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Informed consent for neonatal trials: practical points to consider and a check list

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ABSTRACT

Obtaining informed consent from parents of critically ill neonates can be challenging. The parental decision-making process is influenced by the severity of the child's condition, the benefit–risk balance, their emotional state and the quality of the relationship with the clinical team. Independent of local legislation, parents may prefer that consent is sought from both. Misconceptions about the absence of risks or unrealistic expectations about benefits should be openly addressed to avoid misunderstandings which may harm the relationship with the clinical team. Continuous consent can be sought where it is unclear whether the free choice of parental consent has been compromised. Obtaining informed consent is a dynamic process building on trusting relationships. It should include open and honest discussions about benefits and risks. Investigators may benefit from training in effective communication. Finally, involving parents in neonatal research including the development of the informed consent form and the process of obtaining consent should be considered standard practice.

Key messages

- Key factors influencing parental consent decisions are summarised.
- A checklist of points to consider when talking to parents about the possible inclusion of a neonate into a clinical trial has been built.
- The checklist may help researchers to optimise the setting for seeking parental consent.

BACKGROUND

Children, including neonates, have long been excluded from clinical research due to ethical and practical challenges.[1] This has led to a situation where up to 90% of newborn babies admitted to neonatal intensive care units (NICUs) are treated at least once with off-label or unlicensed medicines.[2–4] This is associated with a higher risk of lack of efficacy, serious adverse drug reactions and medication errors.[5–7]

In 2007, the European Paediatric Regulation governing the development and authorisation of medicines for children, came into force.[8 9] In addition, the European Commission is financing various European projects for the development of a paediatric research infrastructure.[10] In this context, the Paediatric Clinical Research Infrastructure Network (PedCRIN), a 4-year project, was initiated in January 2017.[11] During the PedCRIN project the expertise of the European Clinical Research Infrastructure Network and the European Paediatric Clinical Trial Research Infrastructure was combined with the aim of developing points to consider documents (so-called 'Tools') for researchers to support the setup and management of non-commercial clinical trials in children.[11]

The aim of this article is to summarise the key points researchers may want to consider when preparing for the informed consent discussion for a neonatal trial.

SURVEY

At the beginning of the PedCRIN project, in 2017, an online survey was conducted (4 April to 15 May 2017) among 663 researchers involved in European and international paediatric research networks (eg, ESDPPP, GRiP, INC, ENCePP).[12] The objective was to understand what the needs of the research community are with regards to clinical trials in children. The response rate was 22.2%. Using a Likaert scale of 0 (not needed) to 4 (extremely needed) the survey grouped topics previously identified into six large themes and researchers had the possibility to add a free-text comment.[12 13] Based on the results of this survey, a series of neonatal topics were developed with the aim of responding to these questions and developing a set of practical tools for researchers.[14] The survey questions are provided in online supplemental table 1 and the results are summarised in online supplemental material figure S1.[12]

Table 1 Check list of points to consider when talking to parents about the possible inclusion of a neonate into a clinical trial

Points to consider during informed consent process	Done	Delayed	Not applicable	Comments
Informed consent setting				
Consider approaching parents prior to delivery.[33]	☐	☐	☐	
Both parents should be present.[15]	☐	☐	☐	
Both parents should be asked for consent.[15]	☐	☐	☐	
Offer the possibility to have the responsible nurse and/or doctor, trusted friend and/or family member or a parent from an NICU association joining the conversation.[49]	☐	☐	☐	
Introduce the investigator/HCP who will be seeking consent during routine contacts with the parents.[45 46]	☐	☐	☐	
Ensure parents are comfortable and trust the investigator/HCP seeking consent.[49]	☐	☐	☐	
In multinational trials local beliefs, customs and traditions should be taken into consideration.[55]	☐	☐	☐	
Consent information				
Information needs to be clear and well structured.[58 59]	☐	☐	☐	
Information should be provided in the parent's native language.[15]	☐	☐	☐	
Pause for questions—do not rush.[28]	☐	☐	☐	
Provide written information where parents can find additional, independent information and NICU parent organisations.[48]	☐	☐	☐	
Reassure that their decision to participate or not will not change the level of care.[52]	☐	☐	☐	
Clarify that parents can always change their mind and that this does not have any consequences for the routine treatment of their child.[52]	☐	☐	☐	
Be prepared to re-explain and reconsent.[49 66]	☐	☐	☐	
Adapt communication to what the parents can take in at the time.[23 67]	☐	☐	☐	
If parents are struggling with the decision-making process, acknowledge that it is difficult.[49 52]	☐	☐	☐	
If parents are anxious provide more support and ask how you can help them, reassure them that they should take their time to decide.[49 52]	☐	☐	☐	
Benefits of study treatment				
Do not exaggerate benefits.[49]	☐	☐	☐	
Explain how the study will benefit the child.[52]	☐	☐	☐	
Explain how the study will benefit neonates with the same condition.[52]	☐	☐	☐	
Risks of study treatment				
Be upfront about potential risks of the study treatment and the comparator.[48 49]	☐	☐	☐	
Explain how study related risks will be minimised.[52]	☐	☐	☐	
Address concerns about pain and discomfort proactively.[68]	☐	☐	☐	
Study procedures				
Explain whether and how the study will interfere with routine clinical care.[52]	☐	☐	☐	
Be clear about additional procedures and follow-up—other than what is normally done.[63]	☐	☐	☐	
Explain how additional follow-up (other than routine) will be organised and address any questions about reimbursement of costs for transport and additional child care.[63]	☐	☐	☐	

