Abstract

The critical need for pediatric research on drugs and biological products underscores the responsibility to ensure that children are enrolled in clinical research that is both scientifically necessary and ethically sound. In this chapter, we review key ethical considerations concerning the participation of children in clinical research. We propose a basic ethical framework to guide pediatric research, and suggest how this framework might be operationalized in linking science and ethics. Topics examined include: the status of children as a vulnerable population; the appropriate balance of risk and potential benefit in research; ethical considerations underlying study design, including clinical equipoise, placebo controls, and non-inferiority designs; the use of data monitoring committees; compensation; and parental permission and child assent to participate in research. We incorporate selected national (U.S.) and international guidelines, as well as regulatory approaches to pediatric studies that have been adopted in the US, Canada, and Europe.

Children as Research Subjects

Historically, children were viewed as vulnerable subjects who should be protected from the risks of research. The result was a paucity of safety and effectiveness data that made the use of therapeutic agents a virtual uncontrolled experiment whenever they were prescribed for children (1977). Tens of thousands of children were harmed by therapies that were assumed in the absence of research to be safe and effective (Fost 1998). More recently, pediatric research has come to be seen as a moral imperative (Shaddy and Denne 2010). Additionally, some disorders primarily affect children, necessitating studies to develop therapeutics in these populations.

The vulnerability of children stems from a number of factors (Kipnis 2003). Children commonly lack mature decision making capacity; they are subject to the authority of others; they may defer in ways that can mask underlying dissent; and their rights and interests may be socially undervalued. As with adults, children may have acute medical conditions requiring immediate decisions without adequate time for education and deliberation; they may have serious medical conditions that cannot be effectively
treated; and they may lack important socially distributed goods that would be provided as a consequence of research participation. Kipnis suggests that parental permission and child assent procedures alone cannot mitigate these vulnerabilities. Rather, studies in the pediatric population must be designed to minimize risk and maximize the possibility of therapeutic benefit (Kipnis 2003).

Recognition of this vulnerability has led many countries to develop regulations or guidelines specific to research with children. In 1973, the United States Department of Health, Education and Welfare published its first proposals to develop regulations providing additional protections for vulnerable populations that had “limited capacities to consent” (Department of Health Education and Welfare 1973). The problem of regulating research on children was also assessed by the National Commission (Department of Health Education and Welfare 1978b). The United States Food and Drug Administration (FDA) proposed establishing regulations for the protection of human subjects in 1979, including protections pertaining to clinical investigations involving children (Department of Health Education and Welfare 1979). In 1981, FDA regulations were promulgated regarding informed consent (21 CFR Part 50) and institutional review board (IRB) review of research (21 CFR Part 56). Based on recommendations made by the National Commission, regulations were promulgated in 1983 that governed research on children conducted or funded by the Department of Health and Human Services (Department of Health Education and Welfare 1983). In 2001, similar protections were extended to research regulated by FDA (2001).

Specific guidelines on pediatric research within the European Union were promulgated in 2001. Directive 2001/20/EC required Member States to develop laws, regulations, and administrative provisions for the implementation of good clinical practice in the conduct of clinical trials (2001). Specific protections were to be implemented to ensure adequate protections for minors, including parental permission and assent of able children, assurance of direct benefit for the child or for the group of patients with the particular condition, minimization of risk, and scientific necessity of the research. An ad hoc group responsible for guideline development made further recommendations for implementation of this Directive (2008).

The additional protections for children to be enrolled in a clinical investigation can be divided into four “nested” domains with each protection building on an adequate response to the prior protection. The enrollment of children in a clinical investigation must be considered scientifically necessary before the evaluation of whether the research interventions or procedures present an appropriate balance of risk and potential benefit. A clinical investigation must be found to have an appropriate balance of risk and potential benefit before considering the role of parental permission and child assent. This chapter will address these four nested protections.
The Principle of Scientific Necessity

A fundamental pillar of pediatric research is the ethical principle of “scientific necessity.” This principle holds that children should not be enrolled in a clinical investigation unless necessary to achieve an important scientific and/or public health objective concerning the health and welfare of children. An “important scientific question” may be one that generates information that is necessary and timely for establishing the appropriate pediatric use of investigational therapeutics. A corollary is that children should not be enrolled in studies that are duplicative or unlikely to yield important knowledge applicable to children about the product or condition under investigation. These principles are grounded in regulations and/or guidelines governing human subject protections worldwide. FDA regulations require that risks to subjects are minimized by eliminating unnecessary procedures (21 CFR 56.111(a)(1)), and that the selection of subjects must be equitable (21 CFR 56.111(b)).

Consistent with the recommendations of the National Commission, equitable selection requires that subjects who are capable of informed consent (i.e., competent adults) should be enrolled prior to subjects who cannot consent (e.g., children) (Department of Health Education and Welfare 1978b). There is broad international agreement on this approach, assuming there are no significant scientific reasons to enroll younger children preferentially to older children and/or adults. EMA regulations (2001), ICH guidelines E6 (1996) and E11 (2000), and the Declaration of Helsinki (2008) all state explicitly that vulnerable populations such as children should not be enrolled in a clinical investigation unless their involvement is essential to answer a scientific objective relevant to the health and welfare of that vulnerable population.

The ethical principle of “scientific necessity” has been operationalized in the scientific principle of “extrapolation.” As described in the Pediatric Research Equity Act of 2007 “if the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, the Secretary may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled studies in adults, usually supplemented with other information obtained in pediatric patients, such as pharmacokinetic studies” (2007). The principle of extrapolation also can be found in the International Conference on Harmonization guidance on pediatric research (2000). The need for pediatric studies is assessed by asking a series of questions about the similarity of the adult and pediatric disease, response to treatment, drug exposure-response, and pharmacokinetic and pharmacodynamic measurements that could be used to predict efficacy (see Figure One.)

