When Is Waiver of Consent Appropriate in a Neonatal Clinical Trial?

abstract

It is difficult to do scientifically rigorous research on treatments that must be administered urgently or emergently. Therefore, such treatments are often provided without a strong evidence base. Research would be facilitated if it were permissible to waive the requirement for parental consent. However, that raises a different set of concerns. Federal regulations allow waiver of the requirement for consent but only if studies meet certain conditions. Institutional review boards must decide whether those conditions are met. Sometimes, reasonable people disagree. We present and analyze a protocol for which investigators request a waiver of consent. *Pediatrics* 2014;134:1006–1012

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KEY WORDS

child, ethics, meconium aspiration, equipoise, research, consent

ABBREVIATIONS

CER—comparative effectiveness research

CFR—Code of Federal Regulations

FDA—US Food and Drug Administration

IRB—institutional review board

MAS—meconium aspiration syndrome

MSAF—meconium-stained amniotic fluid

OPRR—Office for Protection From Research Risks

Dr Schreiner helped conceptualize the article; Dr Feltman had the original idea for this article and helped conceptualize the article; Drs Wiswell, Arnold, Tyson, and Lantos helped conceptualize the project; Dr Wootton helped analyze the fundamental issues; and all authors contributed to the manuscript and approved the final manuscript as submitted.

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Federal regulations allow the waiver of consent for research when 3 conditions are met: The research involves no more than minimal risk to the subjects, the waiver or alteration will not adversely affect the rights and welfare of the subjects, and the research could not practicably be carried out without the waiver or alteration. It is often difficult to know whether a particular research protocol does or does not meet those requirements. In this Ethics Rounds, we present a protocol about which reasonable people disagree. We then ask leading researchers, clinicians, and bioethicists to analyze the protocol in light of the federal regulations and to decide whether they apply. Dalia Feltman is a neonatologist at Northshore Evanston Hospital. Thomas Wiswell is a neonatologist and clinical investigator at Florida Hospital in Orlando. He has studied different approaches to meconium aspiration. Mark Schreiner is an anesthesiologist and chair of the institutional review board (IRB) at Children's Hospital of Philadelphia. Cody Arnold and Jon Tyson are neonatologists, and they and Susan Wootton are clinical researchers at University of Texas at Houston. John D. Lantos is director of the Children's Mercy Hospital Bioethics Center.

THE CASE

You are on an IRB, and the following protocol is submitted:

Study question: For nonvigorous infants born with meconium-stained amniotic fluid (MSAF), is it preferable to intubate and suction before ventilating an infant or to stimulate the infant and encourage breathing without suctioning?

Background: Endotracheal suctioning of the nonvigorous infant born with MSAF is recommended by the American Academy of Pediatrics and American Heart Association Neonatal Resuscitation Program. However, there is strong evidence that, in many cases, fetal meconium is passed well before delivery and that intubation

and suctioning does not clear the airway of meconium. A prospective randomized trial of 2000 apparently vigorous (heart rate >100 beats per minute, good respiratory effort, normal tone) meconium-stained neonates showed that there was no difference in outcome between intrapartum oropharyngeal and nasopharyngeal suctioning and expectant management. Researchers concluded that meconium aspiration syndrome (MAS) is usually the result of in utero aspiration of meconium-stained amniotic fluid and cannot be prevented by intrapartum or postnatal therapies. There remains a major question of whether the depressed meconium-stained infant benefits from intratracheal suctioning. This study aims to determine the risks and benefits of endotracheal suctioning for such infants.

Eligibility criteria: Term infants born with MSAF and deemed "depressed."

Study design: We will randomly assign infants to receive endotracheal suctioning via intubation versus no endotracheal suctioning.

Outcomes: Blood gas values in the first 24 hours of life, need for supplemental oxygen in the first 24 hours of life, need for noninvasive positive-pressure ventilation, need for mechanical ventilation, length of NICU stay, and hypoxic ischemic encephalopathy.

