Intensive Care Med (2008) 34:198–202
DOI 10.1007/s00134-007-0917-3



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# Ethical assessment of pediatric research protocols

Received: 19 August 2007
Accepted: 30 September 2007
Published online: 3 November 2007


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**Abstract** Specific regulations regarding oversight of research in children vary from country to country, but most share common principles derived from major consensus documents. Whereas the permissibility of research on adults depends heavily upon the informed consent of the subject, the regulation of research in pediatrics is focused primarily upon protection of the subjects from research risks. Since patients who require intensive care are commonly at high risk for complications related to the severity of their illnesses, justifying the risks of research on critically ill children may therefore be particularly challenging. Use of an approach known as "component analysis" can be very helpful in separating the risks attributable to the medical care itself from those that should be ascribed to the research. After identifying and isolating the research interventions, a three-step approach is helpful for evaluating the "net risks" of the research: (1) Separate each component of the research into discrete interventions. (2) Any intervention for which the benefits equal or exceed the risks is ethically justified. (3) For interventions in which the risks exceed the benefits, the "net risk" for each intervention needs to be justified, as follows: (a) the interventions may not exceed the locally defined threshold for pediatric research (e. g., not greater than a minor increment more than minimal risk, as in the U.S. regulations); and (b) the scientific value of the study for improving the care of future children must be sufficient to justify the sum of the net risks of the research interventions.

## Introduction

Evidence-based medicine is universally recognized as an essential guide to improving clinical care. Clinical trials in children have lagged well behind advances in the rest of medicine, however, both because of the limited financial incentives to develop new treatments for this generally healthy population, and because of the ethical barriers to performing research on children [1]. As a result, almost half of all drug prescriptions for children in Europe are for off-label indications or for unlicensed medications [2].

Specific regulations regarding oversight of research in children vary from country to country, but most share common principles. For example, CIOMS states that "Before undertaking research involving children, the investigator must ensure that: (a) the research might not equally well be carried out with adults; (b) the purpose of the research is to obtain knowledge relevant to the health needs of children; (c) a parent or legal representative of each child has given permission; (d) the agreement (assent) of each child has been obtained to the extent of the child's capabilities; and (e) a child's refusal to participate or continue in the research will be respected [3]. The Declaration of Helsinki and the recommendations of the Ethics Working Group of the Confederation of European Specialists in Paediatrics (CESP) contain very similar principles [4, 5].

In this article I provide a broad overview of a process for the ethical evaluation of pediatric research protocols

in the critical care setting, and highlight some of the differences between the ethics of research on adults versus children. While the approach outlined herein is compatible with the existing international codes, it is more conceptual in nature and does not address specific details of local regulations.

## "Autonomous choice" vs. "Paternalistic protection"

In their landmark paper, "What makes clinical research ethical?", Emanuel and colleagues list seven ethical requirements [6]. Two requirements that are particularly relevant to this discussion are that (a) "individuals should be informed about the research and provide their voluntary consent"; and (b) that there be a "favorable risk-benefit ratio."

The first requirement deals with respecting the subject as an autonomous individual, the second with protecting the subject from harm. For any particular individual, there is a trade-off between these two requirements. Consider, for example, a fully autonomous adult who is capable of completely comprehending the details of a research protocol, and who is able to dispassionately and rationally consider the potential benefits and risks to himself as well as the value of the research to society. As Miller and Wertheimer have recently argued, one could say that there is no need to protect this individual from research risks, and that indeed it would be unfairly paternalistic of us to prevent this person from entering into a study in which he wanted to enroll because we disagree with his assessment of the benefits, risks, and societal value [7].

On the other hand, consider a small child who is incapable of autonomous choice. Some would say we have no right to expose this child to *any* risk of harm for the benefit of others. While this view is understandable, this position would preclude virtually all research on children and deny countless future children the health benefits that come only with scientific advancements. Even so, in the absence of the possibility of informed consent, researchers have an obligation to protect children by doing everything reasonably possible to minimize the risks of the research and to refrain from research that is excessively risky.

So at the adult end of the spectrum, there is a heavy emphasis on informed consent and little emphasis on protecting the subject, whereas at the pediatric end of the spectrum the weighting is reversed, with a heavy emphasis upon subject protection. Indeed, although we commonly say that the parents have "consented" for their child to be in a research study (and many regulations require it), it is more accurate to say that the parents have given their *permission* for the child to be enrolled in the study, since true informed consent is impossible in this situation [3, 8, 9].

While it would be ideal to treat potential research subjects individually, depending on where they fell on the spectrum (Fig. 1, top), this approach would not be feasible for multiple practical reasons. As such, two sets of rules have been developed, one for adults and one for children, and a (somewhat) arbitrary line has been drawn between them at the age of majority (generally 18 years; Fig. 1, bottom).