Appropriate Balance of Risk and Potential Benefit

The additional safeguards for children enrolled in research are based on two ethical principles. First, the risks to which children would be exposed must be low if there is no prospect of direct therapeutic benefit (PDB) to the enrolled children. Second, 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. Consequently, the data necessary to initiate a pediatric investigation must demonstrate either an acceptably low risk of the experimental intervention or a sufficient prospect of direct benefit (PDB) to justify the risks of the intervention. A major challenge facing the development of a new product for the treatment of a pediatric disorder or condition is bridging this “risk gap” between (a) research involving procedures and/or interventions that present only a low risk given the absence of sufficient data to establish the PDB, and (b) the conduct of either “proof of concept” or pivotal trials for dosing, safety and/or efficacy that offer a sufficient PDB to the enrolled children to justify exposure to interventions that present greater than low risk.

There are several pathways to pediatric licensure of investigational products. If the product is being developed for a pediatric indication alone (if no comparable adult indication exists) sufficient preclinical data must be developed to support the initiation of pediatric clinical trials. In this case, a major hurdle is establishing a sufficient PDB using a preclinical animal model. If the product is being developed for an indication that occurs in both children and adults, the goal should be concurrent licensure unless there are safety concerns that would delay or even preclude pediatric studies. Adult and pediatric development may proceed either sequentially or concurrently, depending on the product and factors such as the anticipated risks to children and availability of alternate treatments. However, concurrent development still requires sufficient information about PDB in children to support initiating pediatric trials.

If safety or efficacy results of adult trials are necessary to inform pediatric development, sequential development may be necessary. Importantly, sequential development does not necessarily mean that concurrent licensure cannot be achieved. For example, if a phase 2 study of an antiviral agent showed decreased viral burden in adult studies, this information may help to provide the proof of concept necessary to support PDB in children. Dosing and safety studies could then be performed in children while the pivotal efficacy trial was initiated in adults. Particularly if the efficacy of the agent were extrapolated to some or all subgroups of the pediatric population, sufficient pediatric data may be available at the conclusion of the adult phase III studies to support concurrent licensure.

Component Analysis and Additional Safeguards for Children
For adult subjects, the risks of research participation can be justified either by the anticipated direct benefits to the subjects or by the importance of the anticipated knowledge. Investigations involving children that pose more than low risk cannot be justified by the importance of anticipated knowledge. In pediatric studies, the allowable risk exposure for an intervention or procedure not offering a PDB must be restricted to low risk. Thus, the individual research interventions and procedures that are contained in
an investigational protocol must be categorized and assessed according to whether they do or do not offer PDB - an approach referred to as “component analysis.”

Component analysis has come under recent criticism for using the norm of clinical equipoise as the standard for determining the ethical acceptability of therapeutic interventions or procedures (Miller et al. 2003; Miller and Brody 2007). The concept of clinical equipoise will be discussed more fully below. A related (albeit unconvincing) criticism of component analysis is directed towards the manner in which the distinction between therapeutic and non-therapeutic procedures is made (Wendler and Miller 2007). Wendler and Miller argue that the consequences of the intervention are what matters to the determination of the PDB, rather than the intent of the investigator or the design of the individual intervention (2007). All parties to the debate agree on the need to avoid the term “therapeutic research” which may justify (or offset) the risks of non-beneficial procedures through the inclusion of unrelated beneficial procedures in the same protocol (i.e., the fallacy of the “package deal”) (Department of Health Education and Welfare 1978b; Institute of Medicine 2004; Medical Research Council 2004). Otherwise a non-beneficial research intervention that presents considerable risk could be justified by adding unrelated therapeutic components to the protocol, such as free health care.

The analysis of a proposed clinical investigation can be approached either (1) by assessing whether or not each intervention or procedure does or does not offer the PDB, followed by an assessment of the risks of each component, or (2) by assessing the risks of each intervention and procedure, followed by an assessment of the PDB for those components that present greater than minimal risk. An intervention or procedure that presents no more than minimal risk may or may not offer a PDB. We will discuss the “minimal risk” category under the heading of interventions or procedures that do not offer the PDB.

**Interventions or Procedures that Do Not Offer the Prospect of Direct Benefit (PDB)**

There is general international consensus that a child’s exposure to risk in pediatric research must be minimal/low in the absence of direct therapeutic benefit to that child. Although there are differences in terminology (minimal risk, minor increase over minimal, low risk, minimal burden, etc.), international regulations share the ethical commitment to limit a child’s exposure to non-therapeutic risk. General guidance from European directives is supplemented below by a more detailed review of the U.S. Code of Federal Regulations (CFR)—exploring the categories of “minimal risk” and “minor increase over minimal” in the context of no direct benefit for the individual pediatric participant.

**Minimal/Low Risk -- No Direct Benefit**

For research on non-consenting subjects that does not offer direct therapeutic benefit, the International Conference on Harmonisation (ICH) E6 Guidelines specify that
“the foreseeable risks to the subjects are low” and that “the negative impact on the subjects’ well-being is minimized and low” (1996). FDA regulations use the term “minimal risk” (21 CFR 50.51) and define it 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” (21 CFR 50.3(k)). This definition appears to allow for a “relativistic interpretation” indexed to the research participants’ own experiences as well as provides two comparators for assessing minimal risk: (a) ordinary daily life, and (b) routine physical or psychological examinations or tests (Institute of Medicine 2004). There is well-documented variability in the interpretation and application of “minimal risk” (Shah et al. 2004; Institute of Medicine 2004; Kopelman 2000).

Three U.S. based advisory panels -- the Institute of Medicine (IOM), The Secretary's Advisory Committee on Human Research Protections (SACHRP), and The National Human Research Protections Advisory Committee -- recommend the international use of a uniform standard for minimal risk (Fisher et al. 2007). Grounded in the ethical principle of justice as fairness (Institute of Medicine 2004), this approach indexes minimal risk to the normal experiences of average, healthy children rather than to risk levels routinely experienced by the research participants. According to this standard, research interventions and procedures should not involve potential harm or discomfort beyond that which average, healthy, normal children may encounter in their daily lives or in routine physical or psychological examinations or tests (Institute of Medicine 2004). This protects children with a disorder or condition or children who are at increased risk due, for example, to poor socio-economic status from research unrelated to their condition that is considered greater than minimal risk for a healthy child.

