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Defining the Boundaries of a Right to Adequate Protection: A New Lens on Pediatric Research Ethics

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We argue that the current ethical and regulatory framework for permissible risk levels in pediatric research can be helpfully understood in terms of children's moral right to adequate protection from harm. Our analysis provides a rationale for what we propose as the highest level of permissible risk in pediatric research without the prospect of direct benefit: what we call "relatively minor" risk. We clarify the justification behind the usual standards of "minimal risk" and "a minor increase over minimal risk" and explain why it is permissible to impose any risks at all on child participants who do not stand to benefit directly from enrollment in research. Finally, we illuminate some aspects of the concept of "best interests."

Keywords: *adequate protection, best interests, moral rights, parental obligations, pediatric research ethics, research risks*

I. INTRODUCTION

Children cannot ethically or legally consent to accept risks for the benefit of others in biomedical research. Yet, the advancement of pediatric medicine requires children's participation as research subjects. Pediatric research

participants are entitled to greater protection than adults who can give their informed consent. Rooted in the seminal work of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission, 1977), the current ethical and regulatory framework for pediatric research is consistent with respected work in ethical theory and bioethics. This framework embodies several critical protections, including independent review, parental permission, and meaningful child assent when appropriate. Perhaps the most fundamental protection is a limit on the level of risk to which pediatric research participants may be exposed; pediatric research generally may not pose more than minimal risk to participants unless there is (1) a prospect of direct benefit to participants or (2) a likelihood of yielding generalizable knowledge about the participants' condition (and, then, risk of harm may not exceed a minor increase over minimal risk).

We argue that the limits to permissible risk in the current ethical and regulatory framework can be helpfully understood as capturing an idea with considerable independent plausibility: that children have a moral right to adequate protection from harm. (Moral rights, as explained more fully in a later section, are a type of protection afforded by the requirements of morality just as legal rights are a type of protection afforded by the law.) We will show that understanding the limits to permissible risk in pediatric research in terms of this right has several advantages. Although these limits are often understood by reference to "minimal risk" and "a minor increase over minimal risk," the current framework leaves open the possibility of higher levels of permissible risk (with no corresponding prospect of direct benefit) in exceptional cases. This provokes the question of whether there is a ceiling to permissible risk in these exceptional cases and, if so, how we may conceptualize and justify this risk ceiling.

Our analysis of the right to adequate protection provides a rationale for what we propose as a ceiling of permissible risk in pediatric research without the prospect of direct benefit: what we call "relatively minor" risk. We clarify the justification behind the usual standards of "minimal risk" and "a minor increase over minimal risk" and explain why it is permissible to impose any risks at all on child participants who do not stand to benefit directly from enrollment in research. Finally, we illuminate some aspects of the concept of "best interests."

II. UNDERSTANDING THE CURRENT FRAMEWORK OF PERMITTED RISKS IN TERMS OF A RIGHT TO ADEQUATE PROTECTION

Our first thesis is that the current ethical and regulatory framework for permissible risk in pediatric research, deriving from the National Commission's work and implemented through the U.S. Department of Health and Human Services (HHS) regulations at 45 Code of Federal Regulations Part 46 Subpart

D, is plausibly and helpfully understood in terms of a moral right to adequate protection (HHS, 2014, § 46.401).[1] The basis for this thesis becomes evident when we examine the risk limits more closely—and consider the nature of (negative) moral rights. At the outset, it is important to acknowledge that Subpart D also reflects rights *not* to participate in research; children do not bear an obligation to assume research risks for the benefit of society.

Limits to Permissible Risk in Pediatric Research

It is broadly appreciated that children are (at least presumptively) incapable of providing what the law and the fields of medicine and bioethics consider *informed consent*.[2] In this important way, children differ from competent adults or adults with decision-making capacity. For this reason, children deserve special protections and are not permitted to enter some studies that competent adults may be permitted to enter.