Informed consent: It would be impossible to get informed consent for this study because we usually do not know whether amniotic fluid is meconium stained until delivery. We propose to defer informed consent. We believe that there is genuine uncertainty about which treatment is best for these infants. The risks of not suctioning are that the infant will develop MAS. The risks of suctioning are that delayed resuscitation will lead to hypoxic-ischemic encephalopathy.

As an IRB member, would you vote to approve this study as written, approve

with alternative to waiver of consent versus deferral of consent, or not approve even with consent?

Comments by Dr Susan Wootton, Dr Cody Arnold, and Dr Jon Tyson

This trial is needed for 3 reasons. First, the rationale for immediate tracheal suctioning is the assumption that severe MAS results from meconium aspiration at or shortly before birth.^{1,2} In fact, severe pulmonary artery hypertension in fatal MAS is associated with anatomic changes in pulmonary vessels likely to have developed well before birth.

Second, even in expert hands, immediate tracheal suctioning may increase the likelihood of severe lung disease, brain damage, and death by intensifying the hypoxia, hypercapnia, acidosis, and pulmonary artery hypertension in these infants at birth. Physicians can optimize the risk/benefit ratio of tracheal suctioning by reserving it for infants intubated for resuscitation or mechanical ventilation and performing it only after they are well stabilized.

Finally, no randomized trial has demonstrated that suctioning any part of the airway before or after an infant's chest is delivered prevents or ameliorates MAS in vigorous or nonvigorous infants.³⁻⁵ The presumed benefits of immediate tracheal suctioning are inferred from observational studies using historical controls reported in the 1970s.⁶

The trial would be augmented if neurologic and pulmonary outcomes at 2 years could be assessed. However, the trial would contribute valuable information even if it is not feasible to perform this assessment or conduct a large trial. To obtain unbiased estimates of treatment effect, it is better to perform the largest feasible randomized trial than no trial at all.^{7,8}

When consent cannot be reasonably obtained after birth, as in this case, IRBs may require antenatal consent. However, such a requirement would be

misguided for this trial. First, it would result in underrepresentation of infants whose mothers have the least education, least prenatal care, most advanced labor at admission, worst pregnancy complications, or greatest problems with intrapartum care. Such selection bias can greatly increase the likelihood of missing important treatment benefits or hazards and reaching erroneous conclusions harmful to large numbers of future infants.

Second, antenatal consent would not be practicable. Because MSAF is often first identified shortly before delivery, a trial of reasonable length would require seeking consent from all women in labor at ≥ 35 weeks' gestation. Yet very few of them, $\leq 3\%$ in a recent study,⁹ deliver nonvigorous infants with MSAF. This approach to consent would impose unreasonable personnel time and cost per infant enrolled and intrude on many laboring women who would not need and may not want the information provided.

Third, seeking antenatal consent from all these women might be harmful, a legitimate concern^{10,11} that IRBs would not ordinarily consider. Experimental studies in humans^{12–14} and in nonhuman primates¹⁵ indicate that greater anxiety during labor can increase maternal or neonatal complications. There is no reason to assume that adverse outcomes would not be increased by detailed risk disclosure about intubation, tracheal suctioning, and severe MAS to most or all laboring women at ≥ 35 weeks' gestation.

For all these reasons, requiring antenatal consent for this trial may be considered contrary to the ethical principles of respect for persons, beneficence, and nonmaleficence.

Waiver of consent (not “deferred consent”) for this trial may be justified under federal regulations allowing waivers for minimal risk research in restricted circumstances. Some IRB members may assume that any trial in seriously ill patients involves more than minimal

risk. However, the federal IRB guidebook defines risk as “the probability of harm or injury . . . occurring *as a result of participation in a research study*” (italics ours).¹⁶ The Office for Human Research Protections recently emphasized that “the IRB should consider only those risks and benefits that may result from the research (*as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research*).”¹⁷ IRBs should assess risks from the best available evidence. As indicated earlier, the best evidence provides no basis to conclude that patient risk would be greater in this trial than with the immediate tracheal intubation and suctioning that is routinely provided. Federal regulations specifically for emergency research consent waiver provide a strong and less contestable basis for approval. These regulations require that “the human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, [and] the collection of valid scientific evidence . . . is necessary to determine the safety and effectiveness of particular interventions.”¹⁸ The proposed study meets these criteria: The subjects have an increased risk of death, the invasive emergency intervention under investigation is unproven, and valid scientific evidence to determine its safety and effectiveness is most likely to be collected in a proper randomized trial.

