ETHICAL DILEMMA

Insisting on prospective consent in paediatric critical care research may be throwing the baby out with the bathwater

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Australia’s National Health and Medical Research Council (NHMRC) recently sought public consultation regarding revisions to Sections 4 and 5 of The National Statement on Ethical Conduct in Human Research (The National Statement). Section 4 refers to ethical considerations for potentially vulnerable research participants, including patients in emergency and intensive care.1 The draft provides updated definitions of vulnerability: describing it as existing on a spectrum and dependent on circumstances, as opposed to labelling specific groups as vulnerable. It addresses researchers’ ethical obligations to conduct inclusive research with representative samples, so results are generalisable to a wider population. Ambiguous and contradictory sections of the draft remain: particularly relating to emergency and intensive care research participants, and the use of what is often labelled ‘delayed’ or ‘deferred’ consent.

‘Deferred consent’ occurs when a patient is enrolled in a trial and treated according to trial protocols before explanatory discussion or request for consent has occurred. The concept has variously been labelled ‘delayed consent’, ‘consent to continue’, or ‘research without prior consent’. A distinction should be made between the terms ‘deferred consent’ and waiver of consent. Waiver, as referenced in The National Statement, refers to any research occurring without prospective consent, thus encompassing deferred consent.2 While a waiver of consent may include research that never obtains consent from a participant or legal guardian, deferred consent implies consent is obtained at some stage following the intervention.

Accurate definitions of consent processes and clear guidelines to support HRECs are needed to facilitate research with urgent interventions. Children as participants add another layer of complexity to the consent process. Researchers conducting studies focused on critically ill children presenting to emergency departments or intensive care units face an ethical dilemma. Many lifesaving interventions do not allow time for informed, prospective consent to be obtained from parents or legal guardians. All critically ill children are entitled to medical care based on the best available research evidence.3 Restrictive legislation around informed consent in Europe and the USA led to a significant reduction in paediatric clinical trials with emergency interventions.4 As a result, it is a commonplace for children to undergo emergency treatment not supported by quality scientific evidence.3 For research findings to be generalised to a paediatric critical care population and for translation of research evidence into practice, trials need to be conducted pragmatically, in severely ill children requiring emergency care.4,5

This paper explores the practical and ethical challenges to consent in paediatric critical care research and proposes some pragmatic guidance that could be included in the NHMRC National Statement. A literature search of Embase, PubMed, Scopus, CINHAL Complete and Medline was undertaken in 2020 using identified search terms, keywords and Boolean phrases. The P说的是流模式图 (Fig. 1) summarises the articles from identification to inclusion.

Why the National Statement Needs to Facilitate Clinical Research in Paediatric Critical Care

There exists a well-established need for high-quality clinical research in the paediatric intensive care population.5–10 Rigorous research evidence informs clinical decision-making and advances medical knowledge while ultimately saving lives and decreasing the morbidity of critically ill infants and children. The best available care needs to be underpinned by well-conducted studies unique to this clinical area.9

A general lack of research evidence in the paediatric critical care population has resulted in the most vulnerable and severely ill patients often being subjected to untested medical procedures and medications.6 Tasker et al.11 found approximately only 1% of children admitted to paediatric intensive care were enrolled in randomised controlled trials. Current literature indicates off-label paediatric prescriptions occur in Europe at a rate of 45–60% with rates as high as 90% for paediatric and neonatal intensive care patients.12 In an effort to protect the research rights of sick children with insistence on prospective-only consent, the same children may paradoxically be exposed to a risk of potential harm caused by treatment and medicines that are not proven safe.13 For many medications and medical interventions, data simply do not exist for paediatric populations.
Challenges to Prospective Consent in the Paediatric Critical Care Environment

The concept of prospective informed consent from a parent or legal guardian as a principle of ethical paediatric research is a fundamental of good clinical practice intended to protect the safety and rights of all potential research participants. Prospective informed consent in research requires adequate and accurate disclosure of the study; capacity of the participant or proxy for decision-making; and a completely voluntary willingness to participate not subject to coercion or time pressures. Identified challenges in paediatric critical care research are widely published and include: the absence of a parent/guardian; time constraints when the intervention needs to occur in a narrow therapeutic window; and overwhelmed parents/guardians suffering intense emotional distress which may affect the capacity to provide consent. It is possible that these challenges have not been considered in the proposed draft of The National Statement.

