Pediatric research is vital to improving pediatric medical care. At the same time, exposing children to research risks to collect data that might benefit future patients raises important ethical concerns. To address these concerns, US regulations allow institutional review boards (IRBs) to approve pediatric clinical trials only when the risks are minimal or (in some cases) a minor increase over minimal, or when the risks are justified by a potential for direct benefit to the participants. But how should an institutional review board determine if the risks of pediatric clinical trials are justified by a potential for participant benefit? In this Ethics Rounds article, we consider which potential benefits can justify which research risks with a focus on randomized clinical trials.

The Potential Benefits of Research May Justify Certain Research Risks

David Wendler, PhD, a Robert M. Nelson, MD, PhD, b John D. Lantos, MD c

US regulations allow institutional review boards to approve pediatric clinical trials only when the risks are minimal or (in some cases) a minor increase over minimal, or when the risks are justified by a potential for direct benefit to the participants. But how should an institutional review board determine if the risks of pediatric clinical trials are justified by a potential for participant benefit? In this Ethics Rounds article, we consider which potential benefits can justify which research risks with a focus on randomized clinical trials.

THE CASE

A research protocol comes before an IRB. Investigators propose a randomized, double-blind, placebo-controlled trial to evaluate whether treatment with corticosteroids improves the outcome of the Kasai or gall-bladder Kasai procedures in infants with biliary atresia.

Many retrospective analyses, using historical controls, suggest that steroids lead to better outcomes after surgery. Because of their nonrandomized designs, these studies could not be used to address potential adverse consequences of this therapy in young infants with biliary atresia. In a meta-analysis of 8 of these studies, researchers were unable to determine if steroids improve patient outcomes because of an insufficient number of well-conducted studies. Nevertheless, postsurgical steroid treatment has become widely used, but there is significant practice variation.

For this prospective randomized controlled trial, the primary outcome is the percentage of participants in each arm with serum total bilirubin <1.5 mg/dL and with native liver at 6 months. Inclusion criteria include being postconception ≥36 weeks, <6 months of age, having a

abstract

Pediatric research is vital to improving pediatric medical care. At the same time, exposing children to research risks to collect data that might benefit future patients raises important ethical concerns. To address these concerns, US regulations allow institutional review boards (IRBs) to approve pediatric clinical trials only when the risks are minimal or (in some cases) a minor increase over minimal, or when the risks are justified by a potential for direct benefit to the participants. But how should an institutional review board determine if the risks of pediatric clinical trials are justified by a potential for participant benefit? In this Ethics Rounds article, we consider which potential benefits can justify which research risks with a focus on randomized clinical trials.

THE CASE

A research protocol comes before an IRB. Investigators propose a randomized, double-blind, placebo-controlled trial to evaluate whether treatment with corticosteroids improves the outcome of the Kasai or gall-bladder Kasai procedures in infants with biliary atresia.

Many retrospective analyses, using historical controls, suggest that steroids lead to better outcomes after surgery. Because of their nonrandomized designs, these studies could not be used to address potential adverse consequences of this therapy in young infants with biliary atresia. In a meta-analysis of 8 of these studies, researchers were unable to determine if steroids improve patient outcomes because of an insufficient number of well-conducted studies. Nevertheless, postsurgical steroid treatment has become widely used, but there is significant practice variation.

For this prospective randomized controlled trial, the primary outcome is the percentage of participants in each arm with serum total bilirubin <1.5 mg/dL and with native liver at 6 months. Inclusion criteria include being postconception ≥36 weeks, <6 months of age, having a
The proposed study involves a number of interventions: maintaining an IV for up to 1 week, administering steroids or a placebo, and a series of blood draws. Hence, to determine if this study can be approved, the reviewing IRBs must assess whether the risks posed by the different interventions are justified by a potential for participant benefit. When making this assessment, many commentators and authors of guidelines argue that IRBs should not allow “the potential benefits from one component of the research to offset or justify the risks presented by another.” Under this approach, reviewing IRBs should not allow the potential benefits of receiving the intervention being tested (in the present case, steroids) to justify the risks of other procedures or interventions in the study.

US regulations appear to endorse this restrictive approach to risk-benefit assessments. They stipulate that IRBs may approve pediatric interventions as having the prospect of direct benefit only when “the risk is justified by the anticipated benefit to the participants.” The stipulation that the risk of an intervention must be justified by the anticipated benefit seems to refer to the risks and potential benefits of the same intervention. If this reading is correct, it suggests that under US pediatric regulations, the potential benefits offered by experimental treatments to justify the risks of other procedures that are clinically necessary to administer can never be modified, at least to the extent of allowing the potential benefits of experimental treatments to justify the risks of other procedures that are clinically necessary to administer them.