The US-based National Commission listed “routine immunization, modest changes in diet or schedule, physical examination, obtaining blood and urine specimens …developmental assessments… most questionnaires, observational techniques, noninvasive physiological monitoring, [and] psychological tests and puzzles” as minimal risk (Department of Health Education and Welfare 1978b). While not specified here, “obtaining blood” per the above quotation has been understood to mean venipuncture in many settings in the US. Other examples include “obtaining stool samples, administering electroencephalograms, … [and] a taste test of an excipient or tests of devices involving temperature readings orally or in the ear” (Food and Drug Administration 2001). SACHRP lists a number of physical (e.g., measurement of height, weight, and head circumference; assessment of obesity with skin fold calipers; hearing and vision tests; testing of fine and gross motor development; non-invasive physiological monitoring) and psychological (e.g., child and adolescent intelligence tests; infant mental and motor scales; educational tests; reading and math ability tests; social development assessment; family and peer relationship assessments; emotional regulation scales; scales to detect feelings of sadness or hopelessness) examinations or tests as being no more than minimal
risk (Office for Human Research Protections 2005). Finally, some limited exposure to radiation from diagnostic procedures may be viewed as minimal risk (Nelson 2006). However, some of the above procedures may be considered greater than minimal risk depending on the context of the research and the specific population to be enrolled (Office for Human Research Protections 2005).

In assessing for minimal risk, harm or discomfort should be interpreted in relation to the ages (and developmental status) of the children to be studied (Institute of Medicine 2004; Department of Health Education and Welfare 1978a). The duration, cumulative risks, and reversibility of harm also impact on the overall level of risk (Fisher et al. 2007). The use of background risk associated with daily life as a standard for minimal risk has been the subject of debate (Nelson 2007; Wendler 2009; Wendler and Glantz 2007; Wendler and Miller 2007). Data about the risks of “daily life” or “routine examinations or tests” contribute to an informed evaluation of minimal risk, but they alone are not sufficient. The moral acceptability of the risks of research reflects the obligation of a scrupulous parent to evaluate and weigh research risks. These risks should be evaluated against the risks of daily life or routine examinations of a healthy child who is supervised by a prudent parent (Nelson 2007; Nelson and Ross 2005). Some general risks that healthy children experience in daily life as part of their growth and development may be deemed excessive if the risk is introduced only for the purpose of producing generalizable knowledge (Fisher et al. 2007).

**Minor Increase over Minimal Risk -- No Direct Benefit**

FDA regulations also include a classification of “minor increase over minimal risk” (21 CFR 50.53). An intervention or procedure approved under this category must also involve “experiences to subjects that are reasonably commensurate with those inherent in their actual or expected… situations” and be “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.” This category has been the most controversial, garnering two dissenting votes from members of the US National Commission (Department of Health Education and Welfare 1978b). The justification for this classification has included that the increased risk is warranted due to scientific necessity (CIOMS 2002; Institute of Medicine 2004), scrupulous parents can be entrusted with the authority to evaluate such non-beneficial risk exposures (Nelson and Ross 2005), and that the absolute difference in risk exposure is meant to be “slight” (Department of Health Education and Welfare 1978a). The regulations do not define, however, “disorder or condition,” “vital importance,” “reasonably commensurate,” and “minor increase over minimal risk.” These concepts are explored below.

The IOM defined “disorder or condition” as a set of “specific physical, psychological, neurodevelopmental, or social characteristics” that scientific evidence or clinical knowledge has shown to compromise the child’s health or “to increase risk of
developing a health problem in the future” (Institute of Medicine 2004). Therefore, a child could be healthy, but “at risk” for the condition that is the object of the research based on scientific and/or clinical evidence. Consistent with international guidelines, this definition excludes the use of healthy not-at-risk children from greater than minimal risk research without a PDB (CIOMS 2002; European Parliament and the Council 2001; ICH 1996). The IOM also understood the requirement for “vital importance” to be consistent with the principle of scientific necessity and thus closely tied to the child’s “disorder or condition” (2004). The overall plan for pediatric product development should be taken into consideration since information gained from the specific protocol under consideration may be an important yet intermediate step leading to further investigations.

The National Commission uses “commensurate” to describe research activities that are reasonably similar (but need not be identical) to procedures that prospective research participants may ordinarily experience. The IOM elaborated on this approach, noting that “although a child might not have experienced a particular research procedure...the procedure could still be described to the child as potentially presenting levels of pain, immobility, anxiety, time away from home, or other effects that would be similar to those produced by procedures that they have experienced” (2004). The goal is to make the research procedures tangible for the child and parents, thereby improving child assent and parental permission (CIOMS 2002; Department of Health Education and Welfare 1978b).

In assessing whether an intervention or procedure presents no more than a minor increase over minimal risk, there must be sufficient data that any research-related pain, discomfort or stress will not be severe and that any potential harms will be transient and reversible (Fisher et al. 2007). Even if the average risk associated with an intervention or procedure is thought to be low, if the risk estimate is unknown, reflects a large degree of variability, or has not been adequately characterized, then the risks of an intervention or procedure cannot be considered only a minor increase over minimal risk.

