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REVIEW ARTICLE

Deferred Consent in Neonatal Clinical Research: Why, When, How?

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Abstract
Deferred consent has gained traction in some countries as a possible adjunct to prospective consent for evaluating emergency therapies in the neonatal population. This form of consent has been shown to increase recruitment of acutely and critically unwell patients, potentially reduce parent decision-making burden, and provide more robust evidence for clinical treatments where equipoise exists. However, deferred consent raises complex ethical concerns and guidelines for its use vary across different jurisdictions. The views of all stakeholders, including neonatal providers and parents, are important in determining the appropriateness of deferred consent in high-risk patients. Deferred consent may be ethically justifiable for assessing various treatments, particularly those used in emergency medical management. We present a framework based on neonatal deferred consent trials that assess both non-drug and drug interventions, our experience conducting deferred consent neonatal studies in Australia, and the views of providers and parents on how to best implement deferred consent in the neonatal research setting.

Key Points

A deferred consent approach for trials investigating drug interventions used in neonatal medical emergencies can be considered.

Deferred consent in neonatal trials improves enrolment and enhances generalizability of results.

Limited evidence shows deferred consent is acceptable to a majority of parents in certain circumstances.

The balance between maintaining the ethical considerations for parents and infants versus optimizing evidence-based neonatal care is challenging.

We propose a best-practice approach based on key ethical principles and provide practical tips for conducting deferred consent studies in neonates.

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1 Introduction

Advances in neonatal care are underpinned by high quality randomized controlled trials (RCTs). Traditionally, participation in such trials requires fulfillment of the ethical requirement for voluntary informed parental consent, obtained and documented prospectively [1]. However, obtaining prospective consent for research in newborns can be challenging, particularly so for resuscitation research in the delivery room (DR), or for emergency interventions in the neonatal intensive care unit (NICU). There may be little opportunity to prospectively approach parents prior to birth, and as clinical researchers, we hesitate to approach parents in stressful situations; during labor, in the DR, or in the first hours after NICU admission of their baby. Researchers are mindful of factors such as parents' emotional state, pain, and side effects of maternal medication that may erode their capacity to meaningfully consent to research [2].

Consequently, evidence from clinical trials evaluating neonatal interventions soon after birth is often lacking, of poor quality, or may systematically exclude babies whose mothers present emergently, potentially biasing outcomes. The ethical and practical barriers to conducting clinical trials in high-risk newborns, including the need to obtain prospective consent, are key reasons for the limited number of clinical trials that evaluate new drug or practice interventions in these high-stress environments. However, in the last two decades, more neonatal resuscitation research has occurred, with many studies utilizing alternative forms of consent [2, 3] such as waiver of consent, opt-out consent, and deferred

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consent (also known as retrospective or continuing consent), as described in Table 1.

The acceptability of each form of consent may vary between countries and from institution to institution. This review will focus on the use of deferred consent, more accurately termed 'research without prior consent' (RWPC) [4], within the neonatal setting. RWPC describes the process whereby consent is sought after the study intervention has commenced or been completed, and parental permission to use previously collected data to continue study interventions, and to continue to collect data, is requested. The term retrospective consent, although often used interchangeably, will hereafter be avoided, as it seems disingenuous to imply that the participant or proxy agrees that they would have consented had they prospectively had the opportunity to. Rather, it seems more transparent to acknowledge the limitations around gaining prospective consent and seeking deferred consent for ongoing participation in the study.

Regulatory bodies such as the National Health and Medical Research Council, Australia (NHMRC) [5], European Commission [6], and the US Department of Health & Human Services [7] allow deferred consent and/or a waiver of consent within strict, though not uniform, guidelines [8]. However, given that informed consent can only be obtained prospectively, the term 'deferred' consent is not acceptable in some jurisdictions including the United States [9]. Rather, a 'waiver of consent' is provided for the intervention and informed consent is sought for use of the data collected. However, the ethical considerations are similar to those pertaining to 'deferred' consent. Requirements for deferred consent may include situations in which certain criteria apply. These include times when prospective consent is not practicable (e.g. medical emergencies), when the research relates to the presenting condition, when there is potential therapeutic benefit to the child, and when the research undertaken is of 'low risk' (or minimal additional risk) or is 'justified by benefit.' The deferred consent process is most often used in studies investigating care during emergency scenarios when it is not practicable to obtain prospective consent. However, the specific requirements differ between countries and implementation should align with local research ethics boards and governance. Regulatory bodies typically reiterate the principles outlined in the Declaration of Helsinki, including that deferred consent should be obtained as soon as possible after trial enrolment [1].

