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

Beate Aurich,1 Eric Vermeulen,2 Valéry Elie,1 Mariette H E Driessens,2 Christine Kubiak,3 Donato Bonifazi,4,5 Evelyne Jacqz-Aigrain6,7

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.

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 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 the results are summarised in online supplemental material figure S1.12

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.
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’. The challenges surrounding neonatal consent have previously been highlighted by a Delphi survey. Neyro et al reported that parents and healthcare professionals agreed on 58 items to be included in the informed consent information. In February 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. 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. 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. In this context, it may be helpful to remember that parents would have expected to have a healthy baby. Witnessing the severity of their child’s condition is extremely stressful for parents and the NICU setting can be intimidating.

Parents may feel overwhelmed by the large amount of information they receive, time pressure and their emotions. Taking voluntary decisions under such circumstances can be very difficult. 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. However, most parents will respond positively to requests for inclusion into a well-designed clinical trial.

**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. 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. This may provide parents with more time to discuss compared with providing this information only at the time of inclusion. The timing of detailed discussions will depend on whether the diagnosis of the neonatal condition has been confirmed, the delivery date and the individual circumstances of the women and their family. Parental decision making in favour of trial participation is facilitated by parents having sufficient time to consider their decision. 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. However, multicentre studies may need to consider differences in local practices and the acceptability of deferred consent. Depending on local legislation, informed consent needs to be provided either by one or both parents/legal guardians. However, independent of the legislation, parents may prefer that consent is sought from both.

Clinical trial regulations and regulatory documents provide guidance on the informed consent process. 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. 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. 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.

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. 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.
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.56 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.60

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.

Author affiliations
1Department of Paediatric Clinical Pharmacology and Pharmacogenetics, Robert Debré Hospital, 48 Boulevard Séruer, Institut National de la Santé et de la Recherche Médicale (INSERM), Paris, France
2Dutch patient association for rare and genetic diseases (VSOP), Soest, The Netherlands
3The European Clinical Research Infrastructure Network (ECRIN), 5-7 Rue Watt, Paris, France
4Consorzio per le Valutazioni Biologiche e Farmacologiche, Via Nicolo Putignani, Bari, Italy
5TEDDY European Network of Excellence for Paediatric Research, Via Luigi Porta 14, Pavia, Italy
6Department of Paediatric Clinical Pharmacology and Pharmacogenetics, Robert Debré Hospital, APHP, 48 Boulevard Séruer, Paris, France
7Paris University, Paris, France

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Supplemental material

PedCRIN Survey[12]

Questions

Instructions were: “Please indicate, for which of the following activities do you think a research infrastructure for paediatric clinical research should provide support to?” and “Please choose the appropriate response for each item.” A Likert scale ranging from 0 to 4 was used (0 = "No need at all”; 1 = "Slightly needed;” 2 = “Moderately needed”; 3 = “Very needed”; 4 = “Extremely needed”). Other questions in the survey concerned demographic information (e.g. personal information, professional experience, country, paediatric specialty).

Table S1 PedCRIN Survey questions (verbatim wording)

