Considerations for Informed Consent in Clinical Trials Involving Neonates

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Conducting clinical research in newborns requires special protections due to the high vulnerability of this patient population and their parents. Approaches to informed consent for neonatal research require unique considerations. This paper presents a review of the ethics literature on this topic, including factors such as parental attitudes regarding informed consent, the manner in which a healthcare professional presents a family with the option to participate in a trial, and the role of ethics review bodies. This paper also presents guidance developed from our experience working with a multidisciplinary group of bioethicists and patient advocates to consider patient- and parent-centric approaches to informed consent practices in neonatal research, in the context of an ongoing clinical trial for neonates with spinal muscular atrophy (SMA).

Introduction

Conducting clinical research in very young children requires special protections and ethical considerations. The inclusion of children in research has increased substantially in recent history, and advances in genetic research have led to an increase in the number of trials for children with genetic diseases, many of which are rare and affect newborns. A search of the clinical trials registry ClinicalTrials.gov revealed 1829 studies in children that include the word "genetic" in their description between January 2000 and 2009, with an increase to 3015 such studies between 2010 and July 24, 2017. Roche is conducting clinical trials in spinal muscular atrophy (SMA) and other conditions affecting young children. In the context of designing a clinical trial in SMA type 1 (SMA1), the trial sponsor sought to determine best practices for informed consent of parents of neonates with a new diagnosis of a rare genetic disease. This paper presents a review of the clinical research ethics literature on this topic and guidance developed from working with a cross-disciplinary group of bioethics advisors and patient advocates. As research on infants with rare genetic diseases becomes more frequent, this paper is intended to inform best practices in this evolving field.

Of course, newborns, children, and adolescents vary widely in their physical, cognitive, and emotional capacities. While older children may have some

capacity to give assent or dissent to their participation in clinical trials, babies are unable to provide an opinion, and the parents' role might be viewed as that of absolute surrogate decision maker in the sense of being fully responsible for decisions. However, it has been asserted that "surrogacy" is not the most appropriate concept because the parent cannot know or presume the wishes of the neonate. [1, 2] Therefore, the rationale for obtaining parental consent may not be solely because they are a "surrogate" but due to the need to respect parental authority and family decision-making, and to respect the parents' role in wanting to choose the most beneficent option for their child. It has also been asserted that not only parents, but also ethics review boards and researchers, have a responsibility to protect the child. [2]

Recruiting neonates for clinical research is a challenge. There may be an incentive for researchers to emphasize the likelihood of benefit, particularly for those who are also the treating physicians for these neonates, and it may be difficult to separate the goals of research and treatment. Receiving a new diagnosis of a rare condition that may be highly disabling or fatal for their newborn places parents under extreme stress. They may find it difficult to thoroughly consider alternatives to participation in a trial. These issues complicate the investigator's ability to ensure fully informed parental consent in clinical trials of neonates with a newly diagnosed rare genetic disease.

> "...THE PARENTS' ROLE MIGHT BE VIEWED AS THAT OF ABSOLUTE SURROGATE..."

Informed Consent for Clinical Trials in Neonates: Review of the Literature

While facilitating trial enrollment is important, the primary goal during recruitment should be to promote the parents' understanding and their ability to give voluntary consent. [3] There is a body of literature focused on the informed consent process in neonates, only some of which relates to informed consent for clinical trials.

A search of PubMed in early 2017 for peer-reviewed literature using the keywords "neonatal", "clinical trials", and "consent", and subsequent review of the relevant references yielded 12 results. These included questionnaires/surveys, in-depth interviews, analysis of unsolicited comments, and an observational study that addressed many aspects of informed consent among parents of neonates.

Review of the literature yielded several themes described below including parental vulnerability and attitudes, giving sufficient time during the consent process, and potential approaches to mitigate the risk of therapeutic misconception and potential conflicts of interest.

Parental Vulnerability and Parental Attitudes to Informed Consent for Clinical Trial Participation

Parents varied regarding whether they felt pressured to participate in a trial, their emotional state, their level of understanding of the trial, and their sense of whether they had sufficient time to make the decision. Moreover, their recollections varied as to having been given an information sheet and having had the opportunity to ask questions. [4] When asked if parents were comfortable with a model in which consent was presumed unless parents opted out, some parents preferred it, but others did not, and some stated that opt-out did not reduce burdens on parents. [5] For parents who consented to their baby's participation in neonatal studies, multiple studies indicated they were motivated by the potential benefit to their own babies as well as to other babies, doctors, parents, and society. For parents who declined, reasons given included inconvenience to themselves, and more importantly, burdens or risks for their child.

