Quorum

Research in Pediatric Populations

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DESCRIPTION

It is vitally important to develop effective and safe treatments for children based on reliable data from clinical research trials conducted in children. However, conducting research in children presents unique ethical challenges: Children, by virtue of their decreased autonomy and still-developing cognition, are considered to be a vulnerable research population needing special protections.

TOPICS

- WHY CHILDREN SHOULD BE INVOLVED IN CLINICAL RESEARCH
- FEDERAL REGULATIONS
- MINIMAL RISK
- PLACEBO
- PARENTAL PERMISSION
- STORIES FROM THE TRENCHES

The Complexities of Subpart D Determinations

It is vitally important to develop effective and safe treatments for children based on reliable data from clinical research trials conducted in children. However, conducting research in children presents unique ethical challenges: Children, by virtue of their decreased autonomy and still-developing cognition, are considered to be a vulnerable research population needing special protections.
For decades, federal agencies as well as professional organizations such as the American Academy of Pediatrics (AAP) have grappled with balancing the need to develop knowledge about children and the need to protect their welfare. This paper will outline the policies resulting from these deliberations, discuss the assessments upon which they hinge, and explore the concept of informed consent in a pediatric population. Finally, specific examples from Quorum's archives will provide guidance for interpreting these policies.

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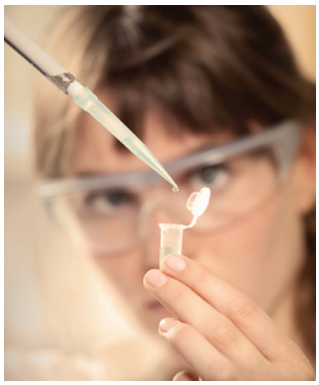
Why should children be involved in clinical research?

Why must research about children be done in children? Why not just extrapolate from data collected in adults? The answers proceed from common sense as well as from historical data. Logically, diseases and conditions unique to children (such as the sequelae of prematurity) can only be studied in children. Other pediatric conditions (such as phenylketonuria) which lead to disability or death if left untreated are also best studied in children. Diseases such as cancer may have markedly different pathophysiology, severity and response to treatment in children compared to adults. Additionally and unfortunately, historical evidence shows that extrapolation of treatment from adult data can dictate incorrect dosing and in some cases result in severe adverse events in children. [1-2]

The variable drug sensitivities of the developing body and brain drive the need to develop therapies specifically tailored to pediatric physiology.[3] Calling out the "urgent need for high-quality trial evidence in children" Klassen and others define

criteria for designing such trials, and emphasize that "...inadequately powered studies should themselves be considered a breach of ethical standards".[4] The conflict between the need to have adequately powered studies and the injunction to use as few children as possible to achieve the goals of the research may be mitigated by the judicious use of placebo arms in trial design, as will be discussed in greater detail below.[5]



Specific guidelines for the ethical conduct of drug studies in a pediatric population have been developed over the last many decades through collaborative work between the FDA, the AAP and others. In 1977 the AAP Committee on Drugs issued a report foreshadowing the principles of beneficence, justice and respect for persons that would be published in the Belmont Report the following year. This and subsequent AAP reports outline the precepts of benefits outweighing risks, equitable subject selection, obtaining informed and voluntary consent, and requiring still greater protections for particularly vulnerable subpopulations such as handicapped or terminally ill children.[6-7]

What are the federal regulations designed to protect children in research?

Federal regulations codifying the protection of children* as research subjects quickly followed the 1977 AAP report. These regulations, titled "Additional Safeguards (FDA) /Protections (DHHS) for Children Involved as Subjects in Research", are referred to as Subpart D, and are found at 21 CFR 50 (FDA) and 45 CFR 46 (DHHS). [8-9]

Distinctions among the categories of Subpart D are made according to levels of risk and probability of benefit for the individual research subject, and the IRB may assign different subpart D determinations to different arms of a single protocol, as will be elaborated below. Subpart D categories are:

21 CFR 50.51 (45 CFR 46.404):

Clinical investigations not involving greater than minimal risk

(a) no greater than minimal risk to the child is presented

21 CFR 50. 52 (45 CFR 46.405)

Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.

(a) the risk is justified by the anticipated benefit to the subjects

(b) the relation of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by available alternative approaches

21 CFR 50.53 (45 CFR 46. 406)

Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition.

(a) The risk represents a minor increase over minimal risk

*The regulations define children as "persons who have not attained the legal age for consent to treatments or procedures involved in the clinical investigations, under the applicable law of the jurisdiction in which the clinical investigations will be conducted."[10] The legal age of consent is 18 years old in all states except Alabama and Nebraska [19], and Puerto Rico [21].

(a) the intervention or procedure presents experiences to subjects that are reasonably commensurate# with those inherent in their actual or expected medical, dental, psychological, social, or educational situations

(b) the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for the understanding or amelioration of the subjects' disorder or condition^

21 CFR 50.54 (45 CFR 46.407)

Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.