An important set of requirements in the current ethical and regulatory framework is helpfully understood as reflecting a child's *moral right to adequate protection from harm*.[3] What constitutes adequate protection from harm varies according to research context,[4] but the specific requirements of the current framework are consistent with the assertion of this right. Our claim is neither that the regulations *must* be understood in terms of this right nor that those who crafted the regulations *actually thought in these terms*. Rather, we claim that understanding the risk limits through the conceptual lens of a right to adequate protection is both plausible from the standpoint of ethical theory and illuminating for pediatric research ethics. The claim that children have a moral right to adequate protection is highly plausible and consistent with leading ethical theories. In this discussion, we simply assume that children have this right. As for the corresponding obligation holders, we assume that children have this right against the state, which has an obligation to protect its people generally, and against their parents (or guardians) who have obligations to protect, nurture, and care for their children. After clarifying the nature of the relevant rights-claim in the next section, we will examine the content of the correlative parental obligations as a means of specifying this right for the research context.

Let us now consider details of the current framework. In most instances, pediatric research may be conducted only if the research presents no more than minimal risk to child participants (HHS, 2014, section 404) or offers the prospect of direct benefit to individual participants that justifies greater than minimal risk (HHS, 2014, section 405). In some cases, pediatric research that poses more than minimal risk without the prospect of direct benefit to participants is permitted, if the risk represents only a minor increase over minimal risk, and the research is likely to yield generalizable knowledge about the participants' condition that is vitally important for understanding or ameliorating this condition (HHS, 2014, section 406). These categories of

pediatric research undergo independent review by the same mechanism as research with adults: review by a local institutional review board, or IRB.

One additional category of permitted research involves research that cannot be approved under the other three categories (HHS, 2014, section 407). Such research is permitted only following national-level review that concludes that "the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children" (HHS, 2014, § 46.407.b.2.i) and that "the research will be conducted in accordance with sound ethical principles" (HHS, 2014, § 46.407.b.2.ii). We will discuss this exceptional category of research—in particular, its complexities in relation to the right to adequate protection from harm—in the next section. Research in all of these categories requires parental permission and child assent when appropriate.

In the context of this regulatory framework, risk is "the probability and magnitude of harm or discomfort anticipated in the research" (HHS, 2014, § 46.102.i). As this definition suggests, an assessment of risk must account for the probability of a harm as well as its magnitude, duration, and reversibility. Risks include potential harms from the intervention tested in research (e.g., a new drug) as well as potential harms from research procedures (e.g., blood draws to test effectiveness of the new drug); harms can be physical, psychological, or social (Institute of Medicine, 2004, 114–5; Presidential Commission for the Study of Bioethical Issues (PCSBI), 2013, 68).

Conceptualizing the relationship between particular risk limits and child participants' right to adequate protection from harm is more straightforward in sections 404–406 than in section 407. Children are permitted to enroll in studies that involve either no more than minimal risk (HHS, 2014, section 404) or a degree of risk that is justified by the prospect of direct benefit to them (HHS, 2014, section 405). Where the risk of harm is minimal, it is no greater than children—including those who are relatively advantaged—face in the course of their everyday lives or during routine medical or psychological examinations.[5] Where the risk level is higher, but there is a prospect of direct benefit to participants (say, in a clinical trial evaluating a treatment that is more promising than alternatives for a participant's disease), the risk can be accepted as part of a risk-benefit combination that it is in the child's interest to accept. In both cases, children are adequately protected from harm.[6]

In minimal-risk research, participants are adequately protected from harm because the level of risk to which they will be exposed is no greater than the risk they face in daily life or at a medical check-up—a level of risk that seems obviously acceptable to us (and has seemed acceptable to the vast majority of scholars working in pediatric research ethics). In research that offers the prospect of direct benefit, the question whether participants are adequately protected from harm must take into account the possible beneficial outcome of that research, that is, the possibility that the *individual participant* might directly benefit from it. Such research is often considered "therapeutic research," and

the decision whether to enroll is guided by the same considerations that might guide clinical decision-making. Indeed, the regulations require that "the relation of the anticipated benefit to the risk" in research "is at least as favorable to the subjects as that presented by available alternative [e.g., treatment] approaches" (HHS, 2014, section 405). For the same reasons that treatment decisions—when made in accordance with a child's best or essential interests—are considered generally acceptable, that is, because they adequately protect the child from harm, therapeutic research conducted within the current ethical and regulatory framework does so as well. Key to this conclusion is that, under the current framework, such research can only proceed if it is at least as promising (i.e., accounting for anticipated benefits and concomitant risks) as treatment alternatives, ensuring that a decision to participate is at least as compatible with a child's interests as a decision for the treatment alternative.