The restrictive approach also has the potential to block procedures that are scientifically necessary to evaluate experimental interventions. For example, in the proposed study, the restrictive approach implies that the potential benefits of receiving steroids cannot justify the research blood draws. For the purposes of protecting children, this seems counterproductive. It has the potential to preclude investigators from adding “biopsies, blood tests, or scans that are unlikely to yield any information of benefit to society by justifying them on the basis of including an intervention that holds the prospect of direct benefit.” This approach protects pediatric participants from the risks of unnecessary procedures. Unfortunately, it also has the potential to prevent IRBs from approving necessary procedures.

Of greatest concern, the restrictive approach, taken literally, implies that the potential benefits offered by experimental treatments cannot justify the risks of procedures that are clinically necessary to administer them. For example, this approach suggests that the potential benefits of receiving steroids in the proposed study cannot justify even the risks of the IV for 7 days. That result seems clearly problematic. The IV is not an optional procedure the investigators are adding to take advantage of a captive population. This suggests that the restrictive approach needs to be modified, at least to the extent of allowing the potential benefits of experimental treatments to justify the risks of other procedures that are clinically necessary to administer them.
benefit them. Like the IV in the treatment arm, the research blood draws do not involve an optional procedure that the investigators are adding to take advantage of a captive population. Instead, they are needed to achieve the scientific goals of the study. This supports a further modification of the restrictive approach to the risk-benefit assessment: the potential benefits of receiving experimental interventions can justify the risks of procedures that are clinically necessary to administer them and the risks of procedures that are scientifically necessary to evaluate them. This conclusion raises the question of whether the potential benefits of receiving the experimental medication can justify the risks of interventions in the control arm.

Participants who undergo scientifically necessary procedures in the experimental arm also receive the experimental medication and may benefit from it. Participants in the control arm do not receive the experimental intervention. Hence, the risks to which they are exposed cannot be justified by the potential benefits offered by the experimental intervention. Instead, these risks are necessary to evaluate the experimental treatment, which is administered to others. This suggests that the potential benefits of receiving experimental interventions cannot justify the risks of procedures in the control arm because it is known at the time the individuals undergo them that they will not receive the experimental intervention.

In conclusion, the most widely endorsed approach to risk-benefit assessment maintains that the potential benefits of 1 intervention cannot justify the risks posed by other interventions. Applied strictly, this approach implies that the potential benefits offered by experimental interventions should not be allowed to justify the risks of other interventions in the same study. On this restrictive approach, the reviewing IRBs should approve the proposed study only if they find that all of the other procedures pose minimal risk, or they pose a minor increase over minimal risk and satisfy several additional requirements. In the present analysis, I argue that the restrictive approach is too restrictive. IRBs should allow the potential benefits offered by experimental interventions to justify the risks of procedures in the experimental arm that are necessary to administer them and the risks of procedures in the experimental arm that are necessary to evaluate them. On this approach, the reviewing IRBs should approve the proposed study unless they find that the risks in the control arm do not qualify as minimal or a minor increase over minimal.

The present proposal for evaluating the risks and potential benefits of pediatric research allows for more trials than the widely endorsed restrictive approach. At the same time, it permits IRBs to approve pediatric clinical trials that include a control arm only when the control arm offers a prospect of direct benefit (eg, active control) or poses no more than a minor increase over minimal risk (eg, a placebo pill). This approach therefore will block some valuable pediatric research studies. With that in mind, future researchers might consider whether it is possible to justify some pediatric clinical trials that include control arms that pose more than a minor increase over minimal risk and do not offer participants the prospect of direct benefit.

ROBERT “SKIP” NELSON, MD, PHD, COMMENTS

The ethical framework for enrolling children in research can be summarized in 4 ethical principles: (1) children should only be enrolled in research if the scientific and/or public health objectives cannot be met through enrolling adults; (2) absent the prospect of direct therapeutic benefit, the research risks to which children are exposed must be low; (3) children should not be placed at a disadvantage by being enrolled in a clinical trial either through exposure to excessive risks or by failing to get necessary health care; and (4) vulnerable populations that are unable to consent for themselves, such as children, should have a suitable proxy to consent on their behalf.

The first ethical principle of scientific necessity is reflected in the general regulatory requirement for the equitable selection of subjects and minimization of risk (21 Code of Federal Regulations [CFR] §56.111[a] [1] and [b]). The second and third ethical principles are focused on the appropriate balance of risk and potential benefit, and researchers use component analysis to identify the interventions and procedures in a proposed protocol and then evaluate them against the standards found in the additional safeguards for children enrolled in research (21 CFR §50, subpart D).

