Clinical Trial Decisions in Difficult Circumstances: Parental Consent Under Time Pressure

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Treatments and interventions used to care for children in emergencies should be based on strong evidence. Well-designed clinical trials investigating these interventions for children are therefore indispensable. Parental informed consent is a key ethical requirement for the enrollment of children in such studies. However, if time is limited because of an urgent need for intervention, there are additional ethical challenges to adequately support the informed consent process. The acute situation and associated psychological impact may compromise the ability of parents to give informed consent. Little evidence exists to guide the process of consent seeking for a child’s research participation when time is limited. It is also unclear in what circumstances alternatives to prospective informed consent could be applied. This article describes possible options to manage the informed consent process in an appropriate, practical, and, we believe, ethical way when time is limited.

A team is planning a randomized controlled trial to compare the use of nasal cannulas versus a mask for resuscitating preterm infants immediately after birth. Both techniques are routinely used, each with some advantages and disadvantages, and yet no one knows which is best. The trial team is uncertain about how to conduct the informed consent process because enrollment needs to occur before resuscitation at birth. Because many women go into premature labor unexpectedly, no opportunity exists for the trial team to calmly discuss the trial with women in a timely manner. The prospect of having to walk into a delivery room to discuss research participation when a woman is giving birth to an infant who is potentially severely ill is causing great concern to the trial team. Similar dilemmas are faced by child health researchers across the globe. Randomized controlled trials (RCTs) (Box 1) and other well-conducted clinical studies are necessary to generate evidence to inform decision making about interventions, and, ultimately, to improve child health. The current standard and ethically-accepted practice is to seek prospective informed consent. Consent is usually regarded as an ongoing process, in which, ideally, the patient and the family are provided with information about a study and have an opportunity to deliberate on this over several hours, days or weeks, and to clarify any queries through discussion with the trial team before deciding about trial participation. This process is consistent with the basic tenet that participation in research is voluntary.

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abstract

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The informed consent process in child health research is particularly complex because parents have to make decisions about trial participation on behalf of their child, while trying to avoid interference with their own hopes and wishes. When research is
planned in a setting pressured by the urgency of the intervention, additional ethical challenges are encountered, as the possibility to obtain prospective informed consent may be severely compromised. These challenges have often prevented trials from being conducted in emergency care. As a result, emergency treatments for children are commonly used without a robust evidence base.

Guidelines are currently lacking about the appropriate timeframe and process for seeking informed consent from parents for their children’s participation in research in urgent situations. Questions remain regarding how much time parents need to make a decision about trial entry for their child and what is the most appropriate point in the care pathway at which parents should be informed about the research. Previous trials in urgent situations have used alternatives to prospective consent, involving a process in which a lesser form of permission is sought prospectively to administer the urgent randomized intervention as part of the trial and consent seeking is deferred until after implementation of the randomized intervention and the child’s condition has been stabilized. Yet in such trials, it is not clear what is the most appropriate way to inform parents, “after the event,” that their child has received treatment as part of a trial. Inappropriate timeframes or approaches could adversely affect the informed consent process, jeopardize the clinician-patient relationship, cause parental anxiety, lead to unethical recruitment of children into a clinical trial, or limit fair access to the research.

This article aims to provide a framework to support the design of the informed consent process under different time constraints. We propose possible ways of organizing the informed consent process when time is limited and define circumstances in which prospective informed consent can be deferred. We describe four possible situations: no immediate time constraints (as a reference), limited time, no time to decide, and deferred consent after the death of a child. The development of the framework is outlined under Methods in Box 2, a visualization of the framework to guide decision-making is given in Figure 1. The timeframes linked to the different situations were chosen somewhat arbitrarily. Consequently, some potential solutions may also be applicable in other situations. A limited time setting also has important implications for child’s assent (Box 1), although consideration of this is beyond the scope of our article.

I. PARENTAL INFORMED CONSENT WITHOUT TIME CONSTRAINT

I.1. Trials That “Have No Immediate Time Pressure” for Seeking Consent

We consider a trial as having no immediate time pressure if the point at which the intervention is administered has no implications for the outcomes of the trial.

