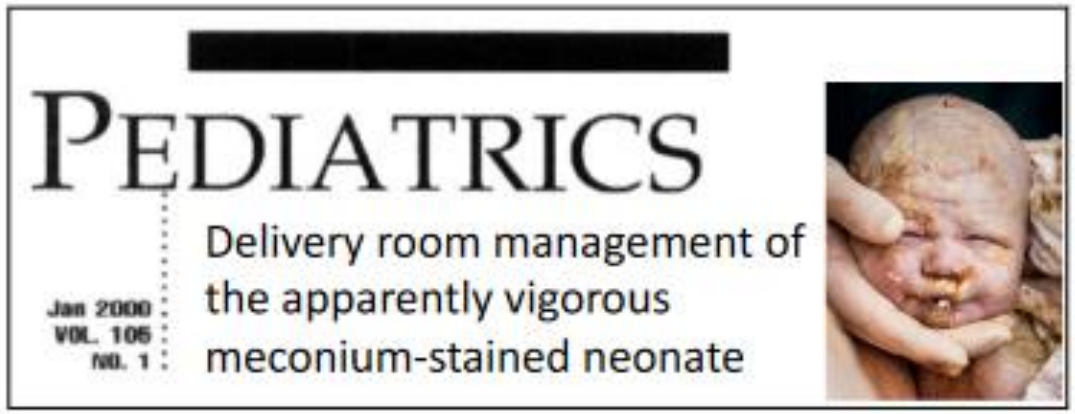
Full consent waiver



Concerns with waiver of consent

1. Potential for psychological harm arising from infringements of a patient's right to autonomous choice
   - Needs to be a low-risk intervention and a high social value of the trial to outweigh this potential harm
   - High social value = ability of the trial to generate real world evidence with a high chance of improving care or reduce healthcare costs, and a high probability of uptake by clinicians/decision makers
   - Patient preferences for a choice will differ for different treatments and patient subgroups → consumer involvement in trial design (including diverse/vulnerable groups who may be less trusting of healthcare and research)[9]

Concerns with waiver of consent

2. Slippery slope argument for uncontrolled use of alternative consent
   - Response: Example of waiver for observational research – scope defined by law, transparent and tightly controlled conditions
   - Response: Open publication of info on all trials granted alternative consent

What do parents say?

Review of studies by Katheria et al 2023:

- They want to know they are entering a study
- In the NICU setting, just over half considered prospective consent as too stressful and unwelcome
  - Only 1/3 of people recall the antenatal consent
- In most studies, majority were accepting of alternative consent models if research not possible without them
- If the infant is less unwell, benefits of the trial might be seen to be less and therefore reducing autonomy is less justified

Don’t throw the baby out with the bath water

- Maintaining respect for participants and parents even if prospective consent isn’t used
  - Exploring opportunities to inform about potential emergency research during routine antenatal care
  - Employing opt out consent rather than a waiver for non-urgent low risk interventions
- Mixed models of consent
  - Benefits: maximising opportunities for autonomy while avoiding biased recruitment
  - Risks: confusion and loss of trust → good communication training for research and clinical staff

Take home messages

- Prospective informed consent is the gold standard but can be challenging or impossible in some neonatal emergency trials
- Alternative consent processes are vital for some types of neonatal research
- Comparative effectiveness trials (pragmatic clinical trials) are considered low risk
- Parents are generally accepting of alternative forms of consent for emergency research
- Maximising opportunities to inform parents, and consider mixed modes of consent

Thank you

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