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COMMENTARY

Deferred Consent in Pediatric Drug Trials: Moving from Why to How

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Medical care of critically ill and injured infants and children globally should be based on best research evidence to ensure safe and effective treatment. There is an ongoing need for clinical trials investigating emergency drug treatments of children with life-threatening conditions as there are still relatively few clinical trials in this setting and severely ill children are under-represented in research. A main challenge of such trials is seeking parents' consent for including their critically ill child in a research study. The reasons are obvious: there is not always someone with parental responsibility present when a child enters a hospital's emergency department, newly delivered mothers may be unable to give consent to emergency investigations or treatment of their baby because of general anesthetic or post-delivery sedation, or parents may be highly stressed in an emergency and struggle to make an informed decision about research in the limited time available.

A solution may be to seek parental permission post-inclusion and post-intervention and use data that has already been collected and consent for the child to continue to take part in the trial. This approach is called 'trial with deferred consent,' or 'research without prior consent' [1]. A trial with deferred consent can be conducted in situations when (a) treatment is required urgently, such as for cardiopulmonary arrest, hypoxia, seizures, hypoglycemia, and shock; (b) urgent action is required for the purposes of the trial; (c) it is not reasonably practicable to obtain consent prospectively because the parent or guardian is not able to either receive or understand the information; and (d) an ethics committee has given approval to the procedure under which the action is taken [1]. In this process, parents who are absent or are affected by situational incapacity are assumed to give initial consent and then actually provide full consent when they can take in the information and making the decision.

In 2008, legislation was introduced in Europe and in the UK that enables researchers to seek parental consent for research *after* their child had been included in the study and has been given the investigational drug (or non-drug intervention). Since this time, research has been initiated to document key stakeholders' perceptions of the acceptability and appropriateness of deferred consent, and their recommendations for future studies. Also, guidance on how to manage specific challenges in conducting these trials, and how to inform peer reviewers and Research Ethics Committees have been published. This research has shown how parents' provision of deferred consent depends on many things, including the trial type, perceived safety of the intervention, and the nature and route of administration of the intervention [2]. Woolfall et al. found that practitioners' views on deferred consent differed depending upon whether practitioners had any experience with this consent method [3]. Menon et al. described the use of deferred and prior informed consent models in a placebo-controlled, randomized controlled trial of corticosteroids in pediatric septic shock in children aged newborn to 17 years with suspected septic shock in seven tertiary-level pediatric intensive care units in Canada [4]. The study found that deferred consent was acceptable in time-sensitive critical care research to most research ethics boards, families, and healthcare providers. Deferred consent resulted in higher consent rates and more efficient recruitment.

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1 Deferred Consent in Neonatology Drug Trials

While deferred consent has many advantages over prospective informed consent in time-sensitive emergency pediatric research, researchers face many challenges when implementing this consent model, especially in neonatology settings. For example, they face ethical dilemmas discussing research participation for children with bereaved parents and are unsure of the best time to discuss deferred consent. **In this issue of Pediatric Drugs**, Imbulana et al. address the ethical and practical issues of using deferred consent in neonatal research and provide guidance to best practice based on the literature and the authors' own experiences [5]. In their review, the authors present indications for this approach, relevant patients' risk profiles and timing of the intervention that fulfill criteria for deferred consent. They show that the deferred consent approach has been used successfully in neonatology trials and should be considered as an acceptable solution for trials investigating drug interventions in neonatal medical emergencies. They demonstrate that the application of a deferred consent approach improves enrolment, reduces bias, and enhances generalizability of results. In fact, by increasing the participation of acutely and critically unwell neonates, deferred consent trials **uphold the ethical principles of equity and justice**, allowing for access to the benefits of research for all neonates. Deferred consent appears acceptable to most parents in specific circumstances. In their detailed discussion, the authors explain the challenges of finding the right balance between maintaining the research ethics considerations for parents and infants versus optimizing evidence-based neonatal care, and propose a 'best practice' approach with practical tips for conducting deferred consent studies in neonates, based on the literature and their experience. They propose that in trials where deferred consent may be a solution, an in-depth discussion on provider concerns, balanced with parental perspectives for its implementation needs to happen **at the trial design stage**. Healthcare providers and trialists involved in asking for and obtaining deferred consent should reassure parents that all clinical trials are prospectively approved by research ethics committees and that trial interventions are only given to patients who meet strict equipoise criteria. The authors present a framework for design and conduct of deferred consent trials, and end by stressing the importance of educating providers on the scope of alternative research consent modes in optimizing neonatal research.