(a) The investigation presents an opportunity to further understand, prevent or alleviate a serious problem affecting children

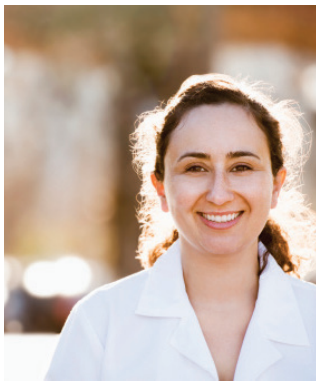
(b) The FDA in consultation with a panel of experts determine that

1. The conditions of 50.51, 50.52, or 50.53 are satisfied **or**
2. The following conditions are met:
    i. (a) above **and**
    ii. the investigation will be conducted according to sound ethical principles.

In all cases (50.51 - 50.54), the assent of the child and the permission of the parent(s) must be sought.

 # Commensurate is understood to mean "reasonably similar to" and refers to familiarity with the experiences that participation will entail. Familiarity does not allow the risk threshold to be changed. [11]

^*Condition is understood to mean a specific set of characteristics that have an established link to children's health or lack thereof and the definition of "vital importance" rests upon clear and significant scientific evidence.* [11]



What constitutes minimal risk and a minor increase over minimal risk in a pediatric population?

When reviewing research involving children, the IRB must make a Subpart D determination. To correctly assign subpart D determinations, the IRB must carefully assess risk levels of the research procedures: minimal risk, minor increase over minimal risk, and more than a minor increase over minimal risk. The distinctions between these various risk levels continue to be debated.§ After all, children are the ones swinging by one arm from a jungle gym.

The regulations define minimal risk as "...the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." [13] In children, risks are considered to "...include all harms, discomforts, indignities, embarrassments, and potential breaches of privacy and confidentiality associated with the research."[14]

Does the minimal risk threshold shift as a function of disease state or other realities of a child's life? Defining a "Uniform Standard" SACHRP and others have established that children who live in less safe environments (for example, in violent neighborhoods or houses with lead-based paint) cannot by that fact be exposed to greater risks in a research context. Thus they recommend that "minimal risk" when applied to subpart D should be interpreted as "those risks encountered during daily life by normal, average, healthy children living in safe environments or during the performance of routine physical or psychological examinations or tests." [12,14,15]

There is, however, a recognition that risks can appropriately be indexed to age and developmental status. Some have suggested that two thresholds be set, both based on the risks average healthy children encounter in daily life but distinguished by the age of the child. Wendler argues that children older than 12-14, by virtue of their intellectual development as well as by virtue of the risks they are permitted to take by their parents and society, can understand and thus should be allowed to undertake research with a higher level of risk than younger children.[16]

§ Differing risk levels may be illustrated by comparing methods of urine collection: via a bag (minimal risk), via a catheter (minor increase over minimal risk) or via suprapubic tap (more than a minor increase over minimal risk). As additional examples, venipuncture or a finger stick is minimal risk, a skin punch biopsy with topical pain relief is minor increase over minimal risk, and an organ biopsy is more than a minor increase over minimal risk.

The IRB must additionally decide what constitutes a "minor increase over minimal risk," but unfortunately the regulations do not provide a precise definition of this term. According to SACHRP, a minor increase over minimal risk means that the added risk should be only slightly more than minimal, any potential harm should be transient and reversible, and there should be "no or an extremely small probability" that any of the harms could be perceived as severe by the participant. [11, 12]
Should sick children be allowed to assume greater research risks if there is a

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prospect of direct benefit? Do the medical treatments they undergo change what they would perceive as "severe" harm? The regulation at 50.53 (b) states that the procedures must be reasonably commensurate with those they would expect to undergo as part of their actual medical experience. Given that the ceiling on an acceptable level of risk is determined by proportionality to the probability and magnitude of benefit, common sense would dictate that they may assume greater research risks, as long as the procedures are commensurate with procedures known to them, and as long as the individual child (50.52) or the class of children with a particular disease (50.53) may reasonably stand to reap the greater benefit of disease mitigation.

Can clinical trials in children include placebo arms? How is the risk level defined for placebo-controlled studies?

A challenge of pediatric research devolves from the small numbers of subjects typically available, as well as from the ethical obligation to expose as few children as possible to the risks of research. Placebo-controlled trials can increase the likelihood of being able to detect small differences in effect size with a smaller sample size.