Frequently a parent/guardian is not present, especially if the child has been retrieved or arrived by ambulance. Child victims of trauma may be unaccompanied as their parent/guardian may have been injured, or even killed, in the same traumatic event.
A study of traumatic brain injuries found children arrived within 1–2 h of injury, but parents did not arrive until 2–3 h or more later.8 Paediatric care strives for a family centred approach and every effort is made to keep children with a carer including during transport. It is not always possible to transport a family member with the child. Space and weight restrictions of retrieval vehicles and medical needs of other family members if also injured may be contributing factors.

Children in foster care may have guardianship orders in place requiring considerable time to obtain consent from the appropriate authority. Kinship is not recognised as guardianship in many jurisdictions.6 Children may be cared for by extended family members, their ‘kin’, who do not necessarily have legal guardianship of the child, thus preventing them from providing consent. In some situations, the child’s understanding of who their parent is, is at odds with the legal definition of who their responsible adult is.

Parental/Guardian distress and capacity to consent to research in an overwhelming environment poses a real challenge in the paediatric critical care setting. ‘Situational incapacity’ describes the inability to absorb or process information and make an informed decision in a stressful situation.7 Some guardians may be incapable of prioritising research information over concern for their child’s immediate wellbeing and may have difficulty making a fully informed decision about their child’s participation in research.3,4,6,7 The need for prospective consent may also result in parents/guardians feeling a degree of coercion or compulsion to participate especially if the child requires urgent care.8

Within the philosophy of family centred care, parents/guardians should also be recognised as a vulnerable population. The requirement for prospective informed consent in this complex population may be asking too much of potential participants and their parents/guardians, and alternative consenting processes need consideration to progress research in this context.

Interestingly, the concept of situational incapacity is often not considered regarding consent for clinical procedures, perhaps because the treatment is considered in the child’s best interests3 but also likely that clinicians recognise that it is ethical to sensitively time information giving and clinical conversations.

**Ethical Considerations**

The proposed changes to Section 4 of The National Statement remain equivocal in reference to deferred consent. This ensures ongoing ambiguity in reference to deferred consent. This supports against deferred consent suggesting it undermines autonomy by diminishing the right to voluntary participation in research.16 Several sources challenge the term ‘deferred consent’ as a misnomer since it is unfeasible to obtain permission to perform an intervention that has already occurred, and it may be contradictory to treating patients with respect.3,11 Miller17 proposes the concept is nonsensical and should be more accurately termed ‘ratification’. He suggests deferred consent implies the right to refuse but it is impossible to refuse something that has already happened and there is no justification for placing patients at risk in the interests of future patients or for the benefit of health-care advancement. Brierley and Larcher1 write that although the failure to provide information prior to consent may not incur physical harm, it may still result in negative consequences such as a distrust of researchers and ethical processes.

However, there needs to be a balance between autonomy and respect for persons, and the right of vulnerable populations to justice, including the opportunity to be included in research despite being unable to provide informed consent.9,16 Proposed changes to The National Statement specifically refer to conducting inclusive research in representative samples. Ironically, it could be argued that nonmaleficence and beneficence may support the provision for deferred consent by preventing exposure of patients to unvalidated practice (risk of harm), hence improving health outcomes and prognosis by promoting scientific research (right to the best available treatment).18 Pseudo-randomisation of untested treatments occurs every day in clinical practice, dependent on the beliefs and practices of the treating clinician. But to study these differing approaches to treatment in a scientifically robust manner requires much stricter consent directives.

**Does the National Statement Align with Patient, Parent, and Practitioner Attitudes to Deferred Consent?**

Children in the UK are supportive of deferred consent in emergency situations if the trial is judged as safe.18 Children aged 7–15 were interviewed about hypothetical research experiences using deferred consent, and said they trusted clinicians to make decisions on their behalf. They also displayed altruism; wanting to help future children by participating in the research. Some acknowledged their parents may have different views.16

The literature describes parental support for the concept of deferred consent in paediatric emergency and/or critical care research, depending on the nature of the trial.5,9,11,14,19 One study surveyed the level of support for deferred consent and found 91% of parents were satisfied with the consent process.20 In most circumstances, parents trusted practitioners to do right by their child and were largely accepting of the use of deferred consent depending on the nature of the study intervention.21 Parents were less likely to support deferred consent if the intervention carried significant risk. This raises the notion of clinical equipoise: that the intervention is consistent with standard care; and there is genuine uncertainty which treatment is preferable.5,10 The conundrum in critical care research is that while therapeutic interventions carry a risk to participants, they may also benefit the patient directly6 as is the case in trials of novel treatments or drugs.