The proposed protocol would enroll infants <6 months of age who have undergone a Kasai procedure for the treatment of biliary atresia, and randomly assign them to receive methylprednisolone or a placebo. Because the administration of methylprednisolone is associated with known risks, infants who already demonstrate signs that are consistent with corticosteroid adverse events, such as glucose intolerance or systemic hypertension, are excluded. Other interventions included in the protocol involve the placement of a peripheral IV catheter for study drug administration for 21 days (if a catheter is not in place for clinical purposes) and obtaining blood to assess the safety and efficacy of the experimental intervention.
note, the frequency and volume of the blood to be drawn is not specified.

Regarding scientific necessity, the question of the impact of methylprednisolone administration on the outcome of a Kasai procedure can only be answered by assessing infants. The more important question is whether there is sufficient uncertainty about the answer to this question to justify performing a randomized controlled trial. This question of sufficient uncertainty can be separated from what the most appropriate control group would be to answer the scientific question. The term “equipoise” is often used to refer to the presence of sufficient uncertainty; however, equipoise is sometimes used to imply that known effective treatment should never be withheld. Given this ambiguity, the phrase “scientific uncertainty” is more accurate and thus preferable when referring to whether the scientific question the authors of the proposed protocol seek to answer has already been answered.

What is known about the impact of methylprednisolone on the outcome of Kasai procedures in infants with biliary atresia? Researchers in retrospective cohort studies using historical controls suggest an improvement in clinical jaundice at 6 and 12 months after surgery. A recent meta-analysis weakly supports this conclusion. Researchers in retrospective cohort studies using a comparison with historical controls are subject to selection bias and changes in clinical care that undermine the reliability of drawing a causal inference about the role of methylprednisolone. On the basis of available data, it is fair to say that we just do not know whether the postoperative use of corticosteroids provides any meaningful clinical benefit or whether the suggestion of short-term improvement in jaundice-free survival is offset by the potential for serious risks (some of which are difficult to assess in a short-term study, such as impact on neurodevelopmental outcome). Thus, an appropriately designed clinical trial of sufficient duration is needed to answer this question.

There are at least 2 major issues to point out with respect to the short description we have of the proposed clinical trial. First, do we consider jaundice-free survival with a native liver at 6 months to be a sufficient outcome measure? Would it be more appropriate to extend the duration of follow-up to 1 or 2 years and include important safety measures, such as neurodevelopmental outcome (which at a minimum would need to be evaluated at 2 or 3 years of age)? Second, once we agree on an appropriate and meaningful clinical end point, what is the predicted effect of our intervention, and how does this translate to the necessary sample size for the clinical trial? Given our current state of knowledge and the widespread and potentially unjustified use of corticosteroids after a Kasai procedure, there is a great need for an adequately powered and well-conducted clinical study using a meaningful outcome measure. Anything short of this would be unethical because it would subject research participants to the risks of the trial (whatever they may be) without the benefit of producing rigorous results.

Does the protocol as designed offer an appropriate balance of risk and potential benefit to the enrolled infants? To answer this question, we must identify the interventions and procedures in the protocol that either do or do not offer a prospect of direct clinical benefit, a procedure that is referred to as component analysis. This approach is consistent with the recommendations of the National Commission and the corresponding regulations. Interventions or procedures that hold out the prospect of direct benefit must be considered under 21 CFR §50.51 or §50.53. The interventions to be considered in this protocol are methylprednisolone administration, placebo administration (including IV placement), and a series of research blood draws. Although important, in this commentary, I will not address the donation of leftover blood into a repository for future research.

There appears to be evidence for a sufficient prospect of direct benefit to justify the risks of methylprednisolone administration (21 CFR §50.52). In fact, many clinicians appear to have already concluded that the clinical benefit of methylprednisolone outweighs the potential risks even in the absence of compelling controlled clinical trial data. If so, there may be reluctance to enroll an infant in a controlled clinical trial that would involve the administration of a placebo. Nevertheless, the withholding of known effective treatment is permissible if it does not present more than a minor increase over minimal risk (21 CFR §50.53). Placebo administration does not offer a prospect of direct benefit. The risks to the placebo or control group can only be assessed properly if one does a postrandomization analysis of benefit; otherwise, the potential clinical benefits of the active investigational drug would be used to justify the risks to the placebo group. This approach is simply nonsensical. However, this concern presumes that methylprednisolone is a known effective treatment, which is in fact the question that the research study is designed to answer. In the absence of a known effective treatment, using a placebo control group is ethically and scientifically appropriate.