Alexander is 6 years old. He was diagnosed with chronic kidney disease a year ago. When Alexander comes for his quarterly checkup at the hospital, his pediatrician informs his parents about a trial investigating a new antihypertensive agent that is hoped to cause fewer side effects than the standard high blood pressure treatment. The doctor explains that this hospital is one of the centers in which a trial is to be performed comparing the new agent with the standard treatment. After giving all the information and responding to the parents’ questions, the doctor asks the parents to consider whether they are willing to give consent for their son to participate in this trial. It is agreed that they will communicate their final decision at a later visit.

When parents are asked to consider entering their child into a trial, the ideal situation is one in which the consent process can be tailored to the needs and preferences of parents. This may be key in enabling parents to feel able to make a decision about participation without any sense of pressure or coercion. However, there is insufficient evidence about the optimal amount of time when consent should be sought to enable parents to process the information given and to come to a decision on trial participation.

There are various guidelines regarding the content of information that should be provided to parents to ensure that their consent is informed and the provision of such information is often a legal requirement. Although the informed consent procedure is intended to help parents in the decision-making process, several studies indicate that, and according to the opinion of the neonatologists we consulted, parents often have difficulties understanding the patient information, and perceive the amount of information that they are given to be overwhelming. In a study by Chappuy in which the parents were asked about their knowledge regarding the items included in the informed consent document, only a minority (21%) of parents were found to fully understand all items.

I.2. Potential Solutions

Although it is recommended that sufficient time should be made available for parents to consider participation of their child in a clinical trial what constitutes “sufficient time” depends on how long it takes a parent to consider the procedures, risks and benefits, and alternative treatments. It also depends on the needs and preferences of parents as individuals and the clinical context, including the level of parental anxiety at time of the initial presentation of the clinical trial information, arising from the seriousness of the condition.
of their child. From this perspective, the optimal time frame might range from a couple of hours to a week or even longer.

The information provided to parents could be improved by considering the priorities of parents because some components of the content may be particularly important from their perspective, whereas other components may be of little significance. Parent-friendly,
accessible information (eg, text with a larger font, underlining important information) provided on 1 page, highlighting aspects that are particularly salient to parents (such as the risks and benefits for their child) may be more helpful than the current standard informed consent information.\textsuperscript{18,19} Also, other ways of giving information, including the use of visual tools or electronic methods of information provision that facilitate interactivity on the part of parents could be helpful.\textsuperscript{19,20} These proposals are consistent with changes currently being contemplated in the revision of the US federal regulations governing research.\textsuperscript{21} Parents report a preference for information to be given verbally rather than in writing.\textsuperscript{22} Ongoing explanation and discussion even after formal consent has been given (or continuous consent) may be helpful.\textsuperscript{23}

\section*{II. PARENTAL INFORMED CONSENT WHEN TIME IS LIMITED}

\subsection*{II.1. Trials That Have Time Limitations for Seeking Consent}

In these trials, the investigational interventions must be introduced within a timeframe that is not compatible with the normal process of informed consent. As stated earlier, the normal time frame of informed consent might be defined as a few hours minimally, although in most countries a study team has to justify if the time available for consent is <24 hours. Some have argued that a minimum of 30 minutes is needed to seek meaningful informed consent.\textsuperscript{24}

Due to placental disruption a 32-year-old woman has delivered her premature infant by emergency cesarian delivery. Immediately after birth her infant develops severe respiratory failure and needs ventilatory support. In the hospital, an RCT comparing ventilator support with or without the addition of inhaled nitric oxide is being conducted. Because the mother is still anesthetized, a member of the trial team approaches the new infant’s father about entering the infant into the RCT. For this time-pressured intervention, he has only 10 minutes to decide what to do.\textsuperscript{25,26}