For example, single-dose pharmacokinetic (PK) studies of cough and cold medicines in children may qualify as presenting only a “minor increase over minimal risk,” depending on the associated data. PK studies may be necessary to establish the correct dose to be used in subsequent efficacy studies. However, the single-dose of a product is unlikely to offer a direct benefit to the child (unless symptomatic) and is associated with a small, but higher than minimal risk (based on prior data). Therefore, to be enrolled, children must have a disorder (symptoms) or a condition (asymptomatic, but at risk based on empiric criteria). A child may be considered “asymptomatic, but at risk” using a combination of three criteria: (frequency) > 6 infections per year for children 2 to < 6, > 4 infections per year for children aged 6 to <12; (crowding) 4 or more persons living in a home or 3 or more people sleeping in one bedroom; and (exposure) another ill family member in the home or a child in the family who is attending preschool or school with 6 or more children per group (Nelson 2010).
Procedures that may present a minor increase over minimal risk (depending on the research context, the specific population of children and the skill of the investigator) have included: lumbar puncture, bone marrow aspirate with appropriate procedural sedation (CIOMS 2002; Institute of Medicine 2004), placement of a blood-drawing peripheral intravenous line for a limited time period, selected approaches to procedural sedation (Institute of Medicine 2004) and perhaps limited radiation exposure (Nelson 2006). The risk of a single dose PK study depends on both the approach to blood sampling and on the risks of the drug that is being administered.

Although FDA regulations include this classification of “minor increase over minimal risk”, EU pediatric regulations do not include such a category of research. Instead, EU guidance documents refer to research which offers potential direct benefits to individual research participants and/or to the group (i.e., children affected by the same disease, or a disease which shares similar features and for which the product could be of benefit) (European Parliament and the Council 2001). European regulations that specify direct benefit to the individual are closely aligned with U.S. regulations that require direct benefit, discussed in the next section. The “direct benefit to the group” category allows studies to proceed in Europe that would be approved in the United States under the “minor increase over minimal risk” category. Thus, while differences in nomenclature exist, the US and European approaches are essentially aligned in practice.

In summary, although the ethical importance of restricting risk exposure in pediatric studies in the absence of direct benefit to the child is widely appreciated, implementing associated regulations can be challenging and experts have debated their interpretation. FDA regulations may allow for assessing minimal risk based on the participants’ routine experiences, however, there are persuasive ethical arguments for implementing a uniform standard for minimal risk -- drawing on normal experiences of average, healthy children, tempered by the child’s age, risk duration, cumulative risks, and reversibility of harm. The risks of daily life can also factor into (rather than determine) the scrupulous parent’s assessment of minimal risk. In addition, FDA regulation offers the category of “minor increase over minimal risk” and, with clarification of key concepts, provides guidance for more challenging evaluations of risk acceptability when there is no direct benefit to pediatric participants.

**Interventions or Procedures that Offer the Prospect of Direct Benefit (PDB)**

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. Thus, research guidelines worldwide stipulate that persons who cannot provide informed consent -- including children -- should be enrolled in clinical trials only when the risks are low or the research offers a compensating potential for direct benefit that is comparable to available alternatives (ICH 1996; CIOMS 2002). Similarly, FDA regulations permit pediatric research involving an intervention or procedure that presents more than a minor
increase over minimal risk only if it “holds out the PDB for the individual subject” or “is likely to contribute to the subject’s well-being.” Such interventions or procedures must meet two conditions: 1) “the risk is justified by the anticipated benefit to the subjects;” and 2) “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 50.52). Research that offers a PDB includes several key concepts that require interpretation: PDB/contribution to well-being, justification of risk and available alternative approaches.

**Prospect of Direct Benefit/Contribution to Wellbeing**

Current regulatory frameworks or national and international clinical research guidelines do not explicitly define “direct” benefits, and the literature offers varying views on which benefits are direct. King provided an influential account of research-related benefits in which she distinguishes between direct (clinical benefits arising from receiving the experimental intervention), collateral (arising from other aspects of the protocol, e.g., medical care) and aspirational (social value of scientific knowledge) benefits (2000). Direct benefit must accrue to the individual research participant, and result from the specific research intervention or procedure, not from ancillary benefits such as health care that may be provided in the trial. The consequences of an intervention cannot be determined *a priori*, and thus cannot serve as the basis for an assessment of direct benefit that Wendler and Miller suggest (2007). The determination of the “prospect of direct benefit” is based on the design of the intervention (i.e., choice of dose, duration, method of administration, and so forth) given the available evidence, and not the investigator’s state-of-mind or belief in the therapeutic value. The evidence in support of the PDB is generally based on mechanistic and in vivo studies of the intervention in animal models or studies in adult humans.

This account does not squarely address the status of diagnostic or monitoring procedures that are needed to help answer the scientific questions posed by the study (e.g., additional scans, blood draws, or biopsies). As noted earlier, an appropriate balance of risk and potential benefit is required for each of the interventions and procedures included in the trial. Monitoring procedures may not *per se* offer a PDB, yet may be critical in evaluating the safety of other interventions that do offer a PDB. More recent accounts of direct benefit have explicitly considered these procedures (Friedman et al. 2010; Nelson et al. 2010; Miller et al. 2003).

Under current U.S. regulations, there are two ways that the risks of such a monitoring procedure could be evaluated. If the monitoring procedure is made necessary by the administration of the investigational product, the risks of the monitoring procedure may be justified by the PDB of the experimental intervention. Using this approach, the administration of the investigational product and the monitoring made necessary by that administration could both be considered under 21 CFR 50.52 (greater than minimal risk with PDB). Alternatively, the monitoring procedure may be viewed as not offering a PDB, and thus considered under either 21 CFR 50.51 (minimal risk) or 21 CFR 50.53.
(minor increase over minimal risk). In addition, monitoring procedures that may impact on clinical care may offer PDB. For example, if clinical monitoring of blood levels in order to adjust drug dosing were necessary, the risks of venipuncture would be justified because the blood levels obtained in this way may affect clinical management.