Practitioner attitudes towards deferred consent vary. Attitudes are dependent on the trial intervention and influenced by practitioner familiarity or experience with the deferred consent process. Qualitative research shows practitioners have a positive perception of deferred consent if they feel comfortable with the delivery of the intervention.6

Parents/guardians, practitioners, and children themselves are generally in support of deferred consent for research in paediatric critical care in certain circumstances. Seeking prospective consent under time constraints from distressed guardians may not be the optimal procedure for obtaining true informed consent for research with an intervention in this population.
Implications for Paediatric Critical Care Research Without Clear Guidance on the Use of Deferred Consent

Ideally, research outcomes should be generalisable, display internal and external validity and be free from selection bias. Studies should be conducted pragmatically, with study procedures simulating normal circumstances. If prospective, informed consent is the only option for time-critical, interventional research in paediatric critical care, the consequences may be recruitment difficulties, compromised study validity, and selection bias.¹⁵ Studies may be underpowered due to unachievable sample size, impacting funding and feasibility. Results may not be generalisable to the wider paediatric intensive care population if severely ill or injured children are less likely to be included due to consenting difficulties. If these children are not included, the study population may not accurately reflect the target population, thus undermining generalisability.⁵

The methodical selection of a study population inherently different to the population of interest constitutes selection bias. Use of deferred consent in critical care research may work to reduce selection bias by maximising recruitment and including sicker patients.¹⁰ Selection bias may produce unreliable data and skew randomisation, jeopardising study results.¹² An example of selection bias affecting results is excluding patients predicted to die. These patients are likely very unwell so excluding their data changes the balance between study arms and has an effect on the impact of the intervention, jeopardising the internal and external validity of the study.⁶,²²

A study of a trial enrolling children from both elective and emergency settings found a substantial difference in mortality of patients recruited versus eligible patients who refused, suggesting a degree of selection bias.⁸ Maitland et al.¹³ refer to a fluid resuscitation trial for children and conclude that if prior informed consent was required, it would have resulted in the recruitment of a less critically ill cohort of patients which would have provided inaccurate data. A study by Jansen et al.,²² of critically ill adults participating in an RCT found that if participants recruited using deferred consent were excluded from the analysis, the original significant treatment effect (P = 0.006) became insignificant (P = 0.35). If prospective consent contributes to selection bias in these studies, it is reasonable to assume the validity of study outcomes is also affected. If alternatives to prospective consent are not considered in the paediatric critical care population, many studies investigating life-saving interventions may be unfeasible and unproven therapies will continue to be utilised.⁶

Conclusion and Recommendations

Consent for research in the paediatric critical care setting remains a contentious topic. The importance of emergency research in advancing evidence-based medical treatment is well recognised, and the challenges to obtaining prospective informed consent are widely documented. It seems odd we can simultaneously sanction the unconsented use of unproven and theoretical treatments with no discussion with families, while opposing robust clinical trials without prospective consent. The literature identifies a paucity of research into alternatives to prospective informed consent and recognises a need to evaluate approaches to deferred consent.

The National Statement has a responsibility to provide clear and concise guidance to HRECs and researchers when considering the approval and undertaking of a trial proposing deferred consent. Perhaps the National Statement should sanction the use of deferred consent for trials that meet specific criteria? HRECs may benefit from the development of a pragmatic decision-making framework that considers the urgency of the intervention; examines the equipoise of proposed treatments; and provides some scaffolding around mitigating risk to patients and families.

Continued dialogue is required to seek a balance between providing adequate protection to critically ill children while facilitating research for this vulnerable population. Further investigation, consistent interpretation of guidelines, and objective, tangible evidence is required to support alternatives to prospective consent in the paediatric critical care environment.

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