The placement of a peripheral IV catheter for study drug administration is justified for the methylprednisolone group because the prospect of direct benefit is offered (21 CFR §50.52), and for...
the placebo group, no more than a minor increase over minimal risk is presented (21 CFR §50.53). If the peripheral IV catheter is already in place to provide appropriate clinical care, the risks of the catheter are not considered to be research risks (21 CFR §56.111[a][2]) and do not need to be evaluated under subpart D. The frequency and volume of the research blood draws are not specified in the protocol description, although it is likely (assuming appropriate limits are in place) that these procedures would present no more than a minor increase over minimal risk (21 CFR §50.53).

The inclusion of a placebo control group is justified given the lack of data to support methylprednisolone being known effective treatment. However, it is reasonable to ask whether placebo exposure can be minimized by using a different control group or study design. There are different adjuvant treatments that might impact postoperative inflammation and thus jaundice-free survival with the native liver but none of these have been studied adequately to serve as an active control arm. Unless a study is designed to demonstrate the superiority of the new intervention over an existing treatment, an active controlled design requires an analysis in which a noninferiority margin is used, which can only be established by conducting previous placebo-controlled trials. The use of a concurrent no-treatment control would eliminate the need for the peripheral IV line for placebo administration only but may introduce significant bias in the absence of masking treatment assignment. A dose-response design (for example, low-dose and high-dose methylprednisolone) would require evidence to support a separation between doses. Absent these data, a dose-response design would likely be uninformative. There are other designs that attempt to reduce the duration of placebo exposure, such as a randomized withdrawal design, but such a design would not be applicable in this clinical setting. In conclusion, the proposed study design is ethical (assuming the duration of follow-up and the appropriate sample size have been addressed) and consistent with the additional safeguards for children to be enrolled in research (21 CFR §50, subpart D). The methylprednisolone group is approvable under 21 CFR §50.52 as offering a sufficient prospect of direct benefit to justify the risks, with the balance of risk and potential benefit being comparable to the available alternatives. The placebo group is approvable under 21 CFR §50.53 as presenting no more than a minor increase over minimal risk along with the other nontherapeutic interventions, such as the placement of a peripheral IV catheter (if not present for clinical purposes) and research blood draws.

JOHN D. LANTOS, MD, COMMENTS

In this Ethics Rounds, 2 experts on the ethics of pediatric research come to the same conclusions but for different reasons. Both conclude that the study is important and ought to be permitted. But Dr Wendler suggests that current regulations have the potential to block the study and thus that those regulations should be changed or clarified. Dr Nelson concludes that the study is permissible under current regulations. This disagreement suggests a problem with our current system of research regulation. The rules are detailed, arcane, and subject to different interpretations even by experts in the field. That is perhaps inevitable in any system of regulation. But in research ethics, there is no way to adjudicate the disputes and decide, as a matter of policy, which is correct. The result is widespread and idiosyncratic practice variation in IRB review. We need the equivalent of an appellate court to review disparate decisions and decide which is correct or, at the very least, clear guidance from both the Food and Drug Administration and the Office for Human Research Protections about how to interpret federal guidelines with regard to dilemmas such as these.

ABBREVIATIONS

CFR: Code of Federal Regulations
IRB: institutional review board
IV: intravenous

REFERENCES


The Potential Benefits of Research May Justify Certain Research Risks
David Wendler, Robert M. Nelson and John D. Lantos

*Pediatrics* 2019;143;
DOI: 10.1542/peds.2018-1703 originally published online February 20, 2019;

Updated Information & Services

including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/143/3/e20181703

References

This article cites 8 articles, 0 of which you can access for free at:
http://pediatrics.aappublications.org/content/143/3/e20181703#BIBL

Subspecialty Collections

This article, along with others on similar topics, appears in the following collection(s):

**Ethics/Bioethics**
http://www.aappublications.org/cgi/collection/ethics:bioethics_sub

**Gastroenterology**
http://www.aappublications.org/cgi/collection/gastroenterology_sub

**Hepatology**
http://www.aappublications.org/cgi/collection/hepatology_sub

Permissions & Licensing

Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://www.aappublications.org/site/misc/Permissions.xhtml

Reprints

Information about ordering reprints can be found online:
http://www.aappublications.org/site/misc/reprints.xhtml

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN®
The Potential Benefits of Research May Justify Certain Research Risks
David Wendler, Robert M. Nelson and John D. Lantos
Pediatrics 2019;143;
DOI: 10.1542/peds.2018-1703 originally published online February 20, 2019;

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/143/3/e20181703