WHEN DO THE FEDERAL REGULATIONS ALLOW PLACEBO-CONTROLLED TRIALS IN CHILDREN?

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In March 1998, the National Institutes of Health (NIH) issued a policy requiring the inclusion of children in "all human subjects research conducted or supported by the NIH," unless there are scientific or ethical reasons to exclude them.[1] Two Food and Drug Administration (FDA) directives also encourage pediatric research.[2-3] The first mandates that pharmaceutical firms include children in studies of all relevant indications; the second offers 6 months additional market exclusivity for data pertaining to the use of tested agents in children.

These initiatives are likely to lead to increased enrollment of children in clinical trials. Because placebo-controlled trials are widely regarded as the gold standard for testing treatment efficacy, this increased enrollment of children will increase the frequency with which institutional review boards (IRBs) face the question of whether the federal regulations[4] allow children to be enrolled in the placebo-controlled trials. Because the federal regulations do not specifically address placebo-controlled trials, it is unclear when they allow children to be enrolled in such trials. Indeed, in publicizing its proposal to adopt the federal regulations governing research with children,[5] the FDA explicitly asked for advice regarding when the Federal regulations permit children to be enrolled in placebo-controlled trials.[6] In this article, we attempt to answer this question by drawing on the federal regulations as a whole, as well as the specific regulations governing research with children.

The ethics of placebo-controlled trials remain an issue of considerable controversy. In particular, there is no consensus about whether it may be ethical to include placebo controls in trials of new treatments for some disorders when proven effective treatment exists. Some argue that in this situation, placebo controls are unethical because they violate the principle of "clinical equipoise," under which patients enrolled in clinical trials should not be exposed to treatment (or placebo) known to be inferior to clinically available alternatives.[7] Others argue that when sound methodologic reasons support the use of placebo controls and research subjects will not be at risk of serious harm, short-term placebo-controlled trials are justifiable despite the existence of proven effective treatment.[8-9] The federal regulations for research involving children do not preclude the use of placebo controls in clinical trials when proven effective treatment exists. Our analysis is focused primarily on interpretation of the federal regulations concerning risk-benefit assessment as applied to placebo-controlled trials in children.

FDA	Food and Drug Administration
IRB	Institutional review board
NBAC	National Bioethics Advisory Commission
NIH	National Institutes of Health
PET	Positron emission tomography

THE FEDERAL RISK-BENEFIT CATEGORIES

The federal regulations allow IRBs to approve research with children only when the research qualifies for one of three risk-benefit categories: (1) minimal risk; (2) greater than minimal risk, but presenting the prospect of direct benefit; and (3) greater than minimal risk without the prospect of direct benefit but likely to produce generalizable knowledge about the subjects' disorder or condition.[5]

The "minimal risk" category allows children to be enrolled in research only when the risks they face are no greater than the risks children "ordinarily encounter in daily life."[4] If the IRB finds that the risks of a research study are greater than minimal, it must next assess whether the research offers children a prospect of direct benefit.

The Federal regulations do not define "direct benefits" or explain how they differ from indirect or other types of benefit. We understand "direct benefits" as those benefits to research participants that may result from the research interventions required to answer scientific questions posed by a given study, eg, the benefits of receiving active treatment interventions in a randomized clinical trial. Indirect benefits are those that are extraneous

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to the research design, such as payment for research participation.

The regulations stipulate that IRBs may approve the enrollment of children in research that is greater than minimal risk but offers the prospect of direct benefit only when the prospect of direct benefit "justifies" the risks to subjects, and "the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches."[5] This requirement implies that any chance of direct benefit, even a chance of significant direct benefit, is not necessarily sufficient to approve pediatric research in this category. Instead, the potential for direct benefit must outweigh the risks of the research, and the risk-benefit profile that children face must be at least as favorable as the risk-benefit profile of the treatments available to them outside of the research context.

Finally, the third risk-benefit category allows the enrollment of children in research that poses greater than minimal risk, and does not offer a compensating potential for direct benefit, provided it satisfies three additional conditions: (1) the risks are no greater than a "minor increase" over minimal; (2) the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychologic, social, or educational situations; and (3) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding and amelioration of the subjects' disorder or condition.[5] Importantly, the federal regulations do not define a "minor increase" over minimal risk, leaving this assessment to the judgement of the IRB. This flexibility in the regulatory language concerning what counts as minimal risk and a minor increase over minimal risk permits IRBs to make contextualized judgments concerning allowable risk in studies involving children.