HCP, healthcare professional; NICU, neonatal intensive care unit.

One of the topics highlighted by the survey concerned the informed consent process and one of the free-text comments suggested the development of 'Strategies to improve the enrolment in clinical trial'.[12] The challenges surrounding neonatal consent have previously been highlighted by a Delphi survey.[15] Neyro *et al* reported that parents and healthcare professionals agreed on 58 items to be included in the informed consent information.[15]

In Febraury 2019 a narrative review of the literature was conducted in PubMed and of regulatory guidance

documents issued by the European Medicines Agency. Reviewing the literature, no single publication was identified providing a check list for investigators on the practical points to consider when preparing for the informed consent discussion with parents.

Team discussions including representatives from a patient organisation (EV and MHED), a neonatologist and paediatric pharmacologist (EJA), a paediatrician (BA) and a project leader of paediatric clinical research (VE) were held and the following question was formulated for the development of a neonatal tool:

- What are some of the practical points to consider during informed consent discussions with parents of neonates to be included into a clinical trial?

The rationale for this question was that the consent discussion with parents does not easily fit into established processes of informed consent. It is often obtained in circumstances which may make taking a valid decision challenging.[16–18] The understanding and process of parental consent in such extreme circumstances is informed by ethics guidelines, trial procedures driven by regulations, behavioural science, the needs of parents and feedback from health care professionals (HCPs). For the purpose of developing a tool that can be used by investigators these very varied topics had to be included into one single tool.

Patient and public involvement

The involvement of parents and patient representatives is an integral part of the PedCRIN project with a dedicated team reflecting on processes to improve their involvement in the design, conduct and reporting of paediatric clinical trials.[19] The results of the survey were discussed with representatives of a patient organisation involved in PedCRIN. The tool was then codeveloped with them. The representatives of the patient organisation suggested to publish the tool. The article was written in collaboration with the aim of distributing the tool.

POINTS TO CONSIDER

Obtaining informed consent for a clinical study from parents of critically ill neonates can be challenging.[16 20–22] In this context, it may be helpful to remember that parents would have expected to have a healthy baby.[23] Witnessing the severity of their child's condition is extremely stressful for parents and the NICU setting can be intimidating.[23–25]

Parents may feel overwhelmed by the large amount of information they receive, time pressure and their emotions.[23 26–29] Taking voluntary decisions under such circumstances can be very difficult.[23 28 30] The parent's decision-making process is influenced by the severity of the child's condition, the perceived benefit-risk balance of trial participation, their emotional state, timing of the request and the quality of the relationship with the clinical team, among others.[28 31] However, most parents will respond positively to requests for inclusion into a well-designed clinical trial.[27 32]