In some cases, pediatric research that poses more-than-minimal risk without the prospect of direct benefit to participants is permitted, if the risk represents only a minor increase over minimal risk and the research is expected to yield generalizable knowledge about the participant's medical condition that is vitally important for understanding or ameliorating this condition (HHS, 2014, section 406). A minor increase over minimal risk is only a "narrow" expansion of the minimal risk standard and, as the National Commission stated, "poses no significant threat to the child's health or well-being" (National Commission, 1977, 139). We believe that allowing this level of risk, slightly higher than what is usually permitted where no direct benefit is in prospect, also constitutes adequate protection; the slight increase in permitted risk is compensated for—in our judgment—either by (1) the meaningful possibility that the child participant will benefit, later in life, from the eventual fruits of this research or (2) the likelihood of future benefit to children with the participant's condition. The gain in generalizable knowledge makes such later benefit possible.[7] Although this later benefit is speculative in the present, it is not entirely speculative—the proposed research must be "*likely* to yield generalizable knowledge . . . which is of *vital importance*" (HHS, 2014, § 46.406, emphasis added)—and the increase in permitted risk to the child is minor. Later, we suggest a risk ceiling for the final category of permitted pediatric research (HHS, 2014, section 407) that is consistent with the framework as a whole.

The fact that the current approach requires adequate protection of child participants from harm coheres with the insight that children have a moral right to adequate protection. In order to clarify this idea, it is helpful to consider what negative moral rights are and how they differ from goals.

Negative Moral Rights as Setting Limits on the Pursuit of Goals

There is an enormous philosophical literature on the nature, content, and foundations of moral rights as well as legal rights, for example, Grotius (1625),

Hobbes [1651] 1985, Locke (1690), Mill (1863), Hohfeld (1913), United Nations (1948), Feinberg (1970), Lyons (1970, 45–55), Nozick (1974), Dworkin (1977), Hart (1982), Raz (1984), Sumner (1987), Waldron (1993), Wellman (1995), Shue (1996), Gewirth (1996), Pogge (2000), Wenar (2005), Sreenivasan (2005), Griffin (2008), Beitz (2009), and Buchanan (2010). It is outside the scope of this paper to engage that literature or the controversies reflected in it. What follows is simply an explication of the type of moral right that is exemplified by the child's right to adequate protection from harm. This is what has been defined as a *negative* right, or right of noninterference, as opposed to a *positive* right, or right to the provision of some service or good. Although the distinction between negative and positive rights is difficult to draw in some cases, and has been challenged by some scholars as unhelpful, we find it helpful in the present context. The right to adequate protection is a negative right not to be subjected to excessive risk of harm.

Moral rights, in general, are a type of protection afforded by the requirements of ethics or morality. Moral rights (like legal rights) protect individuals. More specifically, they protect certain essential or vital interests of individuals—such as their interests in life, health, bodily integrity, freedom from undue coercion, freedom of expression, and equitable access to social goods. Sometimes these interests primarily require noninterference for their protection—hence negative rights. Sometimes protection of these interests requires substantial provision of goods such as access to education and health care—hence positive rights (the objects of which are often contested).[8]

Outlining the relationship between negative rights and goals helps to clarify the protection afforded by these rights. Goals are the intended end points of particular actions, activities, or pursuits. At the most general level, the primary goal of biomedical research is to obtain generalizable knowledge that can be deployed to restore, protect, or promote the health and well-being of human beings. Pediatric research has the goal of obtaining generalizable knowledge about children that can be used to benefit them. These overarching goals of pediatric research and biomedical research more generally are enormously laudable.