This article is highly relevant to the field of neonatal and pediatric clinical drug development. It addresses widely felt frustrations with the limitations that current informed consent processes put on the necessary research requirements, leading to sustained use of unproven and potentially harmful (drug) treatment and ongoing research waste.

2 What Next Steps are Needed?

Although there is growing public experience with this approach, it still largely depends on the trial's intervention type and geographical location whether it is acceptable to children, their parents, their care providers, research staff, trial monitors and managers, and members of research ethics committees and regulatory agencies. There are still few studies that explore the perspectives of children. A few things come to mind as immediate next steps.

First, work on international harmonization is needed. While generation of evidence for acute drug treatments in newborns and children is a global challenge, and clinical drug trials can be conducted in many places around the world, local regulations regarding alternatives for traditional prospective informed consent vary widely, even within Europe and North America. While there is general agreement that deferred consent could be the solution in emergency situations in which prospective consent is not practicable and where there is potential benefit to the child, some jurisdictions have additional demands: the research must be of 'low risk' or is 'justified by benefit.' Yet, the highest risk interventions often lack trial evidence from comparative effectiveness trials. Another issue is the variability in local permission to use the patients' trial data after an included patient has passed away, and whether to inform these parents about the trial. To enable international collaborative trials, harmonization on these points is needed.

Second, to involve the public and parents in the design of the informed consent processes for these trials is crucial. There is room to better partner with parents in improving scientific, ethics, and equity issues related to drug trials in emergencies. Woolfall et al. showed how parents' agendas are different from researchers' agendas [6]; parents consider clinical benefit, child safety, practicalities of participation, research for the common good, access to medication, and randomization when deciding about their child's trial participation. There are specific misunderstandings that have the potential to influence their decisions; these are rarely voiced during the informed consent discussion. The implications are that in any trial, providing trial information that is tailored to what parents consider important in deciding about a clinical trial may improve both recruitment and retainment practice and ultimately benefit evidence-based pediatric medicine. In their recently presented seven-step framework to assist recruitment in trials that involve deferred consent [7], Roper et al. highlight the areas in which recruitment discussions in pediatric emergency and critical care settings

are distinct from trials that have time for informed consent discussions. The framework identifies recruitment practices that facilitate parental understanding of trial purposes and the need for research without prior consent. The bottom line, as highlighted in this issue's review [5], is that **drug trials in children need to be developed together with patient and parent partners**, especially when deferred consent is the only way to conduct the trial.

While such efforts are undertaken, researchers should consider the guidance that has been developed to inform recruitment and consent in this challenging setting. The authors of this month's article in Pediatric Drugs and the CONseNt methods in paediatric Emergency and urgent Care Trials (CONNECT) Group (https://www.liv.ac.uk/psychology-health-and-society/research/connect/) have compiled important advice and resources for researchers to guide decisions in preparing the best approach [8]. This guidance will help to conduct deferred consent trials in a way that is ethically appropriate and addresses the needs of families.

In conclusion, implementing deferred consent in drug development trials can balance scientific and ethical aspects in emergency settings. We expect the number of pediatric randomized controlled trials using deferred consent in emergency settings to increase over the next few years. As their number increases, additional research on approaches for consent should be embedded into these trials' design. Sharing experiences in conducting these challenging trials will help peer and Research Ethics Committee reviews, inform practitioner training, and inform normative guidance on the use and appropriateness of deferred consent in emergency settings.

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