

## Delivery Room Research: When Does Poor Quality Evidence Become an Ethical Issue?

The November 2014 Ethics Rounds questioned: "When is waiver of consent appropriate in a neonatal clinical trial?" As neonatal clinical trialists, we believe that a waiver of prospective informed consent is often required and ethically appropriate to conduct scientifically rigorous delivery room clinical trials.

As Drs Wootton, Arnold, and Tyson acknowledged, many emergency therapies have never been rigorously studied. Neonatal resuscitation medicine is especially bereft of high-level evidence. Only 23 of 157 (15%) publications cited in the 2010 ILCOR statement on neonatal resuscitation were randomized trials or meta-analyses of trials (level of evidence [LOE] 1) (Table 1). In contrast, 114 (73%) studies lacked a control group (LOE 4), or worse, were performed in a different population, in animals, or in a mechanical model (LOE 5).<sup>1</sup> We urgently need well-designed studies of the safety and efficacy of delivery room interventions in newborns.

The delivery room presents unique challenges to study enrollment. Neonatal resuscitation occurs immediately after birth, so prospective informed consent must be obtained before delivery. However, predicting the timing of birth is imprecise. Hence,

infants born precipitously or to acutely ill mothers are often excluded from trials that use antenatal consent, which threatens the generalizability of delivery room trials.<sup>2</sup>

A waiver of prospective informed consent may be appropriate when the research could not be feasibly conducted otherwise, such as emergency research. However, in the November article, Dr Schreiner argued that a neonate would not meet the 1996 OPRR requirements for waiver of consent in emergency research because a legally authorized representative is always present in the delivery room. This statement erroneously conflates a parent's physical presence with the ability to participate in an informed consent discussion. The pregnant mother's physical status or concurrent therapy may preclude the ability to provide informed consent. Furthermore, in many scenarios resulting in need for neonatal resuscitation, there is inadequate time to obtain antenatal informed consent.<sup>3</sup> When antenatal consent is not possible, we propose that eligible subjects be enrolled in delivery room studies, followed by a request for informed consent from parents for ongoing study participation as soon as possible after enrollment. This process, called "deferred" or "retrospective" consent in some countries, still allows for some parental participation.

This is not to deny that neonates are a vulnerable population who deserve special regulatory protection. Nonetheless, it is imperative that the desire to protect this population does not perpetuate the use of inadequately studied and potentially dangerous interventions. A waiver of prospective informed consent is often necessary and appropriate to conduct scientifically and ethically sound delivery room trials. We believe that institutional review boards frequently do not balance this consideration.

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### Conflict of Interest:

None declared

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Foglia et al<sup>1</sup> raise an interesting question regarding a stipulation of the common rule in determining whether emergency consent waiver is appropriate: is the legal representative of the infant truly present in the delivery room? In our Ethics Rounds from November 2014,<sup>2</sup> Dr Schreiner argued that because a newborn's mother is physically present at the time of delivery, emergency consent cannot be waived. But Foglia et al's point is well taken; at the time of delivery, the mother is often in physical pain,

**TABLE 1** LOE of Cited Publications in 2010 ILCOR Neonatal Resuscitation Recommendations

LOE	Manuscripts (N = 157), n (%)
1: RCTs or meta-analysis of RCTs	23 (15)
2: Studies using concurrent controls without randomization	15 (10)
3: Studies using retrospective controls	5 (3)
4: Studies without a control group	46 (29)
5: Studies not directly related to the specific patient population (different population or animal or mechanical model)	68 (43)

Data from ref 1. ILCOR, ; RCT, randomized controlled trial.

nauseous, and extremely worried about the well-being of her soon-to-be-born infant. If it is a vaginal delivery, she is also working very hard (literally laboring) to meet her child safely. If there is another legal parent in the room, that person is immediately preoccupied with all of the aforementioned, and additionally worries for the welfare of the delivering mom. Although they are likely not in physical discomfort, both parents would probably agree they are unable to receive information about a research study and are incapable of making a thoughtful split-second decision.

In certain delivery room situations, the time between meeting study criteria and randomization and delivery of the study's intervention can be a matter of seconds. In the proposed study in November's Ethics Rounds, for example, the determination of whether an infant born through meconium-stained amniotic fluid is "vigorous" or not immediately follows intubation for suctioning or no intubation. This is certainly not enough time for the kind of informed consent advocated by the common rule. I agree with these authors of the SAIL study group that not only is the legal decision-maker's "presence" arguable, the time (or lack thereof) makes this an emergency situation.

In November, Dr Wiswell and I argued that consent might be waived with the opportunity for parents to opt out later and with education provided to all laboring moms about the study in case their children were to meet criteria for enrollment at the time of birth. This approach is similar to the approach for which Foglia et al advocate in their "retrospective" consent. The key issue of disagreement we had with Dr Schreiner on the acceptability of waiver of consent was the meaning of "minimal risk." Dr Schreiner maintained that the risks of participating in the study exposed a newborn to risks greater

than those found in "daily life," using the example of risks associated with laryngoscopy, an invasive procedure. Dr Wiswell and I argued that "daily life" for a nonvigorous newborn born through meconium-stained fluid, due to unproven "standard care" practice starts with this invasive procedure thanks to an unproven standard care practice.

What qualifies as "minimal risk" is becoming exceedingly important in how comparative effectiveness studies are being regulated. Joffe and Wertheimer<sup>3</sup> contrast interpreting the risks of such studies as "absolute" versus "incremental." If a literal interpretation of the "daily life standard" is maintained, absolute risks (ie, every risk of the study treatment, including the risks a patient is exposed to from the treatment in regular care) will make few comparative effectiveness studies qualify as "minimal risk." Alternatively, if incremental risks (risks unique to participating in the study that do not accompany the same treatments when outside of the study) are considered by an institutional review board, many comparative effectiveness studies might be considered "minimal risk." Unfortunately, the newest directives from the OHRP's "Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care" issued in October appear to be interested in absolute risks. According to this draft guidance, "at a minimum, identified risks associated with a standard of care that are being evaluated as a purpose of research, should certainly be considered 'reasonably foreseeable.'"<sup>4</sup> This interpretation could make minimal risk determinations nearly impossible for comparative effectiveness research.

The OHRP is currently processing the general public's input on this draft guidance.<sup>5</sup> For the sake of our

patients who deserve to receive evidence-based therapies, I hope the OHRP reconsiders their stance on which risks should be considered by institutional review boards. If a patient is harmed as a result of an unproven standard care treatment, and there's no one there to research it, doesn't the patient still suffer?

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None declared

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#### Author's Response

Three ethical principles govern research with human subjects: respect for persons, beneficence, and justice. Respect for persons demands that, whenever feasible, we ask parents for permission before

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