But, it is one thing to judge that a goal is laudable or valuable; quite another to judge that a particular *means* to achieving the goal is appropriate. In the research context, increasing the fund of generalizable knowledge regarding pediatric health is a goal of paramount importance. But not every means to achieving this goal is permissible. For example, while it would be valuable to learn about the effects of automobile accidents on young children who use a particular kind of car seat (with the ultimate goal of promoting children's automobile safety), it would be impermissible to conduct studies that intentionally place children in automobile accidents—even if the research promised valuable prevention data. The research goal in question must, from a moral standpoint, be pursued by means other than those that impose unacceptable risks on pediatric participants. To impose such risks is to violate the children's right to adequate protection from harm.

Thus, negative moral rights and goals have different moral "shapes." A goal represents a destination. There may be multiple possible ways of pursuing the goal, multiple paths to the destination. Negative moral rights set limits or constraints on the pursuit of goals, like signs that say "Don't go here; take a different path." Although it is important to get to school on time, it does not follow that you may hop the guardrail at the subway station in an effort to do so. The same is true for biomedical research. Only some paths to the valuable destination are permissible. Participants' negative rights set limits on the permissible routes.

The goals of biomedical research are connected with human beings' essential interests in life and health. Rights, including negative rights, are also connected to certain essential interests of persons serving as research participants. It might therefore seem natural to think of negative moral rights and morally important goals such as the goals of promising studies as lying on the same moral "scale" and, hence, as appropriately subject to "balancing" (Appelbaum, 1997; Beauchamp, 2006). However natural and common this image of the relationship between such rights and goals is, this image is potentially confusing and may encourage an overly consequentialist approach. Below, we consider a way of interpreting the balancing metaphor that avoids the difficulties noted here.

The balancing metaphor invites the understanding that a gain with respect to research goals can justify overriding participants' negative rights so long as the expected gain is greater than, or "outweighs," the expected compromise of rights. This understanding suggests that negative rights and valuable goals are elements of the same sort of moral consideration—interests or utility—in which case negative rights are simply interests of participants to be weighed against the interests of members of society who stand to benefit from biomedical progress. If so, then participants' "negative rights" would no longer function as such: They would no longer provide significant protection against claims of public benefit or societal utility. In that case, there would be no need to consider whether research posed more-than-minimal risk to participants or offered them the prospect of direct benefit. All that would matter is whether any expected harms to participants would be more than (and maximally) offset by the expected gain to people in the society at large. Under this view, if a study that involved children in deliberately caused car accidents promised more valuable data than studies that did not involve children in this way, then the former study should be examined closely to see whether, all things considered, it would be worth conducting. From an ethical perspective, however, such a study would clearly be impermissible, because it would egregiously violate children's right to adequate protection from harm. It is paramount to appreciate the function of negative rights, which is to set strict (if not absolute) limits or constraints on the pursuit of goals. These constraints are connected to the idea that research participants, and persons more generally, are not to be used as *mere means*

or instruments to society's ends—including society's exceptionally important end of biomedical progress.

At this point, one might object that children's right to adequate protection in the biomedical context entails a *positive* right to fruits of high-quality pediatric research insofar as such research is needed for *adequately* protecting children against various threats to their health. But, this positive right to high-quality pediatric research may conflict with the child participants' negative right to adequate protection if only *high-risk* research promises the needed scientific data. If so, then *balancing* the negative right against the positive right seems appropriate, in which case child participants' right to adequate protection cannot be seen as setting strict limits on risk levels. Furthermore, a positive right to high-quality pediatric research might entail a moral *obligation* on the part of children to serve as research participants, contrary to what the present paper assumed earlier.