The parents should be asked to consent to the collection of outcome data, there should be oversight from a data and safety monitoring board, and there should be prior community disclosure and consultation. To meet these requirements the investigators might post information in prenatal clinic waiting areas and seek input from women attending these clinics, parents of high-risk infants attending neonatal follow-up clinics, or members of a parental advisory

board for perinatal research in the study centers.

Antenatal consent is not practicable or appropriate for this important trial. As indicated earlier, waiver of consent is allowable under the federal regulations for emergency research consent if not also the regulations for minimal risk research.

This study highlights a very common situation. Many therapies, particularly emergency therapies, have never been rigorously studied. They may have little value or even be harmful.

Studies such as this ought to be encouraged. Current regulations are based on outdated and simplistic distinctions between research and practice^{19,20} and inadvertently discourage proper testing and encourage routine use of unproven therapies.^{19–21} An approach to regulation and to informed consent based on whether there is foreseeable incremental risk over that in clinical practice will help foster a learning health care system to accelerate advances in patient care and outcomes.²²

Comments by Dr Dalia Feltman and Dr Thomas Wiswell

We would analyze the issues in this case by focusing on 2 questions. First, is there clinical equipoise between the 2 treatments so that randomization is ethically defensible? Second, is waiver of consent the best approach to conducting this study?

Randomly assigning a subject to 1 of 2 treatments is considered morally acceptable if the treatments are believed equally effective or if there is not enough scientific evidence to prefer one to the other. Randomization is ethical if there is “honest, professional disagreement among expert clinicians about the preferred treatment.”²³ That is the case here. As noted earlier, this study addresses an important scientific question. There is good reason to believe that at least some infants born with MSAF would

be better off without immediate intubation and suctioning in the delivery room. This situation is analogous to one that existed with regard to vigorous infants 20 years ago. Before a multicenter study by Wiswell et al¹⁵ in 2000, the Neonatal Resuscitation Program standard was intubation for endotracheal suctioning of every infant. After studies were done (using waiver of consent), a Cochrane meta-analysis concluded, "Routine endotracheal intubation of vigorous term babies born through meconium-stained amniotic fluid cannot be recommended. For non-vigorous babies endotracheal intubation is probably indicated until more information becomes available."²⁴ This study is designed to provide more information.

One could argue that endotracheal suctioning of a vigorous infant who has inhaled meconium while crying may not be effective, whereas a depressed infant may still benefit from removal of meconium before it moves to the lower respiratory tract. On the other hand, in utero aspiration of meconium might be what led to the newborn's depressed state. In that case, postnatal endotracheal suctioning is unlikely to prevent respiratory complications. Furthermore, intubation entails risks such as laryngeal trauma and reflex bradycardia. Delaying resuscitation attempts while suctioning may compound the state that caused depression, possibly worsening hypoxic ischemic injury. Given these balanced risks and benefits, we believe that randomization is justified.

We now turn to the proposed consent waiver. We know that 2 previous randomized studies of interventions for newborns born with MSAF waived parental consent. That decision was based on the federal regulations, noted earlier, that allow waiver of informed consent if 4 criteria are met.

These 2 previous studies emphasized the value of testing common practices

in defending consent waiver. According to Vain et al, "Use of unproven policies and practices should not be perpetuated and proper testing of emergency procedures will result in improved medical care."²³ Both studies led to changes in standard practices regarding newborns with MSAF. The proposed protocol carries no more risk to its subjects than did the previous protocols for which consent was waived. According to US Department of Health & Human Services regulations, "*Minimal risk* means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."¹⁸ Determining minimal risk for the "ordinary daily life" for the non-vigorous infant currently born with MSAF is problematic because by default this life starts with endotracheal intubation, which carries more than minimal risk. However, because random assignment to intubation or no intubation probably carries equal risk to the patient, we believe study enrollment carries no more than minimal risk compared with standard care.