HOW SHOULD THE RISK-BENEFIT CATEGORIES BE APPLIED?

When reviewing a study that proposes to enroll children, some IRBs may apply the federal risk-benefit categories to the *entire* study. On this approach, the IRB assigns to the entire study a single risk-benefit category based on its total risks and total potential benefits. For instance, when reviewing a study that involves administration of a drug, a positron emission tomography (PET) scan, and 5 blood draws, the IRB would determine a risk-benefit category by weighing the cumulative risks and potential direct benefits of these interventions.

The problem with this approach is that, in describing the three risk-benefit categories, the federal regulations instruct IRBs to assess whether an "intervention or procedure" offers a prospect of direct benefit that justifies its risks.[5] This wording suggests that IRBs should calculate the risks and potential direct benefits of each of the interventions included in a given study, and consider whether each intervention qualifies for one of the three risk-benefit categories. On this components approach, the IRB should calculate the risk-benefit profile of the PET scan in the previous study and determine whether it qualifies for one of the three risk-benefit categories, independent of the blood draws and drug administration. Similarly, if a study proposes to randomize children to receive either a drug or psychologic counseling, the IRB should not calculate a risk-benefit profile for the overall study by averaging the risk-benefit profiles of the two interventions.

Because research studies may include procedures that have very different risk-benefit profiles, this components approach implies that the IRB may end up assigning the various interventions in the same protocol to different risk-benefit categories. When this happens, the regulatory requirements that apply to the different interventions will be different. For a protocol that includes an experimental drug treatment and a research PET scan, the IRB may deem the drug treatment to qualify as greater than minimal risk with a prospect of direct benefit, and the PET scan as greater than minimal risk with no prospect of direct benefit. In that case, the IRB could approve the PET scan component of the protocol, only if the PET scan poses no greater than a minor increase over minimal risk.

The components approach to risk-benefit assessment is not only consistent with the language of the regulations governing research with children; it follows from the ethical and regulatory requirement of minimizing risks. The first requirement for IRB approval of any research involving human subjects is that "Risks to subjects are minimized...by using procedures which are consistent with sound research design and which do not necessarily expose subjects to risk."[4] An intervention or procedure of a study posing risks without the prospect of compensating benefits that is extraneous to answering a scientific question should be eliminated. Additionally, if an alternative research procedure with less risk can be substituted without compromising scientific validity, then it should replace the higher risk procedure. In both cases, application of the requirement of minimizing risks depends on risk-benefit assessment of the components of the protocol.

The National Bioethics Advisory Commission (NBAC), following an approach developed by Weijer,[10] endorses assessing the risk-benefit profiles of individual interventions or procedures: "A major advantage of this approach is that it avoids justifying the risks of procedures that are designed solely to answer the research questions based on the likelihood that another procedure in the protocol is likely to provide a benefit."[11] For example, using the approach of applying risk-benefit categories to *entire* protocols, an IRB could not approve a study that involves only a no-benefit procedure that is determined to be more than a minor increase over minimal risk, such as a liver biopsy. However, on this same approach, the IRB might approve this procedure in children if the investigator adds it on to a drug treatment study, by arguing that the potential benefits of receiving the drug are sufficient to compensate for the combined risks of the drug and the biopsy. In contrast, assessing the risk-benefit profiles of individual interventions would not allow the investigator and IRB to justify the biopsy on the grounds that another proce-

dure in the protocol offers a compensating potential for direct benefit. In this way, risk-benefit assessment of separate research interventions avoids what Levine has termed the "fallacy of the package deal."[12]Although it is important to assess the risk-benefit profiles of individual interventions, this assessment alone is not sufficient to protect pediatric subjects adequately. The National Commission's report, *Research Involving Children*, which articulated the current federal regulations for pediatric research, stipulates that "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in a protocol must be evaluated individually as well as collectively."[13] To make this collective risk-benefit assessment, IRBs should consider all the risks children face that are not compensated by the respective interventions' potential for direct benefit, and ensure that these additional research risks are within the federal guidelines. For instance, assessing only the risk-benefit profiles of individual interventions would entail that a series of research blood draws could qualify as minimal risk, no matter how many blood draws are included in the series, as long as each individual blood draw poses minimal risk. However, each research blood draw poses a very minor risk that is not compensated by the intervention's potential for direct benefit. Hence, as the number of blood draws in the series increases, discomfort and risks of fainting would eventually add up to more than minimal risk. To ensure that children do not face unacceptably high risks, the IRB should total up the cumulative, additional research risks that a given study poses to children, and ensure that this total falls within a minor increase over minimal. On this combined approach, then, IRBs should first assess the risk-benefit profiles of a study's individual interventions, and then assess the study's cumulative research risks that are not compensated by the prospect of direct benefits to determine whether both the components of the study and the study as a whole have an acceptable risk-benefit ratio.

