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).[1] 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.[2]

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.

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.[3] 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

REFERENCES

1. Perlman JM, Wyllie J, Kattwinkel J, et al; Neonatal Resuscitation Chapter Collaborators. Part 11: Neonatal resuscitation: 2010 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. *Circulation*. 2010;122(16 suppl 2):S516–S538
2. Rich W, Finer NN, Gantz MG, et al; SUPPORT and Generic Database Subcommittees of the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Enrollment of extremely low birth weight infants in a clinical research study may not be representative. *Pediatrics*. 2012;129(3): 480–484
3. 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

doi:10.1542/peds.2015-0546A

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Foglia et al[1] 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,[2] 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,

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Pediatrics 2015;135;e1368
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