Controversies regarding deferred consent exist as regulations rightly seek to protect patients from the potential risks associated with research. However, the lack of research studies undertaken in emergency clinical situations in neonatology continues to expose vulnerable neonates to the unknown risks associated with practices that are not evidence-based [10, 11]. Deferred consent may reduce both the enrolment bias resulting from exclusion of babies born in emergency situations and the burden of decision making on parents [12]. However, ethical and legal concerns arise as we move beyond the widely accepted standard of prospective consent, to one of approaching parents to obtain permission for research after the event.

This article aims to provide an informative 'best practice' approach for considering the use of deferred consent in neonatal trials by reviewing its use in both drug and non-drug trials in neonatology and reviewing the ethical and practical aspects of trials using deferred consent with respect to parental and provider views of conducting deferred consent studies in neonates.

2 Deferred Consent in Neonatal Research

Several studies have evaluated the use of a deferred consent process in neonatal research. The impact of reliance on antenatal consent and the importance of recruiting a broader neonatal population was first suggested by Rich et al. [13, 14], in relation to the Surfactant Positive Airway Pressure and Pulse Oximetry Randomized Trial (SUPPORT) in extremely preterm infants. This trial used prospective antenatal consent to randomize newborns in the DR. However, many newborns were not enrolled in the study because the emergent presentation of the mother precluded antenatal consent. The need for antenatal consent resulted in the enrolment of a disproportionate number of mothers from higher socioeconomic backgrounds, who had more often received antenatal corticosteroid treatment, compared with the eligible but not enrolled population [13]. The analysis raised concern over the potential lack of generalizability of the study results due to the nature of the recruitment.

Table 1 Definitions of alternative forms of consent

Waiver of consent	No parental consent is required for the inclusion of their child in the study
Opt-out consent	Parents are invited to prospectively 'opt out' (i.e. decline consent if they do not want their child to participate in the study), otherwise their child will be included
Deferred/retrospective consent	Parental consent is obtained 'as soon as reasonably possible' after the child has been enrolled into the study and received the randomly allocated intervention

A few studies have examined the differences in participant inclusion and outcomes within neonatal trials where some infants were recruited using prospective, and others using deferred consent. The Vermont Oxford Network Heat Loss Prevention (HeLP) multi-center trial investigated the effect of polyethylene occlusive wrap on preterm infant mortality in the delivery room using both deferred and prospective consent [15]. Of the 38 participating centers, four used deferred consent. One Canadian site allowed any infant born within the first 24 hours of maternal hospital admission to be enrolled under deferred consent, and three US sites allowed deferred consent to be used at any time. Their secondary analysis compared mothers and infants approached and recruited by each of the two consent pathways. The authors reported that mothers of infants enrolled via deferred consent were less likely to have received antenatal corticosteroids than mothers of infants enrolled after prospective consent. There were also important differences in infant characteristics, including significantly lower Apgar scores in the infants enrolled via deferred consent [12]. Whilst no difference was seen in the study primary outcome (mortality at 36 weeks' gestation), the differences in participant characteristics suggested that mothers and infants at higher risk of obstetric and neonatal complications had less opportunity for prospective consent and were more likely to be enrolled retrospectively. The authors concluded that deferred consent should be pursued as a strategy to support inclusion of the sickest infants, who potentially have the most to gain from research in the DR and NICU.

Songstad et al. [16] conducted a secondary analysis using data from the 'HIPSTER' Trial (High Flow Nasal Cannulae as Primary Support in the Treatment of Early Respiratory Distress), comparing the effect of the availability of prospective and retrospective consent. The HIPSTER trial was a comparative effectiveness study that compared two modes of primary non-invasive respiratory support for preterm infants following stabilization in the delivery room and admission to the neonatal unit [17]. Songstad's secondary analysis compared recruitment over two time periods at a single study site, where deferred consent was introduced partway through recruitment. When deferred consent was available, a higher proportion of eligible infants were recruited and mothers were less likely to have received sufficient antenatal corticosteroid treatment compared with the period when only prospective consent was available. The analysis did not demonstrate any important differences in outcomes [16].

A further analysis, currently published in abstract form [18], evaluated enrolment and outcomes from the SAIL trial (Sustained Aeration of Infant Lungs), where extremely preterm infants were randomized in the DR to receive standard DR care or a protocol including one or two sustained lung inflations [19]. This sub-analysis compared study sites with access to deferred consent with sites reliant on prospective (antenatal) consent. Results demonstrated that sites using deferred consent recruited a higher proportion of eligible infants, the mothers received less antenatal corticosteroid treatment, the infants were more likely to be born vaginally, without intrauterine growth restriction, and were less likely to be intubated in the DR. There was no difference in study primary outcome (death or bronchopulmonary dysplasia at 36 weeks' postmenstrual age) by consent availability. However, there were higher rates of intraventricular hemorrhage and necrotizing enterocolitis in infants born at sites with access to deferred consent, strongly suggesting enrolment bias away from the highest risk infants when only prospective consent was used.