In the following sections, we apply this interpretation of risk-benefit assessment under the federal regulations to placebo-controlled trials that enroll children.

APPLYING THE FEDERAL RISK-BENEFIT CATEGORIES TO PLACEBO INTERVENTIONS

On the approach of applying the federal risk-benefit categories to entire protocols, the IRB would determine a single risk-benefit profile for each placebo-controlled trial. To do this, the IRB calculates the risks and potential benefits of the experimental treatment, the risks and potential benefits of the placebo intervention, and then weights them by the chances that subjects will be assigned to each arm. Notice that, on this approach, the risk-benefit profile of placebo-controlled trials is determined *before* children's randomization to a particular arm. One could defend this approach on the grounds that, before randomization, one does not know which intervention—placebo or experimental treatment—children will receive.

The problem with this approach is that providing research subjects with a placebo is a very different intervention from providing them with a drug treatment. It follows, according to the wording of the federal regulations, and the position statement of the NBAC, that the IRB should calculate the risk-benefit profile of the placebo intervention *separately* from the risk-benefit profile of the experimental treatment. On this components approach, the IRB may approve a randomized, placebo-controlled trial in children only when both the placebo intervention and the drug intervention qualify in one of the three Federal risk-benefit categories.

PLACEBO RISKS AND POTENTIAL BENEFITS

The risks of placebo interventions come from two sources: the risks of the placebo intervention itself, and any risks subjects face as a result of receiving placebo rather than potentially effective treatment for their condition. The latter risk is exemplified by some placebo-controlled asthma trials. A substantial proportion of children with asthma who have received inhaled corticosteroids as part of their clinical care get worse, when randomized to placebo, on objective outcome measures such as forced expiratory volume in one second, and subjective outcome measures, including asthma symptom scores, night-time awakening, and global clinical assessment.[14-17] The potential direct benefits of a placebo intervention consist of the improvement in research participants' condition that can be attributed to their receiving the placebo.

Subjects who receive the placebo intervention may face significantly different risks and potential benefits compared with subjects who receive the active treatment. For this reason, the placebo intervention may fall into a different risk-benefit category than the active treatment intervention, in which case the two interventions would be subject to different regulatory requirements. When this occurs, the trial may be approved only when both interventions satisfy the requirements for one of the three allowed risk-benefit categories.

PLACEBO CONTROLS THAT POSE MINIMAL RISK

In some cases, a placebo intervention poses minimal risks. Daily administration of a small sugar pill is likely to pose essentially no risks to children. However, when making this assessment, IRBs should consider whether there is any evidence that the administration of placebos in the context in question may pose risks, so-called "nocebo" effects.[18] For instance, it is possible that children who are informed of the side effects of the active medication may, because of expectancy effect, have these side effects while taking the placebo. Assuming there is no solid evidence of any nocebo effects that are greater than minimal risk, IRBs must determine whether the risks subjects face from not receiving standard treatment for their conditions makes the placebo intervention exceed minimal risk. When there is no known effective treatment for the condition under study, the use of placebo poses minimal risks to children. The category of "no known effective treatment" includes both no treatment and a treatment whose safety and

efficacy have not been established. In these cases, children who receive placebo in research are receiving essentially the same thing they would receive outside of the research context, namely, no effective treatment for their condition.

For other conditions such as allergic rhinitis or mild headaches, failure to receive effective treatment, particularly for short periods, may also pose minimal risks. With children who regularly have mild-to-moderate symptoms, the harms of forgoing treatment are likely to be minimal, provided that the trials are short-term, the investigators have specified reasonable criteria for stopping trial participation in case of symptom worsening, and trial participants are carefully monitored. Accordingly, the mere fact that proven effective treatments exist for alleviating the symptoms of allergic rhinitis and headaches does not imply that a placebo-controlled trial in children who have these conditions poses more than minimal risk. At the same time, the fact that a placebo intervention poses no greater than minimal risks does not necessarily imply that it is approvable in children. Rather, the intervention must also satisfy the Federal requirements that apply to all human subjects research.[4]