Informed consent setting

Routine antenatal visits are a unique opportunity to provide general information to all future parents about neonatal research currently being conducted at the hospital.[33] For certain neonatal and maternal conditions, these visits can also be an opportunity to provide more specific information and discuss with parents the potential inclusion of their child into a study.[34] This may provide parents with more time to discuss compared with providing this information only at the time of inclusion.[23 28 30 35] The timing of detailed discussions will depend on when the diagnosis of the neonatal condition has been confirmed, the delivery date and the individual circumstances of the women and their family.[36 37] Parental decision making in favour of trial participation is facilitated by parents having sufficient time to consider their decision.[38–40] Antenatal discussions may also provide an opportunity to introduce the investigator to the family. Deferred consent may be used for the recruitment into studies of life-threatening neonatal conditions.[41] However, multicentre studies may need to consider differences in local practices and the acceptability of deferred consent.[41] Depending on local legislation, informed consent needs to be provided either by one or both parents/legal guardians.[42] However, independent of the legislation, parents may prefer that consent is sought from both.[15]

Clinical trial regulations and regulatory documents provide guidance on the informed consent process.[43 44] If informed consent is sought by an investigator, who is not the treating physician, parents may have difficulties establishing a trusting relationship and this should be addressed proactively by the study team.[45 46] On the other hand, if informed consent is requested by the treating physician parents may find it difficult to decline the request and may create conflicts of interest for the physician.[47] One way of addressing these challenges is to introduce the investigator to the parents during standard clinical practice, for example at a routine visit to the clinic or on ward rounds.[45 46]

The decision-making process of families during consent is dynamic and will be facilitated by building trusting relationships through the provision of transparent and clear information on the benefit–risk of available treatment options and ensuring the needs of families are addressed proactively.[44 48–52] Attention should be paid to the possible misconceptions parents may have about the absence of any risk and unrealistic expectations about the benefits of the clinical trial, as this may lead to misunderstandings and harm the trust parents have placed in the clinical team.[23]

Consent information

Awareness of the difficulties some parents may experience may help to ensure that trial procedures and communication are optimised to meet their needs.[53]

Cultural differences should be taken into account and information should be provided in the parent's native language.[15 54 55]

Parental decisions are strongly influenced by how the information is provided, timing and content.[28] While, from a legal perspective, the written informed consent form is important, many parents feel that the conversation and verbal information provided is more important.[56] Having a script or check list which can be gone through together with the parents may help ensuring all relevant information is not only provided but also understood by the parents/legal guardians. Written informed consent documents can be difficult to read and parents may feel that they are lengthy.[57–59] Understanding the perspective of parents on the conduct of neonatal clinical trials is important for successful recruitment. Requesting input from parent organisations has been shown to increase recruitment numbers and improve the quality of trial protocols and consent forms.[42 43 60–64] Involving parent organisations should follow a structured process such as described by Babies Born premature or Sick (BLISS), for example.[65]

A variety of techniques are available to improve the understanding of the information provided during the informed consent process.[38 51] Spending more time with parents appears to be the most effective measure in obtaining parental consent, while time pressure may lead to difficulties in having their agreement.[38–40] Jansen-van der Weide *et al* have proposed to adapt the consent process to the time constraints depending on the urgency for treatment.[40] However, it is important to remember that parental decision making in extremely stressful situations may be difficult and their ability to provide voluntary consent may be temporarily impaired.[66] Miller *et al* have developed a tool to assess the degree of the voluntariness of a parent's decision.[66] Furthermore, continuous consent can be sought in trials where it is unclear whether the free choice of parental consent has been compromised.[17 18] Continuous consent provides the opportunity to initially seek parental assent, followed by full consent once parents had the opportunity to make a valid informed consent decision.[16] An example would be assent for trial inclusion in an emergency situation, followed by full consent once the neonate is stabilised.

Finally, it can be challenging to ensure that the informed consent conversation provides all the relevant information and that the language used is understandable.[57] Sponsors may consider training investigators on effective communication and what kind of information needs to be included.[57]

To support researchers preparing for the informed consent process of a neonatal trial a checklist of points to consider was developed, which summarises key information from this article (table 1).

CONCLUSIONS

Obtaining informed consent for neonatal research is challenging. This was confirmed in a survey of paediatric researchers in the context of the PedCRIN project. Therefore, a tool was developed which is described in this paper. The tool is providing background information on specific aspects of consent for neonatal trials. A check list of points to consider was developed which may be used by researchers preparing for informed consent. Future research may examine how this tool performs and how it can be improved. Finally, involving parents at all stages of neonatal research including the development of the informed consent form and the process of obtaining consent should be considered standard practice.

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