It is plausible that the use of deferred consent may result in more scientifically rigorous research with reduced research waste, by enabling the recruitment of a more representative proportion of the most at-risk neonates. There are some emergency clinical scenarios that could be considered for future neonatal research using deferred consent. These include DR processes, procedures, and medications for neonatal resuscitation (e.g. adrenaline dosing and delivery route), the use of drugs in the DR to stimulate breathing (e.g. caffeine), or the use of drugs in the NICU for emergency procedures (e.g. analgesia or sedation for endotracheal intubation and/or exogenous surfactant administration for preterm infants).

3 Ethical Controversies

Informed consent is one of the cornerstones of ethical research involving human subjects, established by the Nuremberg code in 1947 [20]. The principles underpinning all research and clinical practice are the four pillars of medical ethics: autonomy (patient's right to make their own decisions), beneficence (physician's moral duty to act in the best interests of the patient), non-maleficence (physician's obligation to do no harm), and justice (the fair and equitable treatment of all persons) [21]. These pillars can be difficult to balance when conducting research that involves patients highly dependent on medical care, such as newborn infants, or sick neonates admitted to the NICU. This group of patients have unique ethical circumstances due to their developmental vulnerability, informed consent given by proxy, and potential for interventions to have long-term effects on growth, development, and health outcomes [22].

High-quality research is necessary to evaluate new therapies, to challenge accepted but untested treatments, and to assess practice variations between individuals and regions. Translating the results from studies in older populations risks harming vulnerable neonates [23]. As deferred consent trials may increase the participation of acutely and critically unwell neonates, it upholds the ethical principle of justice,

allowing for fair distribution and access to the benefits of research for all neonates. Whilst deferred consent may provide a balance between the need for unbiased research, respect for parental autonomy, and protection of patients, there is still an inherent limitation of parental autonomy leading to debate on the ethical acceptance of this type of consent. Therefore, conducting deferred consent studies must be performed with care, to maintain parental trust in the medical team and in neonatal research.

Trials typically suited to a deferred consent approach have often been comparative effectiveness treatments, rather than assessments of novel medications or interventions. This may be because researchers and research ethics committees feel more comfortable that studies comparing two clinically accepted practices places participants at 'minimal risk', which *may* be a formal requirement for the use of deferred consent in some jurisdictions [24]. However, defining what constitutes 'minimal risk' in research is challenging when the population of interest is already at high risk of morbidity and mortality by the very nature of their underlying disease or condition, such as in the case of extremely preterm infants [25]. There are several recent examples in neonatology, where one practice has ultimately proven inferior to the other, with important clinical implications. One example is the PREMOD trial that assessed umbilical cord milking in preterm infants compared with delayed cord clamping, which aimed to increase neonatal blood volume and improve outcomes. This large RCT, using deferred consent, recently ceased recruitment in the lowest gestational age stratum following unanticipated findings of higher rates of intraventricular hemorrhage in those exposed to cord milking [26]. The SAIL trial also ceased recruitment early after a safety review found higher rates of early death in the smallest infants exposed to the intervention [18, 19].

Researchers and research ethics committees may be understandably hesitant to utilize a deferred consent approach due to the ethical and legal implications in the event that unforeseen additional risks are associated with a clinical pathway. The controversy following the SUPPORT trial suggested that deferred consent could be more problematic as parents have not provided informed consent for any reasonably foreseeable risks prior to their infant's participation in the study [27]. Furthermore, given that some jurisdictions have traditionally used healthy children as the comparator when considering 'minimal risk' [28], even comparative effectiveness trials assessing two commonly used practices will not consistently be considered 'low risk' and thus not be ethically acceptable under those definitions in some jurisdictions [28, 29]. The concept of 'minimal additional risk' may need to instead be applied [30]. 'Minimal additional risk' acknowledges that the judgment of the magnitude of the risk of trial participation is not significantly higher than the participants existing risks, due to their baseline vulnerability. It requires careful consideration as to whether a risk should be attributed to the disease process or the trial intervention. US pediatric research regulations consider a similar concept called 'minor increase over minimal risk' for research participants enrolled in non-beneficial research interventions or procedures to ensure that the research undertaken is important and ethically defensible [29]. When there is a foreseeable additional risk, the scientific merit of the study must be assessed to ensure that the potential for improving the care of future neonates (benefits) sufficiently outweighs the risks of the intervention [31]. On the other hand, it may be equally ethically unjustifiable to continue the routine use of untested clinical treatments without supportive evidence. For instance, the widespread, accepted use of early postnatal corticosteroids in preterm infants, to assist with weaning from mechanical ventilation, was eventually challenged when clinical trials demonstrated a significantly increased risk of adverse long-term neurodevelopmental outcome [32].