As in the previous studies, the emergency nature of the detection MSAF and infant's depressed state make traditional parental informed consent impossible. Recent neonatal trials with similar time constraints have sought antenatal consent, which causes problems. Rich et al²⁵ showed that such an approach was inefficient and led to selection bias. Investigators in 1 such study had to obtain consent from 5 times as many pregnant women as needed to enroll enough infants in the study. Those who did enroll were more likely to have had prenatal care and to have received antenatal steroids than those not enrolled, leading to decreased generalizability.

Institutional consent in lieu of parental informed consent with the opportunity

for parents to opt out was used by Vohra and Reilly's Vermont–Oxford Network Heat Loss Prevention Study.²⁶ The results are not yet published.

A third approach is described by Allmark and Mason²⁷ in which participation in a hypothermia study was presented in a stepwise fashion to parents of children who might be eligible. Although their approach included traditional informed consent of a parent before randomization (afforded by the longer therapeutic window intrinsic to the cooling protocol), their process of continued engagement with the parents allowed people to drop out of the study at several points.

Proponents of waiving informed consent argue that a mother in the emergency situation of labor complicated by an urgent newborn condition is unable to give proper informed consent because of her physical and emotional distress.^{28–30} Clearly, the issues surrounding emergency consent in the delivery room for a study on an unstable infant may preclude ideal parental informed consent. But we believe that some shared decision making is better than none. Allmark and Spedding³¹ suggest that preserving societal respect for the family unit may be a more important goal of traditional parental consent than protecting the child from risks, because the latter task is shared by most research investigators and IRBs. Care must be taken to ensure that circumventing traditional parental consent does not erode parental trust in the medical team or in future neonatal research.

With these considerations in mind, we would allow waiver of parental consent to randomization. We suggest that, when possible (ie, when time and circumstances allow), parents be given an opportunity to opt out. This could be done by giving all laboring mothers who are admitted at ≥ 37 weeks some written information about the study.

This information should include the study goals and an assessment of the risks and benefits. It should clearly explain that most infants will not be eligible for the study but that determination of eligibility cannot be determined before birth. At that point, parents will be asked only whether they want to opt out of the study. If they do not opt out, and if their infant meets enrollment criteria, then randomization will occur.

For those ultimately enrolled, debriefings must occur in person between parents and the treating physician, and more specific information with investigators' contact information should reiterate the parents' option to decline further participation (ie, information collection).

To inform future practices, we recommend a secondary analysis of parents' perspectives on this opt-out process.

Comments by Dr Mark S. Schreiner

The case study describes a randomized, double-blind clinical trial that compares 2 commonly used treatment approaches. This is an increasingly common scenario. Clinicians often must choose between treatment options based on bias, inadequate data, and anecdote rather than solid evidence. Comparative effectiveness research (CER) strives to compare treatments in common use where there is a lack of consensus about which is best. Considerable controversy exists about which risks should be taken into account when reviewing CER.^{32–34}

The federal requirements for approval are outlined in 45 Code of Federal Regulations (CFR) 46.111 and for this study Subpart D: Additional Protections for Research Involving Children as Subjects.³⁵ Rather than examining each regulatory requirement, I will focus only on the most controversial issues raised by this study, specifically the requirement for the research to minimize risk, the risk and benefit assessment, the determination of the

appropriate Subpart D risk/benefit category, and finally the informed consent requirements.

DOES THE RESEARCH MINIMIZE RISKS BY USING SOUND SCIENTIFIC DESIGN?

To minimize risk, the research must use sound scientific design that does not unnecessarily expose subjects to risk. Based on the previous discussions, it is clear that the proposed trial meets the criteria for being scientifically sound.