Some parents felt they did not have enough time to make a decision and that being approached about a trial at an already difficult time added stress and anxiety. [4] Some parents indicated they felt no additional stress when asked about participation in a clinical trial, but some did not want to make the decision.[4] Even those who wanted to make the decision noted the importance of getting input, not only from their spouse and wider family, but also from their doctor, whom they trusted to recommend a good decision. [4]

Should the Principal Investigator Administer Informed Consent?

Ethical concerns about the boundary between research and clinical care have been longstanding, and center on the differing aims of the two pursuits. The purpose of research is to further scientific knowledge, while the purpose of clinical care is to benefit the individual patient.

Therapeutic Misconception

"Therapeutic misconception" (TM) is a phenomenon first described in 1982 by Applebaum and colleagues [6] which the National Bioethics Advisory Commission (NABC) later defined as, "the belief that the purpose of a clinical trial is to benefit the individual patient rather than to gather data for the purpose of contributing to scientific knowledge." [7] Applebaum and colleagues found their research participants often believed the medications they were given were for their own benefit, rather than part of the study design. Participants misunderstood the implications of randomization and control groups in particular. Participants under TM may underestimate potential risk of harm and overestimate potential benefit. [8] Even in studies that are not placebo-controlled, research protocols, by definition, restrict some discretion in flexibility of care. This requirement to follow a protocol may be poorly understood by a parent if the goals of research and treatment are conflated. Whether or not consent is in fact impaired in the presence of TM for parents of neonates is unclear but it is reasonable to consider that misunderstanding the goals of research and potential outcomes during a time of parental stress could affect the decision to participate in a trial.

> "...THE PURPOSE OF CLINICAL CARE IS TO BENEFIT THE INDIVIDUAL PATIENT."

Conflicts of Interest and Potential Undue Influence

Clinical investigators might have secondary reasons for enrolling patients in clinical trials, including potential publication and academic promotion, and well as payments from a trial sponsor. Undue influence is when an offer of something desirable, such as promise or suggestion of benefit, or payment, influences decision-making in inappropriate ways.[9] Trials for rare pediatric diseases may be more difficult to enroll and there may therefore be increased pressure on the investigator to influence consent and enrollment. However, it should not be assumed that investigators would inappropriately influence parents, and this specific issue in the context of neonatal trials has not been studied. Clinical trial participants (or their parents in this case) might also receive reimbursement payments to cover expenses for travel and logistics to make it possible to come to clinical trial sites, and such reimbursement is generally not considered undue influence (9).

Because of potential issues such as therapeutic misconception, conflicts of interest, and undue influence, some have proposed that the principal investigator (PI), who may potentially have a conflict of interest, should not administer consent, but rather other members of the study team could do this. [10] The rationale for this preclusion is that parents can distinguish the differences between clinical care and research more easily if someone other than their child's treating physician administers the consent process. [3] However, studies have shown that some parents are more comfortable talking with their attending physician regardless of that person's role in research, while others prefer to talk with a researcher who is not involved in their child's clinical care. [3] Clinicians have expressed an understanding of their responsibilities to both the conduct of the clinical trial and to parents. Some viewed them as equal responsibilities while others took the view that the parents' interests should be prioritized over those of the trial. [11]

Shah emphasizes the importance of the professional obtaining consent being aware of his or her potential for exerting undue influence, rather than excluding certain professionals from obtaining consent from parents. [3] She states that the trusting relationship with the infant's family is of critical importance and suggests two strategies to help: (1) offering three reasons some parents choose to participate and three reasons some do not; and (2) offering parents the opportunity to talk with another person about the study before making a decision.