Although deferred consent trials generally have higher consent rates and therefore the ability to rapidly yield robust evidence for comparative effectiveness studies, it is important to consider the effect of withdrawal of data after the intervention has occurred, if parents decline consent. Parents may decline deferred consent for various reasons, such as experiencing an adverse event, infant deterioration or death, or for unrelated reasons or desire not to participate in research. Exclusion of infant data within a deferred consent approach may result in an inaccurate representation of the sample population exposed to the intervention, potentially affecting trial efficacy. Whilst this premise cannot provide an argument for violating the principle of parental autonomy, the aim must also be to conduct research for the benefit of patients. Consultation with an appropriate consumer group that includes recent and prospective parents, during the early stages of trial planning, may assist with formulating an acceptable consent process and understanding the perception of risk in the broader community.

3.1 Ethical Issues for Drug Trials

Studies evaluating new drugs or those with limited evidence carry additional risks for our most vulnerable patients and result in increased parental concerns. Efficacy and safety of medications for newborns cannot reliably be derived from adult data as pharmacokinetics and pharmacodynamics vary substantially with age [33]. However, very few pharmacological interventions have been appropriately studied in the neonatal population, meaning many drugs are used 'off-label', potentially leading to unintended and undocumented harm. The principle of justice and ensuring vulnerable populations are not denied the benefits of research is therefore particularly relevant to drug trials in the neonatal population.

Whilst there are no studies to our knowledge that have specifically addressed the ethical challenges of conducting drug trials using deferred consent in neonates, principles of conducting this type of research in the pediatric intensive care setting may be applied. Despite many medications being routinely used beyond their authorized clinical indications, formally trialing off-label medications may not be perceived as 'low' risk by parents or clinicians. Some providers may be concerned that obtaining deferred consent from parents for drug-related research may result in parental feelings that their child was used in 'experimental' research. Additionally, researchers may argue that drug trials in the NICU are not typically time sensitive enough to justify the use of deferred consent over the traditional prospective approach. It may be more ethically acceptable to include deferred consent in medication trials investigating medications given in an emergency, such as during resuscitation or stabilization after birth, whether that comparison is of drug dosage regimens, administration routes (intravenous versus oral), or conventional versus novel therapy, rather than for elective medication administration in the NICU. However, deferred consent may remove enrolment bias and burden of decision making for parents who may contemplate whether their participation in a drug trial could benefit their sick infant's condition. Discussion of drug trials with parents should emphasis the safeguarding processes in place by research ethics committees such as auditing of clinical trials, and requirement that trials be ceased early if the treatment benefit of one pathway is shown to be superior to the other.

Due to the complex ethical nature of drug trials in neonates, and the lack of stakeholder opinions on this issue, we would recommend the use of prospective consent where possible. However, in medical emergencies such as drugs for neonatal resuscitation where prospective consent cannot be obtained and there is a desperate need for evidence-based practice, deferred consent should be considered.

3.2 Seeking Deferred Consent from Bereaved Parents

The inclusion of all eligible patients, including those who experience a serious adverse event or death during a study, is critical to the integrity of any study and to avoid selection bias. This is relevant for some countries (e.g. Australia) where data from a deceased infant cannot be used without parental consent or prior ethical approval [34]. However, finding an appropriate time to seek parental consent to use participant data when adverse events have already occurred can be challenging. Although essential, this is even more fraught when an adverse event is potentially attributable to the intervention or inclusion in the trial. Gamble et al. [35] surveyed bereaved parents whose child received emergency care prior to their consent, and reported that the majority would rather researchers disclosed their child's participation in a trial even after their death. Situational context and timing of discussion for deferred consent is important to avoid exacerbating the distress of grieving parents. Due to the intensive medical environment and vulnerability of neonatal patients, consideration of whether some parents may prefer non-disclosure if their infant death is unrelated to their inclusion in the trial needs to be investigated. One of the most difficult conundrums for researchers may be determining whether infant death is unrelated and whether non-disclosure would risk loss of transparency and trust for parents. Ideally, researchers should seek deferred consent from parents soon after the intervention is administered. It is critical to involve the treating clinical team in ascertaining the best time for this approach in order that the consent process is sensitive to the family's circumstances. A management plan should be considered for circumstances where ascertaining deferred consent is considered no longer feasible (e.g. the family have refused contact with the hospital following a death). Prospectively seeking ethics approval for use of an anonymized minimal data set may assist in maintaining data integrity and respecting family wishes under such difficult circumstances [2]. An anonymized minimal data set capturing serious adverse events or mortality should also be considered for patients where deferred consent was declined in order to prevent introduction of bias and enable an accurate analysis of patient safety. Anonymity of data protects the patient's privacy and prevents further potential harms [36].