The time constraints in trials of urgent or emergency treatments give rise to considerable difficulties for parents, but these trials also raise difficulties for the trial team responsible for recruiting participants. It is their responsibility not only to provide relevant information about the research and what participation will entail but to also ensure that this information is understood.\textsuperscript{3} When there is limited time, parents are likely to struggle to understand even basic information about the trial. Moreover, when parents are anxious due to the psychological impact of their child’s condition and the need for urgent intervention, fear could push them to make quick, poorly informed decisions.\textsuperscript{26,27}

Nevertheless, even when a decision must be made in a time-limited situation, parents do seem to value the consent process. Parents of surviving infants who had been enrolled in a neonatal trial comparing 2 methods of life support using conventional randomization took part in qualitative interviews about their attitudes toward the consent process. About half of the parents did not wish to see this process replaced with alternatives such as a Zelen approach,\textsuperscript{28} in which randomization precedes consent and consent is not sought for those allocated to the control group.\textsuperscript{29} In another study, ~90% of the parents who consented to trial participation of their newborn child were against letting doctors decide about participation.\textsuperscript{12,30} Despite the stressful situation and the complicated information, parents generally want to be involved in decisions about their child’s research participation.\textsuperscript{31,32} From this perspective, it is important to consider the engagement of parents while safeguarding a proper informed consent process.\textsuperscript{8}

\subsection*{II.2. Potential Solutions}

The clinical circumstances in which there is limited time for private deliberation are not described in national or international laws or guidelines. The informed consent process in these circumstances is likely to be less than optimal, and adaptations to the requirements for the informed consent process and information content will be inevitable.

When there is only a short time to think about trial participation, it is unlikely that parents will be able to read and process all the information given during the standard informed consent process. Even in the standard informed consent process in trials without time constraints, parents often report information to be overwhelming, as noted earlier: A modified version of an informed consent document, in which the readability (reading grade levels 7–8) and accessibility (eg, use of pictographs) was improved, while all required elements for consent were retained, improved parental understanding compared with the standard version.\textsuperscript{33} Therefore, by restricting extraneous detail in informed consent documents and including only the most important or core points, providing easy-to-read information, and incorporating images could be helpful.\textsuperscript{18,33} The core content should be determined through consultation with relevant stakeholder groups but might include the trial’s purpose, the benefits and risks, randomization procedure, concept of clinical equipoise, and the possibility of withdrawal. From literature, and according to the opinion of the neonatologists, the opportunity to consult with others or to have some private time for discussion is seen as an important aspect of the informed consent process, even when facing a limited time frame.\textsuperscript{7,34}

Given the demands that parents will face in considering a trial in a limited timeframe and in stressful circumstances, any opportunity to provide anticipatory information about research to those parents who...
are “at risk” of being asked to enter their child into a trial and before consent needs to be sought should be taken. Especially for those with chronic illness or for pregnant women at risk for complications, there may be opportunities to explain relevant research studies in advance. For example, (future) parents with an imminent premature birth could be informed about possible research before the urgent situation arises. However, this needs to be balanced against the potential to cause unnecessary anxiety in those who, although at risk, do not go on to have the complications that make them eligible for a trial. The neonatologists who we consulted with stated that in their trial, this preemptive information approach was the standard practice; they felt that the time available to ask for informed consent immediately after birth was insufficient and that introducing the concept of a trial at this point was inappropriate. This is consistent with the experiences of practitioners in another study.

Improvement of the logistical processes, such as ensuring that all professionals who might discuss trials with families during night shifts have relevant training and ensuring that there are good channels of communication between different departments involved in a child’s care, such as obstetrics and neonatology, could facilitate this process of preemptive explanation and consent seeking in the urgent situation as well (neonatologists’ opinion; see Box 2).

An additional option is to define different levels of information about relevant research options, to allow the incremental scaling up of information based on a risk assessment or deterioration of a child’s clinical status. Such prior information titration might enable an informed consent process to be undertaken, even in a stressful context, or might in some circumstances enable parents to give prospective informed consent in the event that their child becomes eligible for a trial at some point in the future.