Justification of Risk

Whether the risks of an experimental intervention are justified by the potential direct benefits is a complex evaluation, involving a mix of quantitative and qualitative judgments similar to those made in clinical practice (Department of Health Education and Welfare 1978b; National Commission 1979; CIOMS 2002). There should be empirical evidence of sufficient direct benefit (i.e., “scientifically sound” expectation of success (Department of Health Education and Welfare 1978b)) to justify exposure to the risks. Consistent with component analysis, the risks of an intervention or procedure can only be justified by the benefits to be expected from that same intervention or procedure (Department of Health Education and Welfare 1978b). The justification of risk can include: the possibility of avoiding greater harm from the disease; the provision of important anticipated benefit to the individual exposed to risk; the severity of the disease (e.g., degree of disability, life-threatening); and the availability of alternative treatments.

Available Alternative Approaches

The underlying ethical reason for considering “available alternative approaches” is the view that a child’s health or welfare should not be placed at a disadvantage by being enrolled in a clinical investigation (Institute of Medicine 2004). The application of this general principle hinges to a large extent on the interpretation of “available.” Some have argued that the other approaches that need to be taken into consideration include “any other course of action (or non-action)” (Department of Health Education and Welfare 1978b). However, the modification of “alternative” by “available” raises the question whether all alternatives need to be considered, or only those that are “available” to the subjects to be enrolled in the clinical investigation (Wendler 2008). In other words, should the range of available alternatives against which the risks and potential benefits of the experimental intervention are compared be all those that are “universally” available, or should the alternatives be limited to those that are “locally” available (Lie et al. 2004; Macklin 2001; London 2000)?

To help address this question, we turn now to selected ethical issues in the design and conduct of pediatric clinical trials. The topic of clinical equipoise is followed by a discussion of the choice of an appropriate control group, including the use of a placebo control in pediatric clinical trials. The alternative of an actively controlled trial is explored, with special attention to issues of randomized withdrawal and non-inferiority (NI) designs in the pediatric population. Finally, we pursue the question of when to initiate first-in-human studies in the pediatric population, followed by two issues related
to the conduct of trials: optimal safety monitoring practices and compensation in pediatric research.

Selected Ethical Issues in the Design and Conduct of Pediatric Research

Clinical Equipoise

Clinical equipoise is commonly defined as “genuine uncertainty on the part of the expert medical community about the comparative therapeutic merits of each arm of a clinical trial.” Advocates of clinical equipoise argue that it “provides a clear moral foundation to the requirement that the health care of subjects not be disadvantaged by research participation” (Canadian Institutes of Health Research 1998; with 2000, 2002 and 2005 amendments; Medical Research Council 2004).

The concept of equipoise combines two separate principles (Miller and Brody 2007). The first principle is the scientific principle of “uncertainty” (i.e., the null hypothesis between the investigational product and the comparator or control group). However, this principle is a requirement of all ethical research, and the specification and application of this principle of “uncertainty” is complex (Veatch 2007). The uncertainty of the individual clinician is not decisive, but rather the uncertainty of the relevant community. The morally problematic area is where sufficient data have been developed such that clinical equipoise is disturbed, but insufficient data exist to justify a scientific (or policy) conclusion (Veatch 2007; Gifford 2007).

The second principle contained within the concept of equipoise is the ethical norm that no one enrolled in a trial should receive an inferior treatment (i.e., known effective treatment should be provided). Here clinical equipoise is seen as a specification of the “duty of care” (Miller and Brody 2007). From this perspective, the dispute about the role of equipoise is primarily about whether the “duty of care” (carried over from the clinical setting based on the fiduciary duty of a physician to act in a patient’s best interest) should be the ethical framework for clinical research (Institute of Medicine 2004). Proponents of equipoise may argue in favor of actively-controlled comparator trials, as such trials may provide more useful clinical information. However, this approach does not solve the tension between having enough information to make an “individual patient decision” and enough to “warrant making a policy decision” (Gifford 2007).

All parties to the debate over equipoise as a guiding principle of clinical research accept the need for a demarcation between interventions or procedures that either offer or do not offer a PDB. The regulations of many countries are grounded on this distinction. The view that no child should be disadvantaged by participation in a clinical trial bears some resemblance to clinical equipoise. However, an affirmation of the child-patient’s right to competent medical care and to protection from undue risk of harm when participating in a clinical investigation does not require nor entail the principle of clinical equipoise. The patient-subject’s right to competent medical care should be operationalized in the structure of the investigational protocol (London 2007). The nature
of the scientific uncertainty to be resolved by the study design should be specified, and the comparability of alternatives – namely, the ethical and scientific argument in favor of the chosen control group -- should be justified.

Choice of Control Group and Placebo Controls

The choice of an appropriate control group for a clinical investigation should be approached from two perspectives – scientific and ethical. From a scientific perspective, what is the appropriate comparator to use in order to demonstrate the safety and/or efficacy of the intervention? The primary focus is on designing the clinical investigation so that any uncertainty about the research objective(s) is resolved. From an ethical perspective, does enrollment in a clinical investigation place subjects at an unreasonable risk (i.e., one that is not compensated by a sufficient PDB)? Are individuals enrolled in the clinical investigation not receiving a treatment that they should otherwise receive as part of competent medical care? Importantly, the enrollment of a subject in the placebo group does not offer that subject a PDB. No direct medical benefit will be available from the placebo itself, and the avoidance of exposure to an unknown risk of the experimental intervention cannot be considered a direct medical benefit. As noted earlier, direct benefits are limited to good clinical effects arising from receipt of the experimental intervention.

The ethics of the choice of control group has been the subject of much debate, focused on either the use of placebo controls or on the choice of a local standard (which may or may not be a placebo) as the control group. The starting point of this debate is often the Declaration of Helsinki, which currently states that “a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances: (1) where no current proven intervention exists; or (2) where for compelling and scientifically sound methodological reasons the use of placebo is necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm” (World Medical Association 2008). The ICH E-10 Choice of Control Group guidance argues that a placebo-controlled trial may be ethically justified when there would be “no serious harm” from withholding known effective treatment (2001). Even if there would be a good scientific reason to withhold a known effective treatment in order to demonstrate the efficacy of a new treatment, ICH and CIOMS make it clear that withholding proven therapy would only be ethically acceptable if the use of placebo would not add any risk of serious or irreversible harm to the subjects, even if the use of an active comparator would undermine the ability of the clinical investigation to produce scientifically sound results (ICH 2001; CIOMS 2002).