4 Deferred Consent from a Provider Perspective

One reason for slow recruitment in neonatal studies is the reluctance from researchers to approach families of potential research participants, known as 'gate-keeping,' an attitude that may be due to the researchers' fear of placing an excessive burden on parents [33], and their assessment that it might be ethically inappropriate to approach the family. Providers perceive that true informed parental consent is difficult to obtain in the highly stressful NICU environment, and in the immediate antenatal period. This perception is further exacerbated in situations of imminent premature birth, or emergency resuscitation at birth, where researchers do not have adequate time to approach parents and allow them time to make an informed decision [8]. The inability to approach parents at such times results in systematic exclusion of mothers and infants presenting precipitously, supporting equity in treatment and the scientific argument to utilize deferred consent. However, providers and researchers may have similar misgivings in regard to research without prior consent, fearing that families may be unhappy with the process.

Insights into providers' perspectives of first-hand experience in conducting neonatal deferred consent studies are limited. Woolfall et al. [37] conducted the first UK study exploring the views and acceptability of deferred consent amongst 17 research recruiters with first-hand experience of this alternative consent process in the pediatric emergency setting. They described initial hesitation amongst some staff members, due to concern for parents' feelings. Others welcomed the process, as they perceived that it enabled more evidence-based practice, noting that this approach is not dissimilar to standard clinical care where parents are not always informed of treatments used for their child in urgent settings, and that they may be untested interventions.

Similarly, den Boer et al. [38] reported neonatal care providers' perceptions of deferred consent in the DR and attributed their positive experiences to appropriate communication and timing of approaching parents for consent. General acceptability for minimal risk observational studies and comparative effectiveness studies is seen amongst neonatal resuscitation researchers and may be within preconditions set by research and ethics committees, including that the intervention does not add risk, pain or discomfort [24]. Concerns reported by providers include the potential damage to the therapeutic relationship bred by mistrust that interventions are conducted before parental knowledge, and subtle coercion if parents feel they cannot refuse [2, 38]. Educating providers on the scope of research consent modes and the ethical and practical uses is important in optimizing neonatal research. This would support discussion regarding provider concerns, balanced with parental perspectives for the implementation of trials using deferred consent. Parents, and the general public, should be reassured (by providers) that all clinical trials are approved by clinicians and research ethics committees and that interventions are specific to certain medical scenarios, for patients who meet strict eligibility criteria, whilst understanding that many routine practices are evidence-free.

5 Deferred Consent from a Parental Perspective

Parents who have participated in neonatal research studies provide valuable insights into how to best conduct deferred consent trials. Parents and providers involved in the CONNECT (CONsent methods in childreN's emergEncy medicine and urgent Care Trials) study expressed that despite initial concerns about deferred consent, both groups supported deferred consent in the pediatric emergency setting if the interventions were already used in clinical practice [37].

Few studies have examined the opinions of parents of newborns regarding alternative consent processes. Burgess et al. [39] conducted a survey of 29 parents whose newborns had been prospectively enrolled into NICU-based research studies. The majority favored prospective consent, reporting their desire for parental autonomy when faced with a hypothetical scenario of deferred consent. A more recent, larger study by McCarthy et al. [40] surveyed 600 parents regarding consent in neonatal research. Of those, 101 had previously consented to participate in a neonatal research study. However, the type of consent process was not reported. Overall, 40% of parents surveyed thought neonates involved in research received better overall care, 1% thought care would be worse whilst 59% were unsure. More respondents (51%) were accepting of a deferred consent approach for studies assessing urgent interventions such as neonatal resuscitation, rather than for a non-urgent feeding study (27%). However, only 53% were sure they would not feel pressure to consent prospectively in an emergency scenario. Almost 70% of parents completed the survey during an antenatal visit, and it is possible that their responses would differ after experience of the stressful NICU environment. Parents' desire to be part of the research process for less time-restrictive studies should be an important consideration when determining the suitability of a trial for deferred consent.

Forty-nine parents who participated in the PREMOD trial (umbilical cord milking versus delayed cord clamping in premature infants) were asked for their opinion of the deferred consent process. No parent expressed negative feelings towards the process. The majority (71%) had a positive response towards their newborn's participation and 69% felt that their participation had a positive impact on their baby's health [41]. A larger study conducted in parents who had participated in neonatal research where their baby had been recruited using deferred consent was recently reported by Sloss et al. [3]. They explored the views of 100 parents and found that 89% felt deferred consent was a satisfactory approach, mostly as they felt it to be practical and timely, and because it removed some of the decision-making burden. Parents reported a preference for having more time to make decisions at a less stressful period. However, a few parents also expressed concerns regarding their loss of autonomy. Clear explanation of the reasons deferred consent is used in research may ease potential reservations for some parents. Further education of alternative consent options and research investigating parental views is required to determine the best approach for trial design and the language and timing used in deferred consent processes.