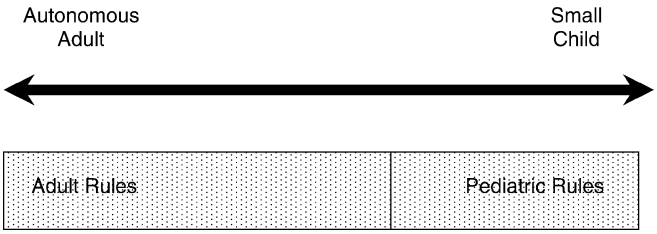


**Fig. 1** *Top:* the continuous spectrum of capacity to consent to clinical research, from autonomous adult to small child; *bottom:* the practical approach of having two sets of rules, one for adults and one for children, divided at the age of majority, generally 18 years

Since not all adults who are potential research subjects meet the high standards of the hypothetical adult described above, in addition to requiring informed consent, the rules for adults also include limits on the risks that the research can entail [7]. Despite being somewhat paternalistic, this is a necessary compromise to protect individuals who lack the capacity to reason clearly about whether to enroll or who may feel compelled to enroll because of desperate medical circumstances or misconceptions about the true purpose of the research (the so-called therapeutic misconception) [10].

Similarly, the rules for potential subjects under the age of 18 years may treat certain mature minors paternalistically by preventing them (without a legal exemption) from enrolling in higher-risk research, even though they have the cognitive and reasoning skills to make an autonomous choice [7]. Again, however, this is a practical solution to the problem of protecting those under the age of 18 years who do not have these capabilities. In any case, in addition to parental permission, investigators should seek the assent of children whenever possible, and should respect the choice of children who refuse to participate [9, 11].

The emphasis upon protection of pediatric research subjects means that the level of risk to which they may be exposed is very limited, compared with what is permitted for research on adults. This protection begins with the requirement that research be performed on children only when the same knowledge cannot be gained by corresponding research on adults. When research is done on children, the threshold for harm that is used varies from country to country. In the United States, this threshold is set at "minimal risk" for healthy children and at a "minor increase over minimal risk" for children who are afflicted with the disease or condition under study and when the research procedures are commensurate with those that the child experiences in clinical care [9].

## Ethical evaluation of pediatric research protocols

Against this background, I suggest a three-step approach to the ethical evaluation of pediatric research in the intensive care setting. This strategy is outlined in Table 1. The first step is to break down the research protocol into its component interventions, to divide those that are part of standard care from those that are necessary for the research [12]. This is especially important in critical care research, since any research involving patients with life-threatening conditions may appear to be very high risk when viewed as a whole.

Next, each of these interventions should be considered individually, in terms of the benefits and the risks they involve for the patient. For purposes of this discussion, by "benefits" or "risks" I mean the sum of all the benefits or risks, weighted in terms of both their magnitude and probability.

The second step of the process, as shown in Table 1, states that any intervention for which the benefits equal or exceed the risks is ethically acceptable [7]. Note that at this stage the approach is very similar to the decision-making process used in clinical practice. In clinical practice, when benefits exceed risks, treatment is generally given; otherwise, the treatment is not indicated.

Most research projects, however, involve some interventions where the risks exceed the benefits. Unlike the situation with clinical practice, in research we are willing to consider exposing children to some degree of risk in order to gain knowledge and improve the care of future children.

The third step of the process in Table 1 involves evaluation of those interventions where the risks exceed the benefits. In these cases, the risks need to be "subtracted" from the benefits, and the "net risk" determined [13]. This is where pediatric research differs most markedly from that conducted with adults. Some adults may be willing to assume substantial net risks. Adult research subjects may be motivated by a variety of factors, including simple altruism, the hope that the research will benefit either themselves or a loved one, or more controversially a payment being offered by the investigators. Potential adult subjects are permitted to assume these risks and enroll in studies out of respect for their right to make autonomous choices. As noted above, however, ethical review boards do not permit subjects to consent to unlimited risk, because of the practical fact that some protections are needed for those adults who are not fully capable of making good choices for themselves.

In pediatric research, the "net risks" to which the child is exposed need to be strictly controlled. Furthermore, there would be no ethical justification for exposing a child to any net risk unless there were potential benefits that compensated for this risk. In research, the compensating benefits must be provided by the potential for the research to contribute to scientific knowledge and the care of future children. Therefore, in the United States, the interventions (individually and in sum) may not involve more than a minor increase over minimal risk for research likely to generate knowledge about the potential subject's medical condition, and the scientific value of the study for improving the care of future children must be sufficient to justify the sum of the net risks of all of the research interventions [9]. (Note that the level of risk cannot be justified independently of assessing the scientific worth of the study. Even a study that had only minimal risk would not be ethical unless there were compensating scientific value.)

Exactly what constitutes "minimal risk" and "a minor increase over minimal risk" are matters of continual debate [14, 15]. The role of ethical review committees is specifically to engage in that debate and make case-by-case decisions on the protocols they review. Over time, experienced committees hopefully develop their own benchmarks for comparison and thereby acquire internal consistency in their judgments.