The use of placebo control groups can be viewed as controversial in studies on adults, and is even more so in the context of research involving children. ICH (2000)[17] CIOMS (2002)[18] and Helsinki (2002)[19] have variously stated that placebo controls should be limited to situations in which there is no proven alternative, when there is no serious harm of withholding effective therapy, and when an active control trial would not yield scientifically valid results.
The Committee on Drugs of the AAP defined its position on the use of placebo controls, specifically that they should be limited to situations 1) where there is no accepted therapy; 2) when the commonly used therapy is of questionable efficacy; 3) when the commonly used therapy carries a high risk of undesirable

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side effects and risks may exceed benefits; 4) when placebo can identify serious side effects produced by adding a new treatment to an established regimen, and 5) when the disease course fluctuates and the efficacy of therapy has not been established.[20]

In the preamble to the final rule on subpart D published February 26, 2013, the FDA commented on risk analysis in placebo-controlled trials in children, and whether placebo arms can be considered to confer "inclusion benefits" such as increased monitoring and care. The Pediatric Ethics Subcommittee of the FDA opined that "the placebo arm of a trial cannot be considered to confer the prospect of direct benefit….and that children enrolled in the placebo arm of a trial should be exposed to no more than minimal risk or a minor increase over minimal risk." [21] In blinded studies providing no information about which arm a child will be assigned to, the Subpart D determination must reflect the highest risk level.

When an IRB is evaluating clinical trials in children, component analysis provides a systematic approach to evaluating the balance of risks and benefits. In a given clinical trial, some interventions anticipate a therapeutic effect while others (such as administering a placebo) are without therapeutic promise but deemed useful for the purpose of answering the scientific question. The first step of component analysis is to designate each research procedure as therapeutic or nontherapeutic. In order for the research to be acceptable, therapeutic procedures must meet the standard of clinical equipoise and a reasonable ratio of risk to potential benefit to the individual subject; nontherapeutic procedures must present the least risk possible, have a favorable ratio of risk to the benefit of knowledge to be gained, and represent no more than a minor increase over minimal risk. Once risk/benefit determinations are made for the different procedures in a trial, a subpart D determination can be made for the trial as a whole. [22-23] The examples provided at the end of this paper will help to illustrate this deliberation process.

Parental permission and child assent should be informed and voluntary; what does this mean and how is it established in the pediatric population?

The requirements for parental permission ("permission" as distinct from an adult consenting to their own participation) and child assent are extensions of the principle of respect for persons. Whether called consent, permission, or assent, the agreement of an adult or a child to participate in research is considered valid if the information upon which they base their decision is complete, if they comprehend the information, and if their decision to participate is made voluntarily and without coercion. Whether and how these criteria can be met is discussed below.

As stated in 21 CFR 50.3: "Assent means a child's affirmative agreement to participate in a clinical investigation. Mere failure to object should not, absent affirmative agreement, be construed as assent." The regulations at 21 CFR 50.55 (a) stipulate that the IRB must determine that assent is solicited from children judged to be capable of providing assent. The validity of child assent is predicated

on some level of understanding by the child as to what he or she is agreeing to do. Given that a child's comprehension of complex scientific concepts is expected to be lower than those of an adult, the challenge is to determine what aspects of the study are important to present to the child.

William Bartholome and the Committee on Bioethics of the AAP define the following elements as essential to valid assent: the child must 1) understand what procedures will be done; 2) voluntarily choose to undergo the procedures; 3) convey this choice unambiguously; and 4) understand they can withdraw. They also note that the child should be helped to gain a developmentally appropriate awareness of the nature of their condition.[22-23]

Parental permission means that the parent agrees that their child or ward can participate in a clinical investigation, and should also be based on the presentation of complete and accurate information. The elements of "informed permission" are the same as those for the adult consenting to their own participation in a clinical investigation, and are subject to the same shortcomings including therapeutic misconception and inability to comprehend complex scientific concepts. However, parents of sick children may have an additional situational emotional burden that colors their thinking and comprehension. Suggestions for improving the consent process for parents include ensuring adequate time for consideration of the information, assessing comprehension, and in cases of high parental stress, obtaining continuous permission (repeating the consent process at intervals throughout the study). [24]

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Even if a child is deemed to comprehend the information given to them, their autonomy must also be evaluated and should be gauged in the context of their age and developmental status. Confounding the notion of voluntariness in younger children is their susceptibility to pressure from, or simply a desire to please, parents and doctors. Parents who may be motivated by compensation or by the desire to "teach altruism" to their children may exert additional pressure. In older children and adolescents, a burgeoning desire to assert autonomy may further complicate an assessment of true voluntariness. [25]

Both HHS and FDA regulations allow assent to be waived if the research offers a therapeutic benefit to the child that would be otherwise unavailable to them. It should be noted that while HHS regulations allow for a waiver of parental permission under some conditions (i.e. for a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, for example, neglected or abused children)[9], FDA regulations do not allow for a waiver

of parental permission for FDA-regulated clinical investigations.[21]

Subpart D in practice: how are determinations made? Stories from the trenches.