Arguably, the clarification of when a placebo control may be used in place of proven effective treatment remains consistent with clinical equipoise. From this perspective, a placebo is acceptable when “patients have provided an informed refusal of standard therapy for a minor condition for which patients commonly refuse treatment and
when withholding such therapy will not lead to undue suffering or the possibility of irreversable harm of any magnitude” (Canadian Institutes of Health Research 1998; with 2000, 2002 and 2005 amendments). However, whether or not subjects would commonly refuse standard therapy for a minor condition is not relevant to the ethical justification of the use of a placebo in the absence of “any risk of serious or irreversible harm to the subjects.” The withholding of a known effective treatment from children enrolled in a clinical investigation may appear to violate the principle of clinical equipoise. Nevertheless, such a violation may be ethically justified if the risk exposure is limited to low risk (Institute of Medicine 2004). In effect, the risk exposure must be limited to that same level of risk that would be acceptable for an intervention or procedure that does not offer a PDB. Thus, the risk related to withholding a known effective treatment from children enrolled in the placebo arm of a study, for example, must be limited to no more than a minor increase over minimal risk because the placebo arm of a study does not offer a PDB.

A variant of the discussion about placebo (or no treatment) controls concerns the use of “local” versus “universal” standards to determine the appropriate control group. In other words, should “proven effective therapy” only refer to treatments that are actually available in the location where the clinical investigation is being conducted? Some argue that the purpose of a clinical investigation is to alter clinical practice. Thus, “it is crucial… to take the study context into account when designing and conducting such studies.” Simply, the appropriate control group (or comparator) should be drawn from actual clinical practice in that setting (Weijer and Miller 2004). However, others argue that the withholding of known effective treatment based on the underlying inequities in the distribution of medical care is unjust and exploits those less fortunate (Shaddy and Denne 2010). A middle ground in this debate requires that the proposed study provide valuable and timely information about a health care need important to the local population, such that there is a reasonable likelihood that the local population could benefit from the research (World Medical Association 2008).

**Alternatives to Placebo Controlled Trials**

If a classical placebo-controlled trial is not ethical or practical, there are several alternatives that may reduce or eliminate the exposure to placebo. In a randomized withdrawal trial, all eligible patients with a particular disease are initially treated with the experimental drug. Patients that have a successful initial response are then randomized in a double-blind fashion to remain on the drug or be switched to placebo (or lower doses). The primary study endpoint is time to relapse, usually defined as the duration of time before which clinical signs and/or symptoms of the disease recur. These designs are useful when a trial of medication withdrawal or change in therapy may be clinically indicated, particularly if the experimental drug is similar to those already marketed (Balfour-Lynn et al. 2006). Any child that relapses may immediately be provided with
“rescue” medication to reduce the harm or discomfort to no more than a minor increase over minimal risk.

If any exposure to placebo is unacceptable, actively-controlled trials may be an alternative. These trials can be designed to test either superiority or non-inferiority (NI) of the experimental intervention relative to the control. Superiority trials generally pose few ethical or interpretational difficulties, provided that the dose of the control product is not artificially low. However, NI designs can pose ethical dilemmas under certain circumstances and deserve further comment.

Non-inferiority trials are intended to show that the effect of a new treatment is not worse than that of an active control by more than a specified margin (Snapinn 2000). The design and interpretation of NI trials is not straightforward. For the NI trial to be valid, one must have historical studies that provide reliable and precise estimates of the effect of the active control regimen relative to placebo (ICH 2001). Further, NI trials do not assure that the experimental agent is “at least as effective” as the active regimen unless superiority of the experimental agent is demonstrated. An experimental intervention may be inferior to the active control and still demonstrate non-inferiority.

Therefore, the primary ethical question is whether it is appropriate to use a NI design for pediatric trials where the inferior performance of the experimental intervention may be associated with serious morbidity or mortality in children. For example, suppose a new antibiotic were tested for life-threatening infections. Even if the experimental drug were shown to be non-inferior, more children may still be at risk of dying due to inferiority of the experimental drug. The ethical acceptability of this design depends on a variety of factors. There may be times when the new treatment offers a potential benefit in lower toxicity or improved usability that may justify using the new treatment in a given population even if it were shown to be slightly inferior to standard care. However, the burden of proof should be on the advocates of the NI study to present convincing evidence that the benefits of the new product outweigh the potential inferiority such that the trial should be allowed to proceed.

Special Concerns in First-in-Human (FIH) Pediatric Clinical Trials

A first-in-human (FIH) trial is a clinical investigation in which a therapeutic intervention, previously developed and assessed through in vitro or animal testing, or through mathematical modeling, is tested on human subjects for the first time. FIH studies are heterogeneous in design, ranging from dose escalation studies testing conventional oncology drugs to gene transfer trials or monoclonal antibodies that target newly-discovered biological pathways. A major ethical question concerning the conduct of FIH trials is whether or not an FIH experimental intervention offers a PDB to the enrolled child. Some take the view that such research can offer a PDB, contending that it should be seen as ‘therapeutic research’ (Ackerman 1995) or arguing for a ‘relativistic understanding of prospect of benefit’ (Kodish 2003). Others believe that the objective of
FIH is not to produce clinical benefits, and that promoting PDB to participants fosters a therapeutic misconception (Ross 2006; Sankar 2004; Miller 2000). A middle ground requires the recognition that a key ethical dilemma concerning FIH trials is not simply about whether or not they offer a PDB, but whether the PDB is of sufficient likelihood, magnitude and type to justify the anticipated risks of the experimental intervention (King 2000). Understanding PDB as an empirical matter laden with uncertainty places the focus on assessing the strength of evidence -- particularly nonclinical evidence -- that provides the scientific rationale for undertaking an FIH trial. There is no consensus, however, on the quantity or quality of nonclinical or adult human evidence necessary to justify a pediatric FIH study.