Another way of supporting parents in a limited time setting is the use of a type of continuous consent, in which prior prospective informed consent with a suboptimal time window is followed by a second informed consent conversation after the study activities that could not be delayed have taken place and some additional time is available. This option could enhance parental understanding, provide another opportunity for parents to withdraw, and allows other relatives to be involved in the consent process.

III. PARENTAL INFORMED CONSENT WHEN THERE IS NO TIME

III.1. Trials That Have No Time for Prospective Consent

Trials in this situation involve investigational interventions that have to start immediately after a patient has presented, leaving no time for seeking prospective informed consent.

An RCT comparing 3 fluid resuscitation strategies in the treatment of children with shock and life-threatening infections enrolled patients across the severity range. The children were randomly assigned to receive boluses of 5% albumin solution or 0.9% saline solution or no bolus at the time of admission to the hospital. To preclude systematic nonparticipation of the most severely ill children, the researchers opted for a deferred consent. This included enrollment and randomization into the trial at the time of admission, with full written consent being sought after stabilizing the child.

Sometimes it is impossible to obtain prospective informed consent for research. This is the case when a delay in implementing the investigational treatment or diagnostic procedure would endanger the child, the family members cannot be contacted in time, or are too overwhelmed to give consent due to physical or emotional trauma.

Internationally, there are few guidelines for situations in which there is no time to obtain prospective informed consent. The US Food and Drug Administration posted a final rule, which described the types of trials that may be eligible for the exception from informed consent (Box 1). Eligible trials included those investigating treatments for immediately life-threatening conditions in which the available treatments are unproven or unsatisfactory, where seeking prospective consent is not feasible, and no other possibilities for research are available. The Helsinki Declaration mentions the possibility of exception from informed consent in emergency situations when a patient’s physical or mental condition prevents him or her giving informed consent and the condition is a necessary characteristic of the research population. In such circumstances, consent should be sought from the legally authorized representative, which in the case of children is usually the parent or caretaker. If no such representative is available and if the research cannot be delayed, a patient may be included in a study without informed consent. The specific reasons why the study needs to recruit patients with the particular condition should be stated in the research protocol, and informed consent still needs to be obtained as soon as possible afterward. Various national legislations have similar statements. Under such a deferred consent process, the only study activities that can proceed are those that cannot be delayed until consent can be sought. Consent in such circumstances involves asking a parent or patient to decide about continuation or withdrawal from the study and to consent to activities that have yet to take place. When study-related activities have ceased before consent could be asked, consent will only concern use of the patient’s data.
care, involving severe, life-threatening conditions (eg, in resuscitation, major trauma, shock, etc). These regulations also apply to situations in which the intervention itself is not lifesaving but there is a limited timeframe to study its effect (eg, a diagnostic test in an emergency). In some countries (eg, the United States), the exception from informed consent is only allowed when there is a prospect that the trial will be of direct benefit to the child (supported by appropriate animal and other preclinical studies), and the risks and benefits are reasonable. Furthermore, in the United States, it requires a process of community consultation and public disclosure.35

Trials in these circumstances are important to determine the optimal treatment of severely ill children. Problems with obtaining informed consent in this patient group could introduce selective recruitment if the more severely affected children are less likely to be included than other groups. This might undermine the generalizability of the results to the target population.36 Although deferred consent helps to avoid this difficulty, clinicians might feel uncomfortable approaching bereaved parents for consent or about conducting study activities such as blood sampling before consent has been sought.35

III.2. Potential Solutions

In cases in which the investigational intervention is necessary to prevent imminent death or serious harm to the child and the research question cannot be addressed without this specific population in an emergency setting, deferred consent is a reasonable option. Important conditions for deferred consent include the relevance of the intervention for the particular patient group involved, the possible beneficial effect of the intervention, a true state of equipoise, and low risks for the patient group. For example, in the case of a minimal risk study, deferred consent may be considered appropriate, whereas a non–minimal risk study could require community consultation.38 In some cases, deferred consent is used as part of a 2-stage informed consent process with prior verbal permission as the first stage and deferred consent after stabilization of the child.38 However, it is questionable whether this approach is feasible and desirable because parents are still asked to consider information at a time when it is expected that they are unable to listen to, ask about, and understand the information.39 Furthermore, even slight delays due to the prior permission-seeking process in emergency situations could lead to avoidable mortality and morbidity in trial participants and underestimate the beneficial effect of treatment.40

