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No child left behind: Enrolling children and adults simultaneously in critical care randomized trials*

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Abstract

Objective—Randomized clinical trials of novel critical care interventions are currently tested in children only after documenting their safety in adults. Although this practice may protect children from research risks, it may paradoxically threaten children's well-being by depriving them of evidence to guide their care. We sought to evaluate the ethical, methodologic, and practical arguments for and against studying critical care interventions in adults and children simultaneously rather than sequentially.

Data Source—Empirical studies and conceptual arguments germane to the objective were reviewed.

Data Extraction and Synthesis—Children are traditionally viewed as “participants of last resort” due to their vulnerability and decisional incapacity. However, critically ill adults commonly share similar features. Thus, structured risk assessments used by Institutional Review Boards to determine the adequacy of research protections for critically ill adults can also help protect children. From a methodologic perspective, interventions may be tested simultaneously in children and adults by enrolling children as a prespecified subgroup within a larger adult randomized clinical trial or by enrolling children in a separate trial conducted in parallel. Both approaches raise practical and analytical challenges that can frequently be met. For example, investigators might choose outcome measures that are appropriate for both adults and children. Additionally, using Bayesian approaches to link the estimates of treatment effects in children to the values observed in adults may enhance the statistical power to detect pediatric-specific effects. Finally, centralized Institutional Review Boards and data monitoring centers may alleviate practical concerns with conducting trials among adults and children simultaneously.

Conclusions—The current standard of testing critical care interventions in adults before children rests on tenuous ethical arguments and is entrenched by the methodologic and logistic barriers encountered with alternative approaches. However, these barriers will frequently be

*See also p. 2673.

surmountable. We therefore propose that the default paradigm be changed such that interventions are examined routinely in critically ill children and adults simultaneously unless unique reasons exist to the contrary.

Keywords

randomized trials; pediatrics; research ethics; Institutional Review Board; Bayesian; subgroup analyses; critical care

Enrolling children in randomized clinical trials (RCTs) presents a conflict between society's interests in protecting children from research risks and its interest in fostering optimal pediatric care. Because research risks are often unforeseen, particularly when studying novel interventions, doctrines of research ethics have long held that such interventions should be tested in adults first (1,2). This paradigm has undoubtedly spared some children from the adverse consequences of interventions that proved unexpectedly hazardous. However, this approach, combined with several practical difficulties in recruiting sufficient numbers of children to RCTs (3,4), impedes the generation of pediatric evidence and thus paradoxically places all children at risk.

Recognizing this problem, Western nations have issued laws (5,6) and guidelines (7,8) intended to promote pediatric trials of new drugs (9). However, many interventions in critical care fall outside of such regulatory review because they involve management strategies rather than drugs. Furthermore, in the European Union, children may be excluded from RCTs anytime investigators argue that "it is appropriate to conduct studies in adults before initiating studies in the pediatric population, or when studies in the pediatric population will take longer to conduct than studies in adults" (5). The National Institutes of Health allows investigators to opt out from including children for similar reasons (8). Because these arguments can often be supported by the logistic difficulty of enrolling children and adults simultaneously, pediatric RCTs are typically delayed, if they are conducted at all. For example, 8 yrs elapsed between the publication of trials documenting the safety of limiting blood transfusions in critically ill adults (10) and children (11). In other cases, initial studies in adults effectively preclude subsequent pediatric RCTs because once interventions are shown to be effective, many pediatricians choose to use these interventions for their patients rather than enroll children in subsequent trials.

The net result is that most interventions commonly used in pediatric medicine have never been tested in children (12). Because interventions commonly have different safety and efficacy profiles in adults and children (9,13), pediatricians must either treat children with interventions whose safety and efficacy during development are unknown or withhold potentially beneficial interventions. In this article, we suggest that the default paradigm for critical care RCTs ought to be changed so that investigators and Institutional Review Boards (IRBs) are obliged to design and approve studies that include children and adults simultaneously—in either the same trial or in separate but parallel trials—unless specific reasons exist to the contrary.

We focus on critical care research because interventions employed in the intensive care unit commonly do not involve specific drugs, because critically ill adults often share with children the inability to make autonomous decisions, and because the risks of delays in evidence generation may be particularly profound for critically ill children. However, similar arguments may apply to other pediatric populations. Similarly, although we use the term *children* to refer to developing humans beyond the neonatal period who lack legally sanctioned autonomy, we acknowledge that some of the arguments may apply to neonates as well.