The Role of the Research Ethics Committee or Institutional Review Board

Based on European research on consent for neonatal study participation, it has been proposed that while parents' consent in trials is vital to their socially recognized parental roles, it may not offer additional protection to that offered by appropriate research ethics, safety monitoring, and governance procedures. Parents should be made aware of these procedures. [12] Some propose that properly qualified ethics committees weigh risks and benefits and make a recommendation to the parents directly [13], with no requirement for parents to follow the recommendation. However, these committees can have inconsistent recommendations overall, even regarding who should inform the parents about research, and across sites in multicenter trials. [3,13]

Timing and Other Elements of the Consent Process

Because information sheets describing the risks and benefits of a clinical trial may be incompletely understood, a multi-step or continuous consent has also been recommended. [14] Some studies have found that parents improve their decision making when given more time to make their decisions. [15]

Multiple-Site Issues

Beyond the process at an individual site, a global clinical trial with multiple sites may add elements of complexity, particularly with regard to the consistency and quality of the informed consent process across study sites. While it seems obvious that training of staff is necessary, the reviewed literature did not address how to ensure that multiple sites in a global program consistently give parents enough time with appropriate counseling to make an informed decision, nor did it describe best practices for training clinical research staff on how to administer informed consent in trials enrolling neonates.

Case Study: A Clinical Trial in Neonates with SMA1

A multicenter, international clinical trial sponsored by Roche Pharmaceuticals (the 'FIREFISH' trial) is designed to assess the use of an investigational medicine known as an oral SMN2 splicing modifier in neonates with SMA1 aged 1 to 7 months at the time of enrollment (ClinicalTrials.gov number NCT02913482). The study is open label, and all patients receive the investigational medicine. The study takes place in multiple countries across four continents.

SMA is a rare genetic disease most commonly caused by a mutation in the *SMN1* gene on chromosome 5. The disease is characterized by loss of motor neurons and progressive muscle weakness. A severe form is SMA type 1, a life-threatening condition affecting very young children. The diagnosis of SMA1 typically occurs during the first few weeks to months of life when babies do not meet motor milestones.

Coming early in the family's experience with the baby, the diagnosis is a tremendous shock for parents. It is during this highly emotional period of recently receiving a diagnosis of a fatal or highly disabling illness that parents would likely be approached regarding their babies' potential participation in a clinical trial.

The psychosocial impact for parents of children living with SMA involves many areas, including confronting premature death, making difficult treatment choices, fearing the loss of functional ability, coming to terms with lost expectations, loss of sleep, stress, stigma, limitations on social activities, independence, uncertainty and helplessness, and family finances. [16] Receiving a diagnosis of a disease with these perceived outcomes could possibly lead parents to agree to anything that might help their baby, without full consideration of the alternatives. Clinical trials may be perceived as 'the only therapeutic option' by parents.

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Evolving Evidence and Availability of Treatments for SMA

At the time the trial was started, there were several other clinical trials available for children with SMA, but there were no approved treatments. After the completion of a large phase 3 clinical trial [17] of nusinersen, the first agent shown to improve the course of clinical progression in SMA, an expanded access program was made available for patients. Though drug supply was adequate, some limitations in healthcare infrastructure necessitated the development of ethical criteria for treatment allocation. [18,19,20,21] Within a few months of the start of FIREFISH in 2016, nusinersen was approved by the US FDA, and then in 2017 in the European Union, Japan, Canada, and Brazil. Despite approvals in these regions, there were still patients who lacked access to treatment or who were not candidates for treatment due to the need for intrathecal administration. [22]

It was important to the study team to adequately convey the availability of new treatments and trials during informed consent. Besides the variable access to nusinersen, it was a newly available treatment with long-term outcomes that are difficult to predict, which complicates the informed consent process. [22] A number of clinical trials with other agents, including gene therapy, have also been available and recruiting participants. The availability of new therapies, several clinical trials, and supportive and palliative care options make the decision-making process for parents of children with SMA particularly complex. Informed consent for parents of children with SMA for the Roche FIREFISH Trial was similarly complex, not only due to the severity of the disease in a highly vulnerable population, but also by the landscape of approved treatments and ongoing clinical trials.

In light of these issues, while setting up the trial, the Roche clinical trial team sought to ensure, to the extent possible, that:

- There is no undue encouragement on parents, consciously or unconsciously, to enroll their babies into the trial
- Newly approved and investigational treatments are presented appropriately in a fair and balanced way, even if they compete with trial enrollment
- Parents receive the information they need in the most appropriate way, supported by sufficient time and space to allow them to reflect and consider potential benefits, risks, pros and cons
- Parents understand that as a consequence of participation in the trial, other investigational medicines, or potentially treatment options, may no longer be available to their babies, and their babies may be required to undergo procedures that are specific to the trial, e.g., placement of a gastric tube
- Ultimately parents make an informed decision on whether their baby will participate in the trial

Given the sensitive nature of informed consent in this highly vulnerable population, the study team sought ethics advice to help develop a plan for training investigators on informed consent.