This is an important objection, and it is important to see that it is misconceived. Negative rights, serving as limits or constraints, take priority (with few if any exceptions) over positive rights, which often—as here—take a more goal-like structure. Even if the only way to get really good data on the efficacy of a new type of car seat required involving children in dangerous collisions, it would not be right to conduct the research; such experiments would violate children's right to adequate protection. Moreover, it is not very plausible to assert that children have a positive right to the fruits of any and all needed types of high-quality research. It would be more plausible to assert that children have a right to the fruits of *whatever high-quality pediatric research a society can reasonably conduct*, where one condition of reasonableness is respecting participants' rights. The positive right would then not conflict with the negative right—and it would not entail an obligation on the part of children to serve as trial participants. The limits of permissible risk in pediatric research are helpfully understood in terms of the negative right to adequate protection to harm, a kind of constraint.

Having criticized the idea of balancing children's right to adequate protection and the goal of advancing pediatric medicine through research—for inviting confusion and moral misdirection—we acknowledge that a subtler way of understanding the balancing of rights and goals is not vulnerable to our critique.[9] According to this understanding, rights are neither reducible to elements of a consequentialist analysis nor absolute in their protection of essential interests; rather, rights are so "weighty" that they maintain their protective function unless overridden by an *overwhelming* gain in net good or by *another right*. This conception preserves a significant protective role for rights while making sense of the idea of balancing. In response to this approach, we find its construal of the normative force of rights largely plausible (even if we doubt that negative rights will often give way to conflicting rights). Yet, the balancing metaphor is potentially confusing *unless specified carefully along the present lines*. Without such clarification, talk of balancing

rights and good consequences tends to slip, at least in our experience, into an implicitly thorough-going consequentialist analysis.

Let us turn now to a different challenge: the claim that rights language is not necessary for an adequate ethical analysis. According to the challenge, we could advance the assertions about the limits of permissible risk and the impermissibility of using participants as mere means to societal ends without mentioning rights by talking instead of the relevant *obligations*. In response, while it is possible to omit the language of rights, this language focuses our attention on the *moral status of persons* in their role as research participants. Doing so helps to explain the *basis* of the corresponding obligations: We have the obligations in large part because the individuals to whom they are directed are individuals with moral status rather than mere tools. Acknowledging the moral status of individuals is another way in which the negative right in question is helpful.

Note further that an analysis that mentions only *conflicting principles*—such as nonmaleficence (which includes the obligation not to impose undue risk) versus public beneficence (which includes obligations to benefit society through research)—without noting the constraints indicated by negative rights draws an incomplete moral picture. The principles are helpful and important to recognize, but only the language of negative rights captures both the relevant constraints and their basis in moral status. Of course, one could *specify* nonmaleficence and beneficence into finer grained norms that arrived at the same constraints, but rights language makes the additional point about moral status. For these reasons, we maintain that the appropriate risk levels in pediatric research are helpfully understood in terms of a negative right to adequate protection.

This thesis provokes a question that is left open by current regulations and leading literature in pediatric research ethics: Does the child participants' right to adequate protection entail a risk ceiling for exceptional cases?

III. BOUNDARIES OF THE RIGHT TO ADEQUATE PROTECTION

In discussing the current approach, we considered how its permissible risk levels—minimal risk (HHS, 2014, section 404), risk that is justified by and proportionate to the prospect of direct benefit (HHS, 2014, section 405), and a minor increase over minimal risk (HHS, 2014, section 406)—all confer adequate protection of child participants from harm in the circumstances in which they apply. But, consider the other category of permitted pediatric research (HHS, 2014, section 407), in which no limit to risks confronting participants is explicitly stated. Is there a way to identify a principled risk ceiling for this research category, namely, one that respects children's right to adequate protection? Is there a coherent explanation for why this risk ceiling differs from those of the other categories of permitted research?

We answer both questions affirmatively by reference to what we call a *responsible parenting standard* (and also invoke the distinction between ideal and non-ideal moral theory in answering the second question).[10] We further argue that our analysis (1) adequately answers those skeptics who doubt the appropriateness of imposing *any* known risks on pediatric participants without the prospect of direct benefit and (2) illuminates the oft-employed, best-interests standard as it applies in the pediatric research context.