Ethical Considerations

The traditional exclusion of children from research involving novel therapies is rooted in the view that research participants should generally be those who are least vulnerable and most able to identify with the benefits of the research (2,14). Imbued with vulnerability (15) and lacking a mature capacity to identify with the goals of research, children might rightly be viewed as “research participants of last resort.” However, given the difficulties extrapolating evidence from adults to children, one might question whether children’s interests are best served through unusually strong protections from research risks even when such protections force them to forgo opportunities to benefit from research that may improve their care. It seems unnecessarily paternalistic to require additional protections beyond parental consent and patient assent for children (2) when similar substituted judgments are considered adequate and prudent for adults with advanced dementia (16) and for those incapacitated by critical illness (17,18).

In the case of research offering limited prospects for direct participant benefit, the arguments for relaxing special protections of children are less palpable (19,20). However, even this dilemma is not unique to children, because the pervasiveness of decisional incapacity among critically ill adults (21) means that ethical distinctions between adults and children are largely blurred in the intensive care unit.

Given such similarities, IRBs can protect children by using the “component analysis” of research risks described by Weijer (22), adopted by the National Bioethics Advisory Commission (23), and advocated for other populations lacking decisional capacity (16,18). Using component analysis, IRBs should only approve studies in which the foreseeable risks of therapeutic interventions are minimized and balanced by these interventions’ potential direct benefits to participants, and in which the risks of nontherapeutic interventions (e.g., additional blood draws purely for the purpose of generating scientific knowledge) are reasonable in light of the knowledge they will produce (22).

We suggest that an additional criterion be satisfied before investigators enroll children in the initial trials of novel interventions: that the therapeutic interventions carry ratios of anticipated risks to anticipated direct benefits that are at least as favorable for children as they are for adults (Table 1). Occasionally, investigators may be unable to estimate *a priori* the risks or benefits that might accrue to children; in such cases, this relative risk/benefit calculus may not be tenable. However, two general principles may enable this calculus to be used adjunctively to help determine the ethics of simultaneous research in adults and children. First, because age and the presence of co-morbid illnesses are strongly associated with intensive care unit mortality, interventions with high anticipated risks may be more difficult to justify in most critically ill children due to their greater prospects for recovering without treatment. For this reason, the pediatric RCT of drotrecogin alfa for severe sepsis (RESOLVE) (3) restricted enrollment to those children who were mechanically ventilated and who received inotropes or vasopressors, whereas the adult RCT (PROWESS) (24) did not require that participants meet equally stringent severity-of-illness criteria.

Second, many types of interventions are known or believed to disturb normal development, making it difficult to justify their study in young children unless similarly unique benefits to developing humans are also hypothesized. For example, investigators may have been justified in excluding children from the initial trials of corticosteroids in septic shock and of tight glycemic control in critically ill patients because steroids and hypoglycemia might affect brain development. In contrast, children could have been enrolled simultaneously with adults in acute lung injury trials of ventilatory (25) and fluid management strategies (26) because the risks and benefits of these interventions would not be expected to vary

significantly across different age groups. Using this relative risk/benefit calculus would have made it particularly difficult to justify excluding children from a study of benign interventions to reduce catheter-related bloodstream infections (27) because the rates of this complication are roughly three times greater for children (28) than for adults (27).

Methodologic Considerations

Simultaneous enrollment of children and adults in critical care RCTs might entail enrolling children as a prespecified subgroup within a larger trial of adults, or enrolling children in a separate but parallel trial. There are at least two benefits to enrolling adults and children in the same RCT. First, doing so could reduce overall research costs by enabling investigators to use the same data collection and management infrastructures for each subgroup. Second, by working together, pediatric and adult investigators can ensure that the research protocols for adults and children are as similar as possible. Protocol similarity would reduce ambiguity in determining whether differences in an intervention's observed efficacy across age groups are attributable to protocol differences or to true differences in the intervention's efficacy. For example, methodologic differences in adult (29) and pediatric (30) trials of ventilator weaning protocols cloud our understanding of whether protocolized ventilation differentially affects the duration of ventilatory support in adults vs. children.

Nonetheless, enrolling children and adults in the same trials raises several methodologic challenges that may require that children be enrolled in parallel but separate trials. First, in order to include children and adults in the same trial, the primary intervention and all cointerventions must be usable across a broad age range. For example, RCTs of drugs may require weight-based dosing for all patients. Protocols for mechanical ventilation trials would need to accommodate the impact of uncuffed endotracheal tubes that are frequently used in infants.