Bioethics Consultation

The Bioethics group within Roche Pharmaceuticals, a multidisciplinary team composed of professionals with expertise in applied bioethics and drug development, operates a company-wide consultation service. Individuals and project teams with clinical research ethics questions, such as the team working on FIREFISH, can consult with this service. For complex issues, advice can also be sought from the Scientific Ethics Advisory Group (SEAG)[a] , composed of international external (non-industry) experts invited by Roche from the fields of genetics, bioethics, law and science policy, and patient advocacy. The SEAG is an advisory body to Roche on bioethical issues and is separate from IRBs and National Ethics Committees that routinely review study protocols, informed consent forms, and study conduct.

In 2016 and 2017, members of the FIREFISH clinical development team, the Roche Bioethics group, and the SEAG met to consider the question of how to encourage thoughtful informed consent in clinical trials in neonates in the context of the upcoming trial. The team requested guidance regarding how best to approach informed consent for the trial, considering the neonatal population, multiple study sites across different geographies, cultures, languages, availability of other trials, and a newly approved treatment. Guidance of the SEAG was considered informative for this specific trial and future neonatal trials for other diseases and investigational agents.

The SEAG offered suggestions to simplify and improve clarity of the Sponsor's informed consent form (ICF) template and the informed consent process. The suggestions were the following:

1. Clearly name alternative options, not only for approved treatments, but also whether or not an expanded access program for a particular agent was available in a given country, without guarantee that it would be effective for their child.
2. Explicitly state the availability of newly approved treatments in the patient's geographic region.
3. Emphasize the differences between an approved treatment and one that is investigational.
4. Inform parents that participating in this trial may exclude their participating in another investigational trial and that current standard of care treatment, including the option of palliative care, is an alternative option to the clinical trial.
5. Incorporate an info-graphic with a calendar of assessments, scenarios or frequently asked questions.
6. Develop language for an FAQ or supportive document for study staff such as: "in this situation, some people have found the following information helpful in making up their minds…"

a http://www.roche.com/research_and_development/who_we_are_how_we_work/ethics_in_rd/ethical_conflicts.htm

7. At some sites, a clinical ethics consultation team, in addition to the PI, could be available to help parents decide whether to enroll their child.

8. An important way to ensure that parents have understood the issues related to enrolling their child in the trial is to ask that they repeat back what has been discussed.

Approaches to cultural differences and geographies were discussed, and it was agreed that cultural differences should be considered, but should not impact the global ethical standards to which the study should adhere, regardless of where study sites are located. Supportive care, rather than medication, may be preferred in some cultures; however, in general, approaches to consent should not vary simply based on arguments of cultural difference without expert evaluation.

The study team communicated guidance for informed consent at the investigator meetings for the trial. Some investigators noted that this increased emphasis on the informed consent process at the meeting provided a helpful review and re-affirmed their commitment to spend extra time and care explaining the study to parents, and how participating in the study differs from usual medical care. Investigators have a variable degree of training in informed consent and a special emphasis during investigator meetings could be useful. Subsequently, one of the sites incorporated a discussion without the PI, and with a patient advocate and a physician who is not involved in the study to assist the family in deciding whether to enroll their neonate. There is not a consensus as to whether or not this assists in parental decision-making or whether it might impact trust in the investigator-parent relationship. The FIREFISH study is currently ongoing.

Conclusion

As the understanding of the biology of rare genetic diseases continues to advance, clinical trials in neonates may increase. Given the high vulnerability of this patient population and their parents, it is critical to consider the ethical aspects involved in conducting such studies, including the impact of a new diagnosis on new parents, and the changing availability of treatments on informed consent. This is one example where study sponsors worked with bioethicists and patient advocates to consider patient- and parent-centered approaches to the conduct of clinical research.

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Transparency Statement

JJS and AK are employees of Genentech, a member of the Roche Group; OK, SJ, and TS are employees of F. Hoffmann-La Roche Ltd.

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