6 Best Practice

We offer advice for the implementation of a deferred consent approach based on previous deferred consent neonatal trials and our own experiences shaped by Australian legislation and national ethics standards for conducting human

Table 2 Approach for deferred consent studies in neonates

A. Indications for deferred consent
Consider whether the indication, risk profile, and timing of the intervention fulfill local criteria for deferred consent
Ensure the trial design is appropriate (e.g. observational studies or comparative effectiveness studies of acceptable clinical pathways)
B. Consult parents during trial design
Acceptability of alternative consent approach
Appropriate trial procedures such as timing of when to approach for deferred consent
Plan an approach for seeking consent from bereaved parents whose babies died before an approach for consent has been made
C. Minimizing bias
Seek ethical approval for an anonymized minimal data set (serious adverse events or mortality) for infants who die or have an adverse event before an approach for consent has occurred, and in those where deferred consent is declined
Consider under which circumstances deferred consent is appropriate whilst balancing potential enrolment bias (e.g. all participants versus only those whose mothers have presented very shortly before birth)
Plan prospectively how to report the flow of participants in the trial if deferred consent leads to (unbalanced) attrition, and what analytical decisions were made
D. Considerations during trial conduct
Provide open disclosure with parents of study purpose, intervention, and procedure
Include evidence of previous use of deferred consent in neonatal trials in parent information and consent forms
Approach parents at an appropriate time soon after trial enrolment, balancing early disclosure with clinical stability and parental distress (based on parental input to the trial design)
Liaise closely with the clinical team regarding appropriate timing for approaching for parental consent (e.g. avoid approaching during parent's first NICU visit and during parent–infant interactions such as skin-to-skin contact or feeding time and ensure parents have had a recent clinical update about their child's condition)
Discuss difficult scenarios with clinical teams using a case-by-case approach for seeking consent from bereaved parents
Pursue ongoing discussions with research ethics committees, providers, and parents

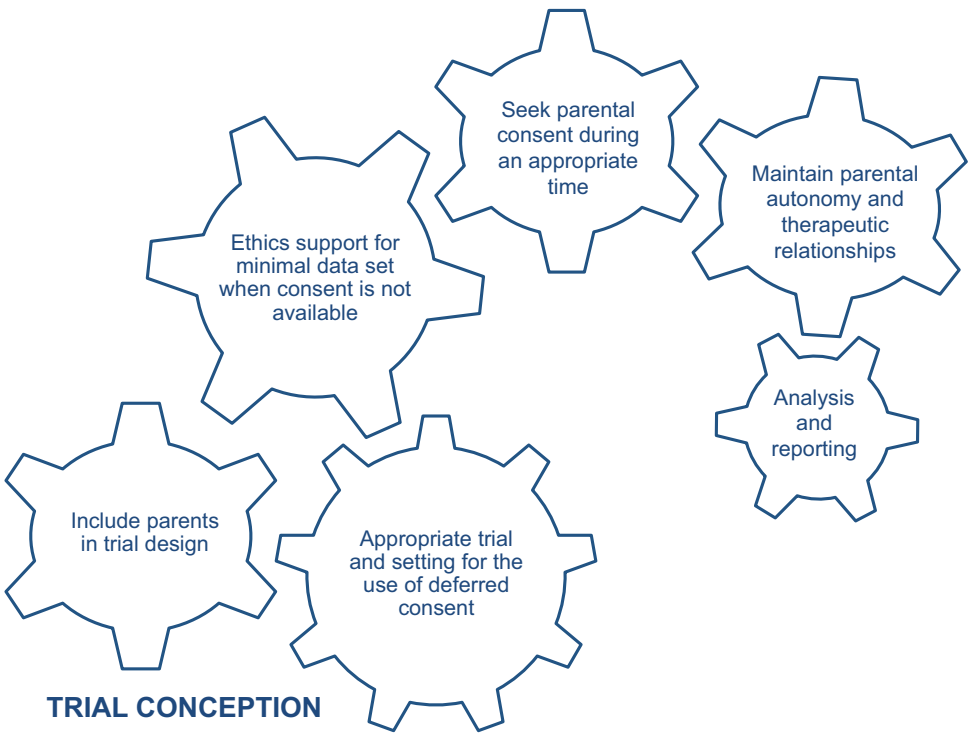

Fig. 1 Framework for conducting deferred consent trials in neonates

research (Table 2). Country-specific legislation and practice will determine how these principles might be applied in other jurisdictions.

