Research ethics boards decision on alternative consent methods in the SafeBoosC-III trial

Background

The use of prior informed consent is the norm in clinical trials. Obtaining prior informed consent must comply with the requirements stated in The Declaration of Helsinki (1). When it comes to children or newborns, the parents or legal guardians must give the informed consent (2,3). æ

To improve pediatric intensive care, randomized clinical trials are of uppermost importance. Unfortunately, the process of obtaining prior informed consent for experimental treatment does not fit well into the clinical reality of acute and intensive care. The intervention often has a short therapeutic window, thus making it difficult to obtain a valid prior informed consent in time. This problem, may seriously reduce the value of the consent and/or the number of enrolled children and thereby inhibit trial execution and completion. Different consent procedures may therefore be more appropriate for intensive care research.

Deferred consent involves enrolling patients into a trial, i.e. randomizing, applying the allocated interventions and initiating the necessary data collection without prior consent. Instead, informed consent is sought later. In pediatric research, parents or a legal guardian is asked for consent. If consent is given, the patient can continue in the trial and if not, any intervention will be withdrawn and data will not be used. After 40 years, the use of deferred consent is still controversial and is only accepted in some countries (4,5).

Another option of consent, is the opt-out method with enrollment as default. When using this consent form, prior information of the study will be given to the parents and it will be specifically outlined, that their child will be enrolled in the trial, unless they decide to 'opt-out'. Clinical staff must record in the infants clinical file, that they have explained the trial and the 'opt-out' consent process to parents. If no record on this, the child will be excluded from the trial. Full informed 'opt-out' consent is a continuous process, where parents will be able to review their decision on an ongoing basis. Parents decision to 'opt-out' must be recorded in the infants clinical file. This is similar to the consent that is typically given for clinical care, and in essence amounts to the acceptance of a recommendation. The opinion towards this method has been evaluated among research ethics committees, parents and health care professionals and was in general considered valid and appropriate for comparative effectiveness research, i.e. for comparing different treatment options that are already in clinical use (6).

Due to the nature of the SafeBoosC-III trial, i.e. patients requiring intensive care and an intervention that is 'conventional' and must start within six hours from birth to give full potential benefit, we believe that consent methods such as deferred informed consent and 'opt-out' consent with enrollment as default, are reasonable options. However, it is uncertain if Research Ethics Boards (REBs) would accept these consent methods. Since this trial involves more than fifteen nations, we can potentially expect a wide range of opinions from different REBs

Objective

To explore the practice of ethics during planning and execution of clinical trials within neonatal/pediatric intensive care research, we aim to evaluate the use of deferred informed consent and opt-out consent in the SafeBoosC-III trial, based on what was chosen by to the local investigators and what was accepted by the Research Ethics Boards across different countries.

Design

The SafeBoosC-III trial is a randomized, multinational, pragmatic clinically open trial with a two-parallel group design. It will include sixteen hundred extremely preterm infants over a 24-month period, at 50 neonatal intensive care units (NICUs) across more than 15 countries. The objective of the trial is to investigate the benefit and harms of treatment based on near-infrared spectroscopy monitoring compared to treatment as usual. The hypothesis is that treatment based on near-infrared spectroscopy monitoring during the first 72 hours of life, will result in a reduction in death or survival with severe brain injury, assessed at 36 weeks postmenstrual age.

The default consent method in the SafeBoosC-III trial is the prior informed consent procedure. However, due to the clinical complexity of extremely preterm birth, the urgency of the intervention and since the intervention is already in routine clinical use in several NICUs and to improve recruitment and efficiency in the trial, we incorporated two possible alternative approaches in the protocol: 1) deferred informed consent 2) prior informed assent (opt-out consent) with enrollment as default. Each principal investigator can choose to apply to his/her local REB for the use of these methods, within his/her NICU. To facilitate the process, we have designed appendix G in the protocol, recapping the latest research on alternative consent methods and the advantages/disadvantages for each consent method.

We invite all principal investigators to join this descriptive ancillary study. The purpose of the study is to describe the decision processes and decisions made by investigators and review committees. Furthermore, we want to describe and analyze concerns or complaints that may arise during the trial.

Outcome

Primary: Number of NICUs using prior, opt-out and deferred informed consent method.

Secondary:

1. Number of investigators choosing to apply for the use of either prior, opt-out, or deferred informed consent
2. Number of applications for ‘opt-out’ and deferred informed consent that were not granted by REBs
3. Number of REBs raising queries towards the consent procedure
4. Time to decision from submission of the application

Exploratory:

1. REBs queries towards the consent procedure
2. Concerns or complaints concerning the consent procedure raised by clinical staff or parents during the first 6 month of the trial

Publication:

One or more reports will be submitted for publication in a peer-reviewed journal. All contributing investigators will be authors, provided they otherwise fulfill the ICMJE (Vancouver) criteria.

Reference list

1. Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. 1964.
2. Caldwell PHY, Dans L, de Vries MC, Newman J, Sammons H, Spriggs M, et al. Standard 1: Consent and Recruitment. Pediatrics. 2012 Jun 1;S118–23.
3. Guidelines for the ethical conduct of medical research involving children by the Royal College of Paediatrics and Child Health: Ethics Advisory Committee. Archives of Disease in Childhood. 2000.
4. Medicines. The Medicines for Human Use (Clinical Trials) and Blood Safety and Quality (Amendment) Regulations 2008. 2008.
5. European Union. REGULATION (EU) No 536/2014 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL. Off J Eur Union. 2014;1–76.
6. Gale C, Hyde MJ, Modi N. Research ethics committee decision-making in relation to an efficient neonatal trial. Arch Dis Child - Fetal Neonatal Ed. 2017;102:F291–8.