Second, selecting outcomes that are appropriate for all age groups may be challenging. For example, because intensive care unit mortality is much greater in adults than in children, using mortality as the primary outcome would substantially restrict the power to detect treatment effects among children. Without adequate power to answer the research question among children, it would be difficult to justify their enrollment in RCTs (31). This barrier may often be overcome by using composite end points such as the time-to-resolution of one or more types of organ failure (32) or longer-term outcomes, such as functional status. However, in cases where mortality or other inflexible outcome measures are deemed optimal for measuring outcomes among adults, separate but parallel trials may provide more accurate age-specific assessments of benefit.

A third concern with including children within the primary RCTs of novel interventions is that doing so may increase outcome heterogeneity for the overall sample, thereby reducing the applicability of the summary treatment effect to individual patients or subgroups (33). However, "adult" RCTs are already imbued with tremendous heterogeneity due to the enrollment of patients with disparate baseline risks of adverse outcomes. Furthermore, there may be little additional heterogeneity resulting from the addition of children because, in both normal health and in many disease states, there are fewer differences between older children and young adults than between young adults and the elderly. For example, among patients without severe co-morbidities, mortality rates from sepsis do not begin to increase until patients are >40 years (34). Thus, excluding patients based on a physiologically arbitrary cut-off, such as 18 yrs of age, does little to abate this problem.

Instead, investigators should strive to detect heterogeneity when it exists by exploring prespecified treatment-by-age-group interactions (35). Although critical care RCTs will rarely be adequately powered to detect such interactions using conventional analytic

approaches, Bayesian methods may improve the power to detect treatment risks and benefits among subgroups. Using Bayesian methods, the analysis of the observed treatment effect among children is linked to an *a priori* estimate of the treatment effect that could be derived from either the observed effect among adults or from the consensus opinion of experts (36). This approach not only increases power whenever the direction of the treatment effect in the pediatric subgroup corresponds to the direction of the *a priori* estimate, but it may also yield conclusions more rapidly, with fewer trial costs and with more precise subgroup information than available by using traditional (frequentist) statistical approaches (37).

Practical Considerations

Finally, there are at least three practical challenges that must be overcome to enroll children with adults in RCTs. First, IRBs that routinely evaluate adult research studies may be uncomfortable approving trials that include children without additional oversight. Thus, these trials may require review by separate adult and pediatric IRBs, or preferably by centralized IRBs equipped to evaluate both adult and pediatric protocols.

Second, incentives may be needed for private sponsors to be willing to enroll both adult and pediatric patients in trials of novel interventions. For example, in the United States, laws providing patent extensions for companies that test their drugs in children after gaining approval in adults (38) may need to provide similar benefits for companies testing their products in adults and children simultaneously.

Third, because the majority of critically ill children are cared for in specialized pediatric hospitals, enrolling children will often require more study sites than would be needed for adults alone. Although this will increase the early burdens and costs of conducting research, the strategy may prove to be logistically and economically efficient by avoiding the need to coordinate multiple trials at different time points and by requiring only a single data coordinating center.

Conclusion

Simultaneously enrolling children and adults in RCTs of novel critical care interventions is an ethical way to improve the care of critically ill children. Using the methods discussed in this essay, investigators may more rapidly produce definitive pediatric evidence while at the same time minimizing the overall number of children exposed to research. We therefore recommend changing the default paradigm for pediatric research so as to better respect children's rights to have their care guided by the same high-quality evidence as adults presently have.

To begin achieving these goals, investigators must recognize their duties to include children in properly selected RCTs of novel critical care interventions, rather than seeking exclusions from existing laws and guidelines. In addition, IRBs must support investigators' initiatives to enroll children in critical care trials without first requiring determination of safety and efficacy in adults. Applying both component analysis and our proposed consideration of interventions' relative risk/benefit ratios in children and adults will ensure the acceptability of such research. Finally, national regulations advocating the inclusion of children in research should be tightened to make it more difficult for investigators to justify decisions to exclude children.

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Recommendations for conducting critical care RCTs in adults first, children first, or in adults and children simultaneously^a

Table 1

Anticipated risks of the primary therapy	Anticipated Benefits of the Primary Therapy		
	Greater for adults	Similar for children and adults	Greater for children
Greater for children	RCT in adults first	RCT in adults first	RCT in adults and children
Similar for children and adults	RCT in adults first	RCT in adults and children	RCT in adults and children
Greater for adults	RCT in adults first	RCT in adults and children	RCT in children first

RCTs, randomized clinical trials.

^aThis evaluation is in addition to the assessment of research risks and benefits proposed by Weijer (22). When there are no data available to guide an *a priori* assessment of the risks and/or benefits of the intervention for children, trials should first be conducted in adults.