## A hypothetical case

Some of these abstract considerations may make more sense in the context of a hypothetical example. Consider, therefore, a simplified protocol for evaluating a hypothetical new drug (DrugX) which has shown promise in adults at modulating the immune response to the systemic inflammatory response syndrome (SIRS). Children with this syndrome and who have a predicted mortality of

**Table 1** Three-step approach to ethical evaluation of pediatric research in ICU

| Process for evaluating pediatric research studies: |
|---|
| Separate each component of the research into discrete interventions |
| Any intervention for which the benefits equal or exceed the risks is ethically justified |
| For interventions in which the risks exceed the benefits, the "net risk" for each intervention (individually and in sum) needs to be justified: |
| The interventions (individually and in sum) may not exceed the locally defined threshold for pediatric research (in the U.S., more than a minor increment more than minimal risk) |
| The scientific value of the study for improving the care of future children must be sufficient to justify the sum of the net risks of these interventions |

25% or more will be enrolled to receive either DrugX or placebo in addition to all standard care. A trial in adults showed an absolute reduction in mortality in similarly ill patients from 31 to 25%. The drug caused transient hepatotoxicity in approximately 20% of adults studied, which was severe and potentially irreversible in about 1% of cases. The protocol calls for the drug to be infused over 4 days, with scheduled blood draws every 6 h to study the drug's pharmacokinetics, to assess the patient's immune response, and to monitor the patient's hepatic function. Finally, the protocol requires a liver biopsy to be performed if the patient's transaminase levels rise to more than twice the upper limit of normal, to aid the investigators in better understanding the pathophysiology of the hepatic dysfunction. No compensation is being offered to the patient or family for participation.

As outlined in Table 1, the first step in evaluating this protocol would be to separate the research into discrete components. This simplified study has essentially three interventions: (a) the infusion of the drug or placebo; (b) the blood draws; and (c) the liver biopsy.

For the first intervention, patients who are enrolled may receive either placebo or DrugX. The benefits and risks of these two options need to be compared with each other and also with a third option, which is non-enrollment in the trial. In the hypothetical adult study, the drug showed the potential for both benefit and toxicity, and may have toxicities in children that were not seen in the adult population. Patients in the placebo arm presumably have no potential for either harm or benefit (excluding the potential benefit of the "placebo effect," which I acknowledge but will not discuss further). Clearly this will require considerable discussion by an ethics review committee, but I think it is plausible that at least some committees would find that this aspect of the protocol could be justified, on grounds that the risk–benefit profile for the experimental arm is no worse than that of the placebo arm, and that the profile for either arm is no worse than that for patients who choose not to enroll.

The second intervention – the blood draws – entail some risks but have no benefit in themselves. The risks relate primarily to the potential increased need for blood transfusions (and their attendant risks) as well as the discomfort associated with venipuncture. The ethical review board could insist on minimization of these risks by limiting the total volume of the blood draws (a commonly used limit is 10% of the patient's blood volume) and by insisting that the blood be drawn only through catheters that have been placed for clinical reasons. In this case, the ethical review board would be charged with determining whether these risks are less than an acceptable threshold for children (in the United States, less than or equal to a "minor increase over minimal risk") and whether they are counterbalanced by the scientific value of the study. Again, I think it is plausible that at least some committees would find these blood draws acceptable.

The third intervention, the liver biopsy, clearly involves potentially serious medical risks. Again, while open to judgment, many boards would likely see this as exceeding the acceptable threshold for pediatric research (clearly this would be in excess of the U.S. limit of a "minor increase over minimal risk"). As such, it could not be counterbalanced by the scientific value of the research, and so would not be a permissible component of the protocol. In contrast, if this research were being done on adults, this part of the protocol might be found to be ethically acceptable. Of course, the physicians caring for patients who develop hepatotoxicity may choose, on clinical grounds, to perform a liver biopsy, but this decision would have to be made on clinical grounds and not dictated by the research protocol.

Finally, readers may notice that this analysis does not depend upon a distinction between "therapeutic" and "non-therapeutic" research, which is a dichotomy that played an important role in shaping the U.S. regulations [9]. These terms are deeply confusing, and indeed "therapeutic research" can be considered an oxymoron, since the whole point of doing the research is precisely to see whether the intervention is, in fact, therapeutic. The value of breaking down the research protocol into its component parts is very useful because it allows for the research interventions and the treatment interventions to be compared, head to head, with the corresponding alternatives, for an examination of their respective risk–benefit profiles.

No recipe exists for judging when pediatric research protocols are ethical. My goal in this article has been to provide a step-by-step procedure for evaluating these protocols, recognizing that most of the hard ethical work is in attempting to balance the identified and potential risks against the benefits, and in making sound judgments about how to weigh potential harm to individuals against future benefits to society.

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