Most importantly, all research involving human subjects must be devoted to answering a valuable scientific question by means of valid methods likely to produce meaningful results. Otherwise, risks to which research subjects are exposed cannot be justified. It follows that placebo controls should be approved only when there is a sound methodologic rationale for their use. Methodologic reasons for including a placebo arm include the lack of proven effective treatments for children with a given disorder, the disorder is characterized by a waxing-and-waning course with frequent spontaneous remissions (as in the case of allergic rhinitis), high rates of placebo response associated with the disorder, and the existence of proven effective treatments that have not consistently been demonstrated to be superior to placebo in previous placebo-controlled trials.[9,19] In addition, in some cases when children are not placed at risk of harm, initial efficacy testing of investigational treatments against placebo may be justifiable before larger scale trials are conducted that compare the new treatment to standard therapy to minimize the number of subjects exposed to ineffective or toxic agents.[9]

PLACEBO CONTROLS THAT POSE MORE THAN MINIMAL RISK WITH A PROSPECT OF DIRECT BENEFIT

Placebo controls may pose more than minimal risk; for example, a placebo intervention of sham surgery is likely to pose greater than minimal risks. Randomization to placebo may require withholding proven effective treatment for a condition that poses greater than minimal risks when left untreated, such as chronic asthma. To approve placebo-controlled trials in these cases, the IRB should assess whether the placebo intervention offers children a compensating prospect for direct benefit.

Numerous placebo-controlled clinical trials for certain conditions provide evidence of improvements, often dramatic, among subjects randomized to placebo.[9] However, before concluding that assignment to the placebo arm of a clinical trial offers a prospect for direct benefit, IRBs must address the complex question of whether these improvements can be attributed to the placebo intervention itself. Patients often improve for reasons that have nothing to do with the interventions they are receiving; they sometimes improve as the result of spontaneous remissions or symptomatic fluctuations characteristic of their illnesses.

A recent meta-analysis of randomized clinical trials with both placebo and nontreatment groups found little evidence of therapeutic benefits of placebo, except for treatment of pain.[20] Some have argued that the design of this study was not adequate to detect the full range of potential placebo benefits.[21-23] These arguments are supported by clinical experience, as well as experimental data, which suggest that, in certain cases, research participants' clinical improvements are due, at least in part, to the existence of a positive placebo effect.[24]

In specific cases where IRBs determine that the placebo intervention itself offers the potential for direct benefit, the federal regulations allow IRBs to approve a placebo control that poses greater than minimal risks to children, provided the potential for direct benefit justifies the risks, and the risk-benefit profile of the placebo intervention is at least as favorable as the treatments available outside of the research context. This latter requirement places a strong constraint on approving the use of placebo controls under this risk-benefit category when proven effective treatments are available for the condition under study.

To consider a specific example, placebo-controlled trials of new treatments for asthma frequently enroll children.[14-17] Those randomized to placebo often must forgo medically recommended therapy with inhaled corticosteroids for the duration of the trial. Although an IRB might be tempted to approve the placebo intervention in the prospect of direct benefit category, the risk-benefit profile of the placebo intervention is unlikely to be as favorable as the risk-benefit profile of controller therapy, which has been proven effective for chronic asthma.[25] Hence, the placebo intervention would not satisfy the federal requirements on greater than minimal risk research that offers a prospect of direct benefit.

PLACEBO CONTROLS THAT ARE MORE THAN MINIMAL RISK WITH NO PROSPECT OF DIRECT BENEFIT

Placebo interventions that pose greater than minimal risk without a compensating potential for direct benefit may be approved only when the risk represents a "minor increase" over minimal. The use of placebo to evaluate antidepressants in children with depression might qualify in this risk-benefit category, provided that the placebo intervention is not judged to have a prospect of direct benefit and the risk to children from untreated depression during a short-term trial is assessed as no more than a minor increase over minimal risk. Although relatively high rates of placebo response have been observed in

placebo-controlled trials of antidepressants in children, it does not follow that placebos have therapeutic benefit in depressed children. These results may have reflected spontaneous fluctuations characteristic of childhood depression or measurement biases associated with subjective outcomes. Accordingly, an IRB might reasonably determine that children randomized to placebo would not have a prospect of direct benefit. Furthermore, high rates of placebo response, coupled with a lack of strong and consistent efficacy of currently available treatments for childhood depression,[26-27] provide the rationale for including placebo controls to generate valid efficacy data.[8] The use of placebo controls in childhood depression appears consistent with criteria promulgated by the American Academy of Pediatrics, which permit placebo controls "when the disease process is characterized by frequent, spontaneous exacerbations and remissions."[19]

Placebo-controlled trials that exclude children suspected to be at higher risk of suicide, limit trial duration to the shortest period necessary to demonstrate acute efficacy, employ reasonable criteria for stopping trial participation in the event of serious clinical deterioration, and implement careful monitoring might qualify as providing placebo interventions that fall within a minor increase over minimal risk.