ARE THE RISKS OF THE RESEARCH REASONABLE IN RELATION TO THE ANTICIPATED BENEFITS?

There is variability between IRBs in their assessment of risk, and the best approach for risk assessment for CER trials remains controversial.³⁶ My approach is to determine the level of risk associated with both treatment arms, ascertain whether the potential risks associated with the 2 treatment arms are identical (unlikely) or different, and then confirm that the risks and benefits are equivalent to those of care outside of the research.

In this study, both treatment arms use an approach that is part of the spectrum of usual clinical care of the meconium-stained newborn. However, the risks and benefits of the 2 treatment arms differ in important ways; those differences are the fundamental motivation for conducting the trial. If tracheal suctioning decreases the incidence of MAS, then as a group, those randomly assigned to receive tracheal suctioning via a tracheal tube will have a better outcome than those randomly assigned to supportive care. If tracheal suctioning is not superior, then the newborns randomly assigned to supportive care will not be at greater risk of MAS, and they also will not be exposed to the risks of laryngoscopy and the insertion of an oral tracheal tube. Tracheal suction

involves passing a tube below the level of the larynx, a procedure that the US Food and Drug Administration (FDA) considers invasive (21 CFR 812.3[k]). The potential harms that could result from laryngoscopy and tracheal intubation include trauma to the oropharynx, larynx, and trachea, cardiovascular instability (bradycardia and cardiac arrest), and hypoxia.³⁷ Although both treatment arms include the possibility of benefit, both also include the possibility of significant morbidity or even death, I must therefore conclude that the risks are greater than minimal. Concluding that the risks are greater than minimal greatly limits an IRB's ability to waive the requirement for prospective informed consent.

DOES THE RESEARCH MEET FEDERAL REQUIREMENTS (SUBPART D) FOR PROTECTING CHILDREN AS RESEARCH SUBJECTS?

An IRB may approve research involving children, provided that it fits into 1 of 3 Subpart D risk/benefit categories. Assignment to a category depends on the level of risk research (minimal, greater than minimal, or a minor increase above minimal) and whether there is a prospect for direct benefit. Having concluded that the risks of the research are greater than minimal, the IRB would need to determine whether there was a prospect for direct benefit. Because there is no evidence to favor 1 arm over the other, both groups have a prospect for direct benefit, and that prospect is least as favorable as that of care available outside the research. Therefore, the study would be approvable under 45 CFR 46.405.

WILL INFORMED CONSENT BE OBTAINED AND DOCUMENTED FROM EACH PROSPECTIVE SUBJECT?

The investigators have proposed enrolling the newborns at the time of delivery and randomly assigning them

to 1 of 2 treatment arms without obtaining consent. Waiver of the requirement for informed consent is possible only if the research entails risks that are not greater than minimal under the criteria of 45 CFR 46.116(d) or if the research qualifies for a waiver of the informed consent requirements under criteria outlined in the 1996 Office for Protection From Research Risks (OPRR) report “Informed Consent Requirements in Emergency Research” (referred to hereafter as 1996 OPRR requirements).¹⁸ In my opinion, neither applies to this research. First, as I argued earlier, the risks of the research are greater than minimal, making waiver under §46.116(d) inappropriate. Minimal risk does not mean that the risks encountered in the research are equivalent to those encountered in clinical care. Minimal risk means that the risks of the study intervention are not greater than those encountered during routine examination or during daily life. Most interpret the risks of daily life to mean the daily life of a healthy individual in a safe environment. Second, the 1996 OPRR requirements for a waiver apply only to research that is either subject to FDA regulatory requirements or in

situations where the subject is unable to consent and the legally authorized representative is not available. This study is not subject to FDA regulations, and the neonate’s legally authorized representative will always be present in the delivery room.

CONCLUSIONS

Because the risks of the research are greater than minimal, the research is not subject to FDA regulations, and the research fails to meet the criteria for waiver under the 1996 OPRR requirements, I would not approve this trial unless there was a plan to obtain prospective informed consent. It is possible, even likely, that the feasibility of the trial could be affected by imposing the requirement of prospective informed consent. The investigators might be forced to abandon their plans for a clinical trial and substitute a less powerful alternative design, such as a large prospective cohort study.