When designing a study that will be implemented in an emergency setting, challenges with the consent process can reduce the number of recruited patients or lead to sampling bias, both of which may limit the study’s value. Therefore, it is important to carefully review different informed consent options. If deferred consent is used, researchers should identify which procedures need to be undertaken before deferred consent is sought and try to ensure that, when possible, study procedures can be scheduled after consent has been sought. In some situations, preemptive information on the study could be offered to risk groups (eg, at the prenatal clinic) or when there is a deterioration of the chronic illness of a child.12,23 The limited available evidence suggests that the attitudes of parents and health care professionals toward deferred consent views may be divergent. Professionals without previous experience of deferred consent have been found to be apprehensive about the approach or find it inappropriate not to give parents any choice before starting the study.35,39 On the other hand, approximately two-thirds of parents of critically ill children reported that deferred consent was acceptable to them,41 or parents suggest that professionals should just get on with treating their child and worry about consent later.39 These different viewpoints indicate the need for further discussion and reflection on the best practice regarding the informed consent process and to consult with parents (and, if feasible, young people) as partners in the design of consent procedures for trials that will be implemented in emergency settings.

IV. WHEN THE CHILD DIES BEFORE CONSENT HAS BEEN SOUGHT

Inevitably, trials in which there is limited or no time for seeking prospective consent are usually conducted in severely ill children, and mortality in these trials may be comparatively high. This raises the question of whether deferred consent should be sought from parents of children who have died. There could be reasons to do so: bereaved parents may want, and indeed have a right, to know that some of their child’s treatment was given within a trial and to decide on what happens to their child’s data; they may feel deceived if information about the trial is withheld and they later discover through various channels that their child had received treatment within a trial without their consent.42-44 Yet seeking deferred consent could compound a parent’s grief and lead to feelings of anger and regret, sometimes with the withdrawal of essential data from the study as a consequence. Molyneux et al concluded that deferred consent should not be sought in this situation.39 The issue of withdrawal of data does not arise in the United States, where the regulations allow
investigators access to data that have already been collected, providing the use of the exception from informed consent has been justified. A recent survey investigated parents' views (including bereaved parents) on deferred consent for a hypothetical trial comparing 2 resuscitation treatments in standard use. In the event of a child's death before information about the trial could be given, the majority of bereaved parents (12 of 18) reported that they wanted to be told about the trial at some time. Bereaved parents also indicated the importance of individualized management of disclosure about a trial after a child's death.

IV.1. Potential Solutions

We conclude that in these cases, consent can and should be sought in a way that is sensitive to the parents' needs and at a time that allows for a considered judgment on their part. This would probably mean after the most acute phase of bereavement. However, the acceptability of this approach needs more study.

SUMMARY

In some circumstances, parents have limited time to consider trial participation of their child. This requires adaptations to the informed consent process, for which this article gives possible options.

Potential Solutions for Current Trial Practice

Figure 1 provides a decision-making framework for the informed consent process. The development of simplified, core information in easy-to-read language could improve parents' understanding, as well as the use of a type of continuous consent, in which prior prospective informed consent is followed by ≥1 subsequent conversations verifying understanding.

When informed consent at the time of enrollment is difficult or impossible, prospective discussions to inform parents about possible research participation of their child in a trial could help optimize the informed consent process.

Researchers should be trained in the informed consent procedure and in communication about consent seeking to enhance the consent process and to understand alternative methods of seeking consent, such as deferred consent, when appropriate.

In trials performed in emergency settings, deferred consent may be an option. It helps to avoid selective sampling and in this way can help answer research questions that would otherwise be off limits and thus improve treatments for the sickest children.