In addition, to approve such a trial, an IRB would need to judge that the use of the placebo control would lead to generalizable knowledge of "vital importance." Several considerations support such a judgment. Depression is a serious disorder of relatively high prevalence in children,[26] and comparatively few antidepressant trials have been conducted in children.[27] Treatments that are effective in adults are not necessarily effective in children, as trials that evaluate tricyclic antidepressants have demonstrated.[27] Finally, without a placebo control, the validity of antidepressant trials is open to question.[8]

A potentially important practical consequence of placebo-controlled trials with placebo interventions that are judged to qualify for this risk-benefit category is that both parents of children enrolled in these trials are required by the regulations to give permission for trial enrollment, unless only one parent is competent and "reasonably available," or when only one parent has responsibility for a child's custody.[5] This is in contrast with trials in which all arms provide a direct benefit, which require only one parent's consent. In the case of double-blind placebo-controlled trials, it would be necessary for both available parents to give permission for all children enrolled in the trial, because it would not be known until the trial ends which children received the investigational drug or the placebo.

CONCLUSION

Efforts to improve treatments for children, encouraged by recent NIH and FDA policy initiatives, are likely to lead to a substantial increase in IRBs being asked to assess the enrollment of children in placebo-controlled trials. It is important, therefore, to determine when such trials may be approved under the federal regulations. We have argued that placebo controls and active treatments are separate interventions; hence, their risk-benefit profiles should be assessed independently. On this approach, a placebo control in a clinical trial involving children may be approved only when the placebo intervention satisfies one of three conditions: (1) it poses minimal risk; (2) it poses greater than minimal risk with a prospect of direct benefit from the placebo intervention that justifies the risk, and is at least as favorable as the available alternatives; or (3) it poses no greater than a minor increase over minimal risk without a prospect of direct benefit from the placebo intervention, provided that the study is deemed likely to produce knowledge of "vital importance" to the subjects' condition or disease. Under all conditions, placebo controls should be approved only if there are convincing methodologic reasons to use them rather than an active control.

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THE TREATMENT OF BEHAVIOR DISORDERS IN CHILDREN WITH BENADRYL

Effron AS, Freedman AM. J Pediatr 1952;42:261-6

An unselected sample of inpatient admissions to a child psychiatric ward at New York's Bellevue Hospital were observed for baseline behavior and stabilization for 10 to 21 days and then placed on a dose of Benadryl that was increased over a period of 4 weeks from 10 mg twice daily to 30 mg four times daily. Numerous behaviors were monitored and scored, only some of which were reported in this communication. There were 44 patients (including 34 boys) with an age range of 6 to 12 years. Twenty of these children were diagnosed as having schizophrenia, 13 were "organic," 8 had a primary behavior disorder (usually with predominant anxiety features), 2 were psychopathic, and one was mentally retarded. The overall improvement rate was 61% with all of the children in the behavior disorder subgroup demonstrating improvement. It is suggested that many of these latter children actually had anxiety-related sleep disorders that were normalized by the Benadryl. The authors compared this overall favorable efficacy rate with the only other two drugs then available in the pediatric psychopharmacopia, dexedrine and hydantoin compounds, and were impressed by how similar the Benadryl results were with those of dexedrine. (The hydantoins were generally much less effective.) Because these children had been hospitalized for acute behavior disturbances, and the drug was discontinued at the end of the 4-week trial period, no long-term effects were reported. If it had been needed longer, tachyphylaxis might have limited its efficacy. Modern diagnostic criteria changes and research design issues make interpreting these results problematic. Nevertheless, the use of Benadryl to treat certain acute sleep disorders remains valid. In addition, any drug with a mildly sedative effect might indirectly decrease behavioral outbursts related to impulsivity and allow behavioral interventions a window of opportunity to modify the environmental expecations that are otherwise negatively affecting behavior. After 50 years, Benadryl still has some limited use in the treatment of child behavior disorders, although many of its more recent psychopharmacologic competitors have yet to demonstrate better efficacy in controlled research designs.

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