Section 407: Research at the Boundary

Pediatric studies that are candidates for approval under section 407 include "only research of major significance, in the presence of a serious health problem" (National Commission, 1977, 12) that an institutional review board judges not to be approvable under sections 404, 405, or 406. Such studies can be approved, following national-level review, in either of two circumstances. In the first possible circumstance, national-level review leads to the conclusion that the research in question is, in fact, approvable under sections 404 through 406—a possibility we may hereafter ignore.

The second circumstance would allow the research to be approved if several conditions are met: (a) the study presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (b) it will be conducted in accordance with sound ethical principles; and (c) adequate provisions are made for soliciting the meaningful assent of children and the permission of their parents or guardians (HHS, 2014, § 46.407). Condition (a) concerns the great promise of the proposed pediatric study, while condition (c) is common across categories of permitted pediatric research. As for condition (b), a frequently noted shortcoming of section 407 is that there is no specification of what the "sound ethical principles" might be.[11] We need a more explicit way to determine what level of risk might be justified in exceptional circumstances in which the limits presented in sections 404–406 seem excessively constraining.

Where should we locate the risk ceiling beyond which pediatric participants' right to adequate protection would be violated?[12] Although it seems impossible to identify any *precise* limit, we endeavor to supply a *principled* one—specifically, a *responsible parenting standard*, which offers a rough guideline in thinking about the limit. A rough, principled guideline, we suggest, is preferable to no guideline or an unprincipled one.

As discussed earlier, the right to adequate protection from harm protects a child's essential interest in personal safety. One way to determine the boundary of this right is to think about the boundaries that a responsible parent would enforce as a matter of obligation. (Our analysis takes advantage of the correlativity of rights and individual-directed obligations, two sides of the same moral coin.) Indeed, some scholars have likened the

process of pediatric research review to assuming the role of the "scrupulous" or "virtuous" parent (Freedman, Fuks, and Weijer, 1993; Nelson and Ross, 2005; Morris, 2012). While other entities—for example, the federal government—also enforce the right to adequate protection in very practical and important ways, these entities do not define the boundary of the moral right as conceptualized here. We submit that thinking about the protective obligations inherent in responsible parenting helps to delineate the right that the government can in turn help to safeguard.

Two additional ideas motivate turning to this standard in the research context. First, responsible parents sometimes allow their children to assume modest or relatively minor risks (beyond minimal risk or even a minor increase above it) for the sake of public good or benefit to others. Second, responsible parents never use, or approve of others using, their children as mere means or mere tools for others' benefit. Or, a bit more precisely, since even responsible parents can make mistakes and occasionally act irresponsibly, responsible *parenting* does not involve using one's children as mere means.[13] Each point merits expansion.

Parents differ greatly in their priorities, strengths, and parenting styles—and, of course, not all parents raise their children responsibly. Even among those who impress most observers as good, responsible parents, there are important differences in how they treat their children depending on differences in culture, experience, and personal values and priorities. One difference among responsible parents is the range of activities in which they permit their children to engage and the risks they permit them to take. For example, some parents might let their 9-year-old child walk home from school alone in a relatively safe neighborhood, whereas more protective parents might wait until their child is older before conferring this option. There is no specific template for raising children responsibly. Differences are inevitable and morally tolerable—*within reasonable limits*.

Importantly in the present context, there are responsible parents who permit their children to undertake some risks beyond the usual ones of ordinary life for the sake of the public good.[14] Consider these examples of activities that some responsible parents would allow their children to engage in: helping to clear a low-income family's overgrown yard when there is a modest chance of contracting poison ivy (assuming the child does not have an extreme allergy to poison ivy); running in an 8-km race on a day that happens to be rainy in order to collect pledges for a charity; helping to rebuild a library that was badly damaged in a storm; and riding a bike a moderate distance with a loaded backpack in order to deliver groceries to an elderly person. Each of these activities poses some risk that the child will be injured or otherwise harmed when acting for the benefit of the public or another person. (Note that parents might permit additional risk when the child is engaged in an activity, such as downhill skiing, in which it is the child himself who is the primary beneficiary; this higher level of permitted

risk is irrelevant to our discussion.) The risk in each case is added to those associated with the child's everyday activities and seems to surpass minimal risk and even a minor increment above minimal risk. Yet, it is a plausible judgment that permitting these activities falls within the range of responsible parenting decisions.