We propose a “sliding threshold” evidentiary approach, arguing that data (whether animal or adult human) necessary to establish sufficient PDB to justify the risks of the experimental intervention varies with the severity of the disease and the adequacy of alternate treatments. The sliding threshold is hierarchical in character: evidence about structure (design) is considered weaker than evidence about function (mechanism of action, e.g., molecular targets, biomarkers, physiologic pathways), which in turn is considered weaker than evidence related to a clinical disease model (surrogate or clinical endpoints). Kimmelman’s principle of “modest translational distance” similarly tries to establish an evidentiary basis for PDB in FIH studies through a critical examination of the assumptions linking nonclinical and clinical models (2010; 2009).

A critical issue in the design of many FIH trials is the question of starting dose. Currently the estimation of a maximum recommended starting dose (MRSD) in an FIH study often is based on the ‘no observed adverse effect level’ (NOAEL), as determined in toxicity studies in relevant animal species. The starting dose for human intervention is then reduced by a substantial safety margin. While this approach may be acceptable in adults, using a very low dose in children may eliminate any PDB from the intervention. Dosing studies in animal models using an appropriate biomarker or physiologic endpoint may therefore be particularly important for establishing a dose in children that is likely to have some biological effect.

Data and Safety Monitoring in Pediatric Clinical Trials

Data Monitoring Committees (DMC) are advisory to the sponsor, and charged with conducting periodic reviews of accumulated data from ongoing clinical trials to assess for substantial evidence of benefit, harm, or futility of collecting additional data (U.S. Department of Health and Human Services 2006). While all pediatric clinical trials require careful safety monitoring, they do not uniformly require a formal DMC. The only mandatory use of a DMC in US regulations is for research studies in emergency settings in which the informed consent requirement has been waived (21 CFR 50.24(a)(7)(iv)).

However, a DMC is recommended in additional circumstances: large, multi-center studies of long duration; strong a priori safety concerns, potential serious toxicity
related to study product use; and populations at elevated risk of death/serious morbidity or in populations deemed potentially fragile (U.S. Department of Health and Human Services 2006). Current guidance from the American Academy of Pediatrics recommends DMCs for all pediatric trials (Shaddy and Denne 2010). In practice, however, DMCs may not be warranted in trials with few or well-characterized risks or at early stages of product development when studies have few participants and are not blinded.

Compensation for Pediatric Research

Compensation for participation in research is a common practice for research studies that involve both children and adults. A number of different types of compensation are used in clinical studies, including material or monetary compensation such as reimbursement for travel, parking, or inconvenience. The amount paid to study subjects can vary from site to site as well as study to study, even at the same institution for similar tasks (Shaddy and Denne 2010). The American Academy of Pediatrics recommends the giving of gifts instead of money to children as a token of appreciation after the child has completed (or withdrawn from) the trial (1995). While this model may be appropriate for younger children, remuneration using a wage model based on time or effort (e.g., a percentage of trial visits or procedures that have been completed) may be appropriate for older adolescents (Bagley et al. 2007).

Offering payment in studies that enroll children requires parents, investigators, and IRBs to weigh the importance of several competing values (Bagley et al. 2007). Incentive payments may be essential to the recruitment and retention of pediatric study subjects. The obligation to treat all patients fairly might include compensating them for their time, effort, and discomfort and for their contribution to the social good. However, payments to parents for their child’s research participation could potentially influence parents to decide in favor of participation without regard for the child’s wishes, because there is no personal risk to them (Shaddy and Denne 2010). Some foreign countries prohibit inducements in pediatric trials, either for the parents, legal representatives or children (Federal Agency for Medicines and Health Products (Belgium) 2004). In other instances, parents/legal representatives can only be compensated for their time and expenses (European Union 2008). These concerns must be carefully weighed to ensure that pediatric research can continue without unduly influencing a parent to enroll a child in a research protocol that is not consistent with the best interests of the individual child (Bagley et al. 2007; Institute of Medicine 2004). The exposure of children to excessive risk due to undue influence may be avoided if pediatric trials are designed with an appropriate balance of risk and potential direct benefit.

We now consider a final protection for children in research: parental permission and the assent of children. We also explore conditions under which parental permission may no longer be needed under the applicable law of the jurisdiction in which research is being conducted.
Child Assent and Parental Permission

The Assent Requirement

The requirement for child assent emerged in a 1978 report by The National Commission (1978b). William Bartholome defined four fundamental elements of child assent: 1) a developmentally appropriate understanding of the nature of the condition, 2) disclosure of the nature of the proposed intervention and what it will involve, 3) an assessment of the child’s understanding of the information provided and the influences that impact on the child’s evaluation of the situation, and 4) a solicitation of the child’s expression of willingness to accept the intervention (Bartholome 1996). Considerable disagreement among experts remains about many fundamental components of assent, including: the definition of assent, the age at which investigators should solicit assent from children; who should be involved in the assent process; how to resolve disputes between children and their parents; the relationship between assent and consent; the quantity and quality of information to disclose to children and their families; how much and what information children desire and need, the necessity and methods for assessing both children's understanding of disclosed information and of the assent process itself; and what constitutes an effective, practical, and realistically applicable decision-making model (Unguru et al. 2008; Carroll and Gutmann 2010; National Commission 1979).

Children must affirmatively agree to participate in research unless the assent requirement is waived. The absence of dissent does not qualify as assent (21 CFR 50.3(n)). U.S. regulations allow the assent requirement to be waived only when the research holds out the possibility of direct benefit that is available only in the research context, or if the child is judged incapable of assent (Department of Health Education and Welfare 1983). Evaluating the capacity of a child to assent to research participation presupposes an understanding of what the giving of assent means. If we expect the child to make an adult-like judgment of the risks and possible benefits of the research, such a capacity may not develop until mid-adolescence. However, if a child simply needs to agree based on their own perspective on the acceptability of the experience (e.g., the pain of having a blood test), a younger child would be capable of assent. While not specifying the elements of assent as Bartholome did (1996), The National Commission opined that children as young as 7 years of age are capable of assent (1978b).

The criteria are found in U.S. regulations are similar to those in international regulations on child assent and participation in research. For example, the EU Directive 2001/20/EC states that the following conditions must be met for any pediatric clinical trial: “(a) consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor; (b) the minor has received information according to its capacity of understanding regarding the trial, the risks and the benefits; and (c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is
considered by the investigator” (European Parliament and the Council 2001). Specific guidance on age requirements and assent procedures is again not included.

Parental Permission

Since children are unable to provide informed consent, pediatric research relies on parental permission to authorize the enrollment of children in research. There is wide international agreement on this requirement of surrogate (usually parental) consent. A parent is generally defined as a child’s biological or adoptive parent, and a guardian is defined as an individual who is authorized under applicable state or local law to consent on behalf of a child to general medical care. The parental permission requirement is intended to protect the child from assuming unreasonable risks (Rossi et al. 2003).

However, the feasibility of obtaining parental permission may be a problem in certain circumstances. For example, great distances, lack of communication infrastructure, social dislocation, or high parental mortality (e.g., HIV affected populations) may serve to make parents unreachable. U.S. regulations governing Health and Human Services-funded research at (45 CFR 46.408(c)) allow for a waiver of the requirement for parental or guardian permission if a research ethics committee determines that the requirement is unreasonable. However, FDA regulations for the protection of children (21 CFR 50, Subpart D) do not include this waiver. Thus, for the majority of FDA-regulated research, parental permission is required for the enrollment of children. The exception from informed consent allowed under (21 CFR 50.24) for research conducted in emergency settings applies to children as well as adults.

The Definition of a Child

Children are defined in FDA regulations as “persons who have not attained the legal age for consent to treatments or procedures involved in clinical investigations, under the applicable law of the jurisdiction in which the clinical investigation will be conducted” (21 CFR 50.3(o)). In effect, whether or not an individual subject is considered a child for the purposes of the application of Subpart D depends on how the age of majority is defined by state law. State law also defines certain conditions under which a child who is younger than the age of majority may be considered emancipated (i.e. not under the control of a parent or guardian) and thus effectively an adult. These conditions generally include marriage, military service, or a court order, but vary considerably from state to state. FDA regulations would allow a minor who meets one of these conditions to be considered an adult for the purposes of research. In addition, state law may allow a minor to consent for certain interventions and procedures such as treatment for sexually transmitted diseases and drug abuse. If the clinical investigation involves one of these conditions, a minor may be considered an adult for the purposes of obtaining informed consent (absent parental permission). Such a determination would be made by the local research ethics committee in consultation with legal counsel.
International regulations do not define the pediatric population according to the age of consent to specific interventions or procedures. For instance, both the European Commission (2008), and ICH E11 (2000) refer to the pediatric population as birth to 18 years. The policy of using local judicial or legal procedures to either appoint a guardian or establish that an adolescent is legally able to consent to the interventions and procedures included in the research is more defensible than relying on the interpretation of particular permission guidelines by individual research ethics committees. The use of established, transparent, and fair judicial procedures to establish the right of an adolescent to consent to research participation under the applicable laws of the appropriate jurisdiction respects the differing moral and legal views of local communities while affirming a liberty interest of parents to raise their children as they see fit (Nelson et al. 2010).

Summary

In recognition of the benefits of pediatric research, research ethics has evolved from a position of excluding children to one of cautious advocacy – acknowledging the critical role of pediatric research, but accompanied by careful consideration of the scientific context, evaluation of risks and benefits, and protection to participants. Many countries have adopted regulations or guidelines to protect children in research. Typically, this requires a careful analysis of the risk associated with each intervention and/or procedure, an evaluation of potential benefits, provisions for child assent, and ensuring adequate parent/guardian permission. The regulatory agencies overseeing pediatric research need to make a careful ethical assessment weighing sometimes complex trade-offs so as to protect children’s welfare and prevent undue risk of harm while generating scientifically valuable information to answer important questions concerning the health and welfare of children.
References

21 CFR 50, Subpart D.

21 CFR 50.3(k).

21 CFR 50.3(n).

21 CFR 50.3(o).


21 CFR 50.51.

21 CFR 50.52.

21 CFR 50.53.

21 CFR 56.111(a)(1).

21 CFR 56.111(b).

21 CFR Part 50.
21 CFR Part 56.
45 CFR 46.408(c).


Medical Research Council (2004) Medical Research involving Children


Figure One: FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation

**FDA algorithm for determining need for pediatric studies using the principle of scientific necessity/extrapolation (under BPCA or PREA)**

1. Is it reasonable to assume that children, when compared to adults, have a similar disease progression?  
   - Yes
   - No
   - Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.

2. Is it reasonable to assume that children, when compared to adults, have a similar response to intervention?  
   - Yes
   - Conduct PK studies in children which are designed to achieve drug levels similar to adults, and then conduct safety trials at the proper dose.
   - No
   - Is it reasonable to assume a similar concentration-response (CR) in children when compared to adults?  
     - Yes
     - Conduct PK/PD studies to establish a CR in children for the PD measurement, conduct PK studies to achieve target concentrations based on CR, and then conduct safety trials at the proper dose.
     - No
     - Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.
   - No
   - Is there a pharmacodynamic (PD) measurement that can be used to predict efficacy in children?  
     - Yes
     - Conduct PK/PD studies to establish a CR in children for the PD measurement, conduct PK studies to achieve target concentrations based on CR, and then conduct safety trials at the proper dose.
     - No
     - Conduct pharmacokinetic (PK) studies to establish dosing, and then safety and efficacy trials in children.