Comments by Dr John D. Lantos

This proposed study highlights the special features of research to evaluate 2 approaches to treatment that are both in widespread use and about which

experts disagree. This research differs from research that is designed to evaluate new therapies. If a study is testing a new therapy, then patients who choose not to enroll in the study know how they will be treated. They will receive the current standard therapy. In CER, by contrast, nonenrolled patients may get either of the therapies. Often, as in this case, we do not know the distribution of current practices. Thus, we do not know whether patients who are enrolled and randomly assigned would, on average, be treated similarly or differently than they would off protocol. Current regulations protect patients (and parents) from risks associated with research but expose many more patients to the comparable risks of idiosyncratic practice variation. Traditionally, however, the risks of practice variation have not been scrutinized or regulated as carefully as the risks of research. The level of risk in such research must be compared with the risk of prevailing practices to determine whether the research itself increases risk. As this discussion illustrates, people disagree about how such increments in risk ought to be assessed. Federal guidance is badly needed to resolve such controversies.

REFERENCES

1. Käähä PO. Meconium aspiration syndrome (MAS): where do we go? Research perspectives. *Early Hum Dev.* 2009;85(10):627–629
2. Ghidini A, Spong CY. Severe meconium aspiration syndrome is not caused by aspiration of meconium. *Am J Obstet Gynecol.* 2001;185(4):931–938
3. Vain NE, Szyld EG, Prudent LM, Aguilar AM. What (not) to do at and after delivery? Prevention and management of meconium aspiration syndrome. *Early Hum Dev.* 2009; 85(10):621–626
4. Vain NE, Szyld EG, Prudent LM, Wiswell TE, Aguilar AM, Vivas NI. Oropharyngeal and nasopharyngeal suctioning of meconium-stained neonates before delivery of their shoulders: multicentre, randomised controlled trial. *Lancet.* 2004;364(9434):597–602
5. Wiswell TE, Gannon CM, Jacob J, et al. Delivery room management of the apparently vigorous meconium-stained neonate: results of the multicenter, international collaborative trial. *Pediatrics.* 2000;105(1 pt 1):1–7
6. Wiswell TE. Handling the meconium-stained infant. *Semin Neonatol.* 2001;6(3):225–231
7. Schulz KF, Grimes DA. Sample size calculations in randomised trials: mandatory and mystical. *Lancet.* 2005;365(9467):1348–1353
8. Lilford RJ, Thornton JG, Braunholtz D. Clinical trials and rare diseases: a way out of a conundrum. *BMJ.* 1995;311(7020):1621–1625
9. Kelleher J, Bhat R, Salas AA, et al. Oronasopharyngeal suction versus wiping of the mouth and nose at birth: a randomised equivalency trial. *Lancet.* 2013;382(9889):326–330
10. Colloca L, Miller FG. The placebo effect and its relevance for clinical practice. *Psychosom Med.* 2011;73(7):598–603
11. Loftus EF, Fries JF. Informed consent may be hazardous to your health. *Science.* 1979;204(4388):11
12. Sosa R, Kennell J, Klaus M, Robertson S, Urrutia J. The effect of a supportive companion on perinatal problems, length of labor, and mother–infant interaction. *N Engl J Med.* 1980; 303(11):597–600