The following examples of protocols reviewed at Quorum Review offer an insight into how different subpart D determinations are made based on the level of risk and the possibility of benefit. They are organized from lowest to highest risk level. A chart-based algorithm for subpart D analysis is also appended.[26]

(a) 50.51 Determinations

Retrospective chart reviews, registry studies, nonsignificant risk medical device studies, and in vitro diagnostic device studies are examples of protocols that would receive a 50.51 determination.

- The development of an immunoassay to aid in the detection and treatment of Lyme disease requires a single blood draw by venipuncture in individuals 11 years old and above.

(b) 50.51 and 50.52 Determinations

When the condition being studied is a relatively benign one, withholding potential treatment to the placebo arm does not confer more than minimal risk.

- A placebo-controlled study in mild to moderate (non-scarring) acne which utilizes a topical IP and minimal risk procedures for assessing outcome receives a 50.51 determination for the placebo arm and a 50.52 determination for the active arm.

When the condition is not benign but the placebo group still receives treatment this determination may apply.

- A placebo-controlled study in asthma permits all subjects to remain on their asthma medications. The determination here was 50.51 for the placebo arm, because there is no increase in risk over that which these individuals normally experience; 50.52 for the active arm because of the increased risk of the IP (with the prospect of direct benefit).

(c) 50.52 Determinations

When the comparator arm is an active compound, both arms may be greater than minimal risk, and both arms offer the prospect of direct benefit to the individual.

- A study in clostridium difficile compares a new drug to vancomycin, an established therapy. The risks of the active comparator are nephrotoxicity

and ototoxicity, but both arms hold out the prospect of benefit, and both arms receive a 50.52 determination.

- A study of a new Tdap vaccine is a modified double-blind design that uses an active comparator. Again, both arms may directly benefit and thus both arms receive a 50.52 determination.

This determination may also be made when the intervention is minimal risk but the outcomes measures entail using more than minimal risk procedures.

- A study to evaluate orthodontic appliances in adolescents is minimal risk except for the fact that additional panoramic x-rays are taken to assess efficacy of tooth realignment. The study was approved under 50.52 to reflect the fact that the additional x-rays render the procedures greater than minimal risk.

(d) 50.52 and 50.53 Determinations

These determinations are often made when there is an active arm and a placebo arm in the study, and the research as a whole presents greater than minimal risk. In these cases, the active arm is assumed to potentially offer the prospect of direct benefit to individual subjects and thus would qualify for a 50.52 determination. The placebo arm does not offer the prospect of direct benefit but may yield generalizable knowledge about the subjects' condition, and thus qualifies for a 50.53 determination.

- A placebo-controlled, seasonally-timed study of allergic rhinitis in which the IP is a tablet containing allergens; the risk of exacerbating allergic responses is higher in the treatment arm. The primary efficacy endpoint is rhinitis symptom scores combined with rescue medication scores, conveying the expectation that symptomatology may (also) worsen in the placebo group. The determination: 50.52 active arm; 50.53 placebo arm, two parents' signatures.
- A placebo-controlled study in asthma in which the IP is a monoclonal antibody that confers risk to the treatment arm of infusion reactions, anaphylaxis and myalgia. The study includes pulmonary function testing and the primary efficacy endpoint is clinical asthma exacerbation, thus is greater than minimal risk for the placebo arm. The determination: 50.52 active arm; 50.53 placebo arm, two parents' signatures.
- A placebo-controlled study of scabies in which the IP is applied topically. In this case, the risk is greater for those in the placebo group because of an exacerbation of a condition left untreated and the possibility of a resultant secondary bacterial infection. The determination: 50.52 active arm; 50.53 placebo arm, two parents' signatures.

(e) 50.53 Determinations

When a subject may receive both active agent and placebo, the determination must reflect the highest risk level.

- A study in autistic subjects that uses a crossover design results in subjects receiving IP for part of the study and placebo for the other part. The determination is 50.53 because there is no prospect of direct benefit to subjects during the time they are receiving placebo.

A 50.53 determination for both arms may be appropriate if the prospect of direct benefit for the active arm is small.

- A placebo-controlled study uses a topical cream for ichthyosis associated with Sjogren-Larsson syndrome. In this study the IP is applied to a very small area of skin, so the likelihood of direct benefit is proportionally small. Thus both arms receive a 50.53 determination.

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About Quorum

In 1991, the founders of Quorum saw a need for an IRB that protected human subjects while providing high-touch customer service. That's exactly what Quorum delivers. Each member of our team brings a wealth of experience in clinical research human subject protection—plus the knowledge, reliability, accuracy, and speed that matters when getting products to market. Our comprehensive customer solutions are tailored to meet the demanding needs of our customers.

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To safeguard the rights and well-being of research subjects while enhancing clinical research processes.

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- Service
- Teamwork
- Respect
- Integrity
- Visionary
- Excellence

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