The goals are to maximize parental autonomy and preserve therapeutic relationships, and most importantly to protect our vulnerable patients. Parents who have been previously approached to participate in a deferred consent trial and potential parents should be involved from the outset of trial design and play an integral part in planning the consent processes to be used (Fig. 1).

During the trial, parents should be approached at a suitable time after their child's enrolment and provided with adequate information regarding the clinical research study and explanation of the reasons for deferred consent for that particular study. Parents should be reassured that providing any consent for research is not a binding decision and that they are free to change their mind and withdraw their child from the study at any stage.

We acknowledge that understanding and balancing the ethical tensions of deferred consent within different jurisdictions can be confronting and challenging. Education and open dialog between all stakeholders (clinicians, researchers, ethics boards, parents) is required. The design and impact of deferred consent trials in neonatal research should be the subject of ongoing evaluation.

7 Conclusions

Whilst a deferred consent approach may offer a solution for improved scientific validity in neonatal medicine, the acceptability and practicality of deferred consent for drug research in the NICU is unclear. Input from all stakeholders, particularly parents, may help determine the appropriateness of deferred consent, carefully balancing concerns of parental autonomy, patient care, optimal trial design, and implementation.

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References

1. World Medical Association Declaration of Helsinki. ethical principles for medical research involving human subjects. J Postgrad Med. 2002;48(3):206–8.
2. Owen LS, Davis PG. Parental consent and neonatal delivery room trials: walking an ethical tightrope. Arch Dis Child Fetal Neonatal Ed. 2021. https://doi.org/10.1136/archdischild-2020-319355.
3. Sloss S, Dawson JA, McGrory L, Rafferty AR, Davis PG, Owen LS. Observational study of parental opinion of deferred consent for neonatal research. Arch Dis Child Fetal Neonatal Ed. 2020. https://doi.org/10.1136/archdischild-2020-319974.
4. Woolfall K, Frith L, Dawson A, Gamble C, Lyttle MD, Young B. Fifteen-minute consultation: an evidence-based approach to research without prior consent (deferred consent) in neonatal and paediatric critical care trials. Arch Dis Child Educ Pract Ed. 2016;101:49–53.
5. Commonwealth of Australia: National Health and Medical Research Council. National statement on ethical conduct in human research 2007 (updated 2018). Canberra; 2018.
6. The European Parliament and the Council of the European Union. In: 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 repaling Directive 2001/20/EC; 2014.
7. Department of Health and Human Services Food and Drug Administration. In: Information sheet guidance for institutional review boards (IRBs) clinical investigators, and sponsors: exception from informed consent requirements for emergency research; 2013.
8. den Boer MC, Houtlosser M, Foglia EE, Davis PG, van Kaam AH, Kamlin COF, et al. Deferred consent for the enrolment of neonates in delivery room studies: strengthening the approach. Arch Dis Child Fetal Neonatal Ed. 2019;104:F348–52.
9. Rich WD, Katheria AC. Waived consent in perinatal/neonatal research-when is it appropriate? Front Pediatr. 2019;7:493.
10. Schreiner MS, Feltman D, Wiswell T, Wootton S, Arnold C, Tyson J, et al. When is waiver of consent appropriate in a neonatal clinical trial? Pediatrics. 2014;134(5):1006–12.
11. Brierley J, Larcher V. Emergency research in children: options for ethical recruitment. J Med Ethics. 2011;37(7):429–32.
12. Vohra S, Reilly M, Rac VE, Bhaloo Z, Zayak D, Wimmer J, et al. Differences in demographics and outcomes based on method of consent for a randomised controlled trial on heat loss prevention in the delivery room. Arch Dis Child Fetal Neonatal Ed. 2021;106(2):118–24.
13. Rich WD, Auten KJ, Gantz MG, Hale EC, Hensman AM, Newman NS, et al. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. Pediatrics. 2010;126(1):e215–21.
14. Rich W, Finer NN, Gantz MG, Newman NS, Hensman AM, Hale EC, et al. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. Pediatrics. 2012;129(3):480–4.