13. Kennell J, Klaus M, McGrath S, Robertson S, Hinkley C. Continuous emotional support during labor in a US hospital. A randomized controlled trial. *JAMA*. 1991;265(17):2197–2201
14. Haverkamp AD, Orleans M, Langendoerfer S, McFee J, Murphy J, Thompson HE. A controlled trial of the differential effects of intrapartum fetal monitoring. *Am J Obstet Gynecol*. 1979;134(4):399–412
15. Myers RE. Maternal psychological stress and fetal asphyxia: a study in the monkey. *Am J Obstet Gynecol*. 1975;122(1):47–59
16. *IRB Guidebook*. Available at: www.hhs.gov/ohrp/archive/irb/irb_guidebook.htm. Accessed January 7, 2014
17. OHRP public meeting. August 28, 2013. Available at: www.hhs.gov/ohrp/newsroom/rfc. Accessed January 7, 2014
18. US Department of Health & Human Services. Informed consent requirements in emergency research. 1996. Available at: www.hhs.gov/ohrp/policy/hsdc97-01.html
19. Wootton SH, Evans PW, Tyson JE. Unproven therapies in clinical research and practice: the necessity to change the regulatory paradigm. *Pediatrics*. 2013;132(4):599–601
20. Faden RR, Kass NE, Goodman SN, et al. An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics. *Hastings Cent Rep*. 2013;(Spec No):S16–S27
21. Kass NE, Faden RR, Goodman SN, Pronovost P, Tunis S, Beauchamp TL. The research–treatment distinction: a problematic approach for determining which activities should have ethical oversight. *Hastings Cent Rep*. 2013;(Spec No):S4–S15
22. Institute of Medicine of the National Academies. *Best Care at Lower Cost. The Path to Continuously Learning Health Care in America*. Washington, DC: National Academies Press; 2013
23. Joffe S, Truog R. Equipoise and randomization. In: Emanuel EJ, Grady C, Crouch RA, Lie R, Miller F, Wendler D, eds. *The Oxford Textbook of Clinical Research Ethics*. Oxford, England: Oxford University Press; 2008: 245–260
24. Halliday HL. Endotracheal intubation at birth for preventing morbidity and mortality in vigorous, meconium-stained infants born at term. *Cochrane Database Syst Rev*. 2001;1(1). doi:10.1002/14651858.CD000500
25. Rich WD, Auten KJ, Gantz MG, et al; National Institute of Child Health and Human Development Neonatal Research Network. Antenatal consent in the SUPPORT trial: challenges, costs, and representative enrollment. *Pediatrics*. 2010;126(1). Available at: www.pediatrics.org/cgi/content/full/126/1/e215
26. Vermont Oxford Network. Proposal to IRB/HREB. Available at: www.vtoxford.org/research/help/help.aspx. Accessed January 6, 2013
27. Allmark P, Mason S. Improving the quality of consent to randomised controlled trials by using continuous consent and clinician training in the consent process. *J Med Ethics*. 2006;32(8):439–443
28. Ballard HO, Shook LA, Desai NS, Anand KJS. Neonatal research and the validity of informed consent obtained in the perinatal period. *J Perinatol*. 2004;24(7):409–415
29. Mason SA, Allmark PJ; Euricon Study Group. Obtaining informed consent to neonatal randomised controlled trials: interviews with parents and clinicians in the Euricon study. *Lancet*. 2000;356(9247):2045–2051
30. Singhal N, Oberle K, Burgess E, Huber-Okrainec J. Parents' perceptions of research with newborns. *J Perinatol*. 2002; 22(1):57–63
31. Allmark P, Spedding M. Clinical trials in neonates: ethical issues. *Semin Fetal Neonatal Med*. 2007;12(4):318–323
32. Magnus D, Caplan AL. Risk, consent, and SUPPORT. *N Engl J Med*. 2013;368(20):1864–1865
33. Drazen JM, Solomon CG, Greene MF. Informed consent and SUPPORT. *N Engl J Med*. 2013;368(20):1929–1931
34. Wilfond BS, Magnus D, Antommaria AH, et al. The OHRP and SUPPORT. *N Engl J Med*. 2013;368(25):e36
35. Department of Health and Human Services. Code of Federal Regulations Title 45: Public welfare. Part 46: protection of human subjects. 2009, July 14. Available at: www.hhs.gov/ohrp/policy/ohrpregulations.pdf. Accessed September 18, 2013
36. Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? *JAMA*. 2004;291(4):476–482
37. Anand KJS, Suresh S. Tracheal intubation in neonates, infants, and children: is there a right way? *Crit Care Med*. 2004;32(2):614–616