<table>
<thead>
<tr>
<th>Topic group/ Survey questions (for which a level of importance between 0 and 4 had to be chosen)</th>
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<tbody>
<tr>
<td><strong>Scientific and methodological expertise</strong></td>
</tr>
<tr>
<td>• Design protocols for paediatric interventional clinical trials (PK, PK/PD, efficacy and/or safety, other)</td>
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<tr>
<td>• Design protocols for paediatric non-interventional clinical studies</td>
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<tr>
<td>• Identification of the target population (age subsets, inclusion/exclusion criteria)</td>
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<td>• Statistical methodology for paediatric clinical trials</td>
</tr>
<tr>
<td>• Application of innovative study design (e.g. modelling &amp; simulation and extrapolation tools/approaches) from adults to children and from older children to neonates</td>
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<tr>
<td><strong>Collaboration and support for clinical trials start-up</strong></td>
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<td>• Identification of relevant network/scientific societies to help the selection of clinical trial sites</td>
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<tr>
<td>• Establishing contacts with Young Patients Advisory Groups/Patients Advisory Boards/Patients Associations</td>
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<tr>
<td>• Identification of relevant calls for funding paediatric trials at EU/international level and support for project application</td>
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<tr>
<td>• Involvement of parties and subcontractors to define the distribution of all the responsibilities and tasks related to clinical trials (including CR0s, insurance companies, etc)</td>
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<tr>
<td>• Preparation of standard models agreements for the implementation of clinical trials</td>
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<td>• Definition of a budget model based on standard costs for general activities, investigation (per patient), services, etc</td>
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<tr>
<td><strong>Regulatory expertise</strong></td>
</tr>
<tr>
<td>• Database of national regulatory and ethical requirements for paediatric trial authorisation</td>
</tr>
<tr>
<td>• Preparing and submitting documents to Ethics Committees/Competent Authorities for the approval/authorisation of paediatric clinical trials</td>
</tr>
<tr>
<td>• Preparing consent and assent models + Patient information sheet, including clinical trials involving special patients populations (PICU, NICU, neonates, neurological impairment, etc)</td>
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<tr>
<td>• Preparing the Investigator’s Brochure for submission</td>
</tr>
<tr>
<td>• Interaction with national/European regulatory agencies</td>
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### Paediatric pharmacovigilance
- Methods for identifying and communicating ADRs in paediatric patients
- Age-adapted scales for severity and causality assessment in paediatric patients
- Targeted Serious Adverse Events notification forms, age-adjusted
- Certification of pharmacovigilance expertise

### Paediatric clinical trials conduct according to GCP and paediatric guidelines/recommendations
- Design Case Report Forms for paediatric studies
- Managing paediatric clinical trial data (data-management) (collection, integration, validation and analysis of clinical trial data)
- Managing paediatric IMPs (drug management) (packaging, labelling, delivering, storing, administering, accountability, disposal)
- Managing paediatric clinical trial technical aspects & logistics (e.g. shipping agent, operative instructions, laboratory procedures, biobank samples management, etc.)
- Preparation of monitoring plans, also based on risk-based approach
- On-site and remote monitoring visits and reporting

### Training
- Training regarding Good Clinical Practices, including responsibilities of principal investigators, co-investigators and study nurses involved in paediatric clinical trials
- Training course(s) designed for specific paediatric/neonatal trials
- Training on drug safety and toxicity stratified by age

### Box for free text to answer the following question:
Please list any other activity for which you think that it is required support from a research infrastructure

PK, Pharmacokinetic; PD, Pharmacodynamic; CRO, Contract Research Organisation; PICU, Paediatric Intensive Care Unit; NICU, Neonatal Intensive Care Unit; ADR, Adverse Drug reaction; GCP, Good Clinical Practice; IMP, Investigational Medicinal Product.
Summary of survey results

Out of the 147 respondents 35 (23.8%) were neonatologists. The results of a separate analysis of their responses did not differ from the overall responses.

Figure S1 Summary of PedCRIN survey results – Number of responses for each question by degree of need (all respondents).

YPAG, Young Persons' Advisory Group; PAB, Patient Advisory Board; Eu, European Union; CT, Clinical trial; ECs, Ethic committees; CAs, Competent authorities; ADR, Adverse drug reaction; IMP, Investigational Medicinal Product.

Free text responses provided more insight into the particular challenges researchers face. These included among others funding, clinical trial set-up and management, networking, involvement of patient/parent organisations, human resources, the need for more paediatric research (outcome, reference values, treatment standards, formulation development, pharmacokinetics/pharmacodynamics, non-clinical research), pharmacovigilance, interaction with regulatory authorities and ethics boards. Concerning informed consent and the recruitment into paediatric trials the following statements were made:

- “Strategies to improve the enrolment in clinical trial”
- “Especially in neonatology a lot of centres are needed to recruit patient numbers to trials in a reasonable time period.”
- “The EC and the regulatory authorities need to learn that studies in babies and children do take time.”
- “The largest problem is that many of the big EU trials in newborns failed to include patients. I think it is time to create infrastructure and clinical trial centres with dedicated young staff and researchers that can include many subjects into trials. 24/7 services need to be set up. A lot of money has been spent but less has come out of it.”
- “… but we need the power to include patients.”