Box 1. Definitions

Randomized Controlled Trial: A scientific experiment in which participants (patients) are randomly allocated to 1 of the treatment groups. The best available treatment (or placebo) is compared with 1 or more regimens that are expected to either improve survival/health or lessen toxicity with equivalence of outcome. This is the study design most commonly used in testing the safety and efficacy of healthcare services (such as medicine or nursing) or health technologies (such as pharmaceuticals, medical devices, or surgery).

Concept of clinical equipoise: The genuine uncertainty of the expert medical community regarding whether an experimental treatment is more beneficial than the best available treatment.

Parental informed consent: In cases of child participants, a child is considered unable to give informed consent, and another person (eg, parent, proxy, caregiver, or other legal guardian of a child) is generally authorized to give consent on his or her behalf. The right of the parents to decide is predicated on the fact that parents understand all aspects of the trial before making a decision.

Child's assent: The possibility to express willingness to participate in research by children who are, by definition, too young to give informed consent but who are old enough to understand the proposed research in general, its expected risks and possible benefits, and the activities expected of them as participants. Assent by itself is not sufficient; informed consent must still be obtained from the child's parents or guardian.

Deferred consent: No or a minimal amount of information is given to the patient and/or the parent in advance. Randomization is conducted at the investigator's discretion according to criteria that have been made explicit during ethical review of the protocol, followed by the request for patients' (deferred subject consent) or representatives' (deferred proxy consent) informed consent in a later phase.

Urgent: Requiring speedy action or attention.

Emergency: An unforeseen or sudden situation that poses an immediate risk to life or health, which requires immediate intervention to prevent a worsening of the situation.

In the United States, the preferred terminology is “parental permission,” recommended by the American Academy of Pediatrics. The basic concept here is that you could not give consent for someone else to use something that is not yours.

In US regulations, the term “exception from informed consent” is used. These regulations state that the term “deferred consent” is inadequate because there is no opportunity to prevent administration of the treatment.
Recommendations for Research

Further empirical research is recommended on parents’ experiences and preferences concerning informed decision-making in an urgent situation, the utility of prior information and of alternative formats for the consent process. Research on the opinions of clinicians in range of relevant pediatric specialties would also be helpful.

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ABBREVIATION

RCT: randomized controlled trial


Literature search: A specific literature search in the databases Medline and Embase (from January 2003 to October 2014) was conducted using the search terms “children,” “clinical trial,” and “informed consent.” This yielded 534 articles (Medline: 253, Embase: 347), of which 78 were relevant. Also, a reference check on the selected articles was conducted. An Internet search using the Google search engine was conducted to identify guidance documents on informed consent. This search yielded 4 relevant guidance papers on this topic by the US Food and Drug Administration, Scottish Children’s Research Network, UK National Research Ethics Service, and the EU Community Research and Development Information Service. The selected articles were used as a scientific base for describing an appropriate consent process in different situations.

Expert group: Pediatric clinical trial experts from the United Kingdom (3), Australia (1), Canada (1), and the Netherlands (4) took part in the expert group to review the evidence and draft the paper. The experts are members of the StAR Child Health group, an international consortium working together to improve global standards for child health research. The experts were selected because of their publications on this topic or their experience with the practical and ethical considerations regarding informed consent in trials. They participated in bimonthly online meetings over 1 year and met face to face on 1 occasion to discuss the content in more depth and to obtain consensus on specific topics where needed. The final manuscript was completed after 4 major rounds of drafting, during which account was taken of feedback from all experts.

Testing by practitioners: We sought the responses of 12 practitioners with relevant firsthand experience of clinical trial recruitment on an earlier draft of the proposed solutions by presenting the draft and asking for feedback during via a face-to-face group meeting. The practitioners were neonotologists from 12 NICUs in Germany who were involved in recruiting premature infants to a clinical trial within 2 hours after delivery. For the development of the potential solutions, all relevant comments of this group were taken into account (for recommendations based on these comments, see the neonatologists’ opinion outlined in the text).

Parental views: To incorporate parental perspectives, we drew on the available research literature regarding the views of parents (as identified through the searches, as well as the literature provided by the experts). Ethics approval was not applicable.

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