15. Reilly MC, Vohra S, Rac VE, Dunn M, Ferrelli K, Kiss A, et al. Randomized trial of occlusive wrap for heat loss prevention in preterm infants. J Pediat. 2015;166(2):262-8.e2.
16. Songstad NT, Roberts CT, Manley BJ, Owen LS, Davis PG. Retrospective consent in a neonatal randomized controlled trial. Pediatrics. 2018;141:e20172092.
17. Roberts CT, Owen LS, Manley BJ, Froisland DH, Donath SM, Dalziel KM, et al. Nasal High-Flow Therapy for Primary Respiratory Support in Preterm Infants. N Engl J Med. 2016;375(12):1142–51.
18. Owen LS, Foglia EE, Ratcliffe SJ, Simma B, Katheria A, Keszler M, et al. What effect does the use of deferred consent have within a neonatal resuscitation trial? J Paediatr Child Health. 2020;56(s1):35.
19. Kirpalani H, Ratcliffe SJ, Keszler M, Davis PG, Foglia EE, Te Pas A, et al. Effect of sustained inflations vs intermittent positive pressure ventilation on bronchopulmonary dysplasia or death among extremely preterm infants: the SAIL randomized clinical trial. JAMA. 2019;321(12):1165–75.
20. Vollmann J, Winau R. Informed consent in human experimentation before the Nuremberg code. BMJ. 1996;313(7070):1445–7.
21. Varkey B. Principles of clinical ethics and their application to practice. Med Princ Pract. 2021;30(1):17–28.
22. Janvier A, Farlow B. The ethics of neonatal research: an ethicist's and a parents' perspective. Semin Fetal Neonatal Med. 2015;20(6):436–41.
23. Spriggs M, Caldwell PH. The ethics of paediatric research. J Paediatr Child Health. 2011;47(9):664–7.
24. Foglia EE, Owen LS, Keszler M, Davis PG, Kirpalani H. Obtaining informed consent for delivery room research: the investigators' perspective. Arch Dis Child Fetal Neonatal Ed. 2017;102(1):F90–1.
25. Duenas DM, Wilfond BS, Johnson LM. Clearing muddy waters: the need to reconceptualize minor increase over minimal risk in pediatric rare disease research. Am J Bioethics. 2020;20(4):8–10.
26. Katheria A, Reister F, Essers J, Mendler M, Hummler H, Subramaniam A, et al. Association of umbilical cord milking vs delayed umbilical cord clamping with death or severe intraventricular hemorrhage among preterm infants. JAMA. 2019;322(19):1877–86.
27. Lantos JD. Neonatal research ethics after SUPPORT. Semin Fetal Neonatal Med. 2018;23(1):68–74.
28. Rose CD. Ethical conduct of research in children: pediatricians and their IRB (part 2 of 2). Pediatrics. 2017;139:6.
29. Rossi J, Nelson RM. Minimal risk in pediatric research: a philosophical review and reconsideration. Account Res. 2017;24(7):407–32.
30. Lantos JD, Wendler D, Septimus E, Wahba S, Madigan R, Bliss G. Considerations in the evaluation and determination of minimal risk in pragmatic clinical trials. Clin Trials. 2015;12(5):485–93.
31. Truog RD. Ethical assessment of pediatric research protocols. Intensive Care Med. 2008;34(1):198–202.
32. Owen LS, Manley BJ, Davis PG, Doyle LW. The evolution of modern respiratory care for preterm infants. The Lancet. 2017;389(10079):1649–59.
33. Kleiber N, Tromp K, Mooij MG, van de Vathorst S, Tibboel D, de Wildt SN. Ethics of drug research in the pediatric intensive care unit. Pediatr Drugs. 2015;17(1):43–53.
34. National Statement on Ethical Conduct in Human Research: National Health and Medical Research Council Australia. 2020. https://www.nhmrc.gov.au/sites/default/files/documents/attachments/National%20Statement/e72.pdf.
35. Gamble C, Nadel S, Snape D, McKay A, Hickey H, Williamson P, et al. What parents of children who have received emergency care think about deferring consent in randomised trials of emergency treatments: postal survey. PLoS ONE. 2012;7(5):e35982.
36. Jansen TC, Kompanje EJO, Druml C, Menon DK, Wiedermann CJ, Bakker J. Deferred consent in emergency intensive care research: what if the patient dies early? Use the data or not? Intensive Care Med. 2007;33(5):894–900.
37. Woolfall K, Frith L, Gamble C, Gilbert R, Mok Q, Young B. How parents and practitioners experience research without prior consent (deferred consent) for emergency research involving children with life threatening conditions: a mixed method study. BMJ Open. 2015;5(9):e008522.
38. den Boer MC, Houtlosser M, Foglia EE, Lopriore E, de Vries MC, Engberts DP, et al. Deferred consent for delivery room studies: the providers' perspective. Arch Dis Child Fetal Neonatal Ed. 2020;105(3):310–5.
39. Burgess E, Singhal N, Amin H, McMillan DD, Devrome H. Consent for clinical research in the neonatal intensive care unit: a retrospective survey and a prospective study. Arch Dis Child Fetal Neonatal Ed. 2003;88(4):F280–6.
40. McCarthy KN, Ryan NC, O'Shea DT, Doran K, Greene R, Livingstone V, et al. Parental opinion of consent in neonatal research. Arch Dis Child Fetal Neonatal Ed. 2019;104(4):F409–14.
41. Rich WD, Katheria AC. Waiver of consent in a trial intervention occurring at birth-how do parents feel? Front Pediatr. 2017;5:56.