This suggests that the activities permitted by parents in the four examples are all within some limit of acceptable risk. Contrast a couple of cases in which parents cross this limit: a parent allows a 10-year-old child to skydive as a means to raise funds for charity; and a couple pressures their 13-year-old adolescent to walk door-to-door in a neighborhood plagued by gang violence in an effort to persuade people to seek a law-abiding, gun-free life. Although the parents just described may have noble ends, they are willing to place their children at excessive risk in seeking those ends.

Some responsible parents allow their children to take risks that are modest but would exceed the "a minor increase over minimal" standard in the interest of helping other people. But responsible parents do not thereby reduce their children to mere means to others' benefit. In a parallel way, society could justifiably permit pediatric research participants, in exceptional circumstances, to undergo similar risk levels without the prospect of direct medical benefit to them so long as the risks are relatively modest rather than excessive, while still adequately protecting children from harm. The limit may be understood as (1) the *maximum* risk that *some* responsible parents would permit their children to undergo in the name of the public good (in other words, the maximum risk that seems compatible with responsible parenting) and (2) a level of risk beyond which intuitively strikes us as using children as mere means to societal ends. The ideas stated in (1) and (2) are unified insofar as they are inconsistent with responsible parenting to allow one's children to be used as mere means to societal ends.

The responsible parenting concept offers a way of accounting coherently for permitted risk levels in pediatric research, those explicitly stated in sections 404–406 and the standard we recommend for section 407. The latter standard, which we will call *relatively minor risk*, is a level of risk that some responsible parents would allow their children to take in an effort to be helpful to particular causes, individuals, or society at large. Or, instead of speaking of what *some* responsible parents *would* allow, we could equally well speak of what parents *could responsibly* allow. As supported by the examples listed earlier, "relatively minor risk" is greater than a "minor increase over minimal risk"; it is more than a narrow expansion beyond the risks of everyday life but remains consistent with what parents or other primary caregivers could responsibly allow. The other specific risk standards, which are more stringent in demanding either a lower level of risk or the prospect of direct benefit, are also within the range of what responsible parents would or could allow.

The responsible parenting concept connects the following two ideas in a compelling way. First, responsible parents would protect their children's right to adequate protection by not permitting them to participate in activities in which the sponsors of those activities were prepared to violate this (or any other) right. Second, sections 404–406 occasionally seem too restrictive in the research they permit, hinting at the possibility of justifying some studies featuring a slightly higher level of risk without the prospect of direct benefit—consistent with the standard of "relatively minor risk" that we propose for section 407.

Some readers may find our proposal—a ceiling of "relatively minor risk" whose extent is determined by judgments about responsible parenting—to be (1) overly vague and/or (2) insufficiently rigorous insofar as it depends on intuitive judgments. First, again, we recognize that the standard is vague. While providing some guidance in the form of a heuristic ("Would it be compatible with responsible parenting to allow one's children to undergo this level of risk for the sake of public benefit?"), much of the hard work will be left to actual decision-makers. But, as moral philosophers have appreciated since at least the time of Aristotle, judgment is indispensable to ethics even where decision-makers have well-fashioned rules at hand. The decision-makers responsible for deciding whether particular pediatric studies meet the present standard would, if our proposal is accepted, have a meaningful heuristic as a basis for guiding their deliberations. Moreover, the standard sets a limit on permissible risk—thereby respecting children's right to adequate protection and improving on the current ethical and regulatory framework. As we said earlier, a rough, principled standard is better than no standard or an unprincipled one.

Further, while the standard we propose is vague, it does not seem vaguer than the standards employed in the current regulatory framework. Our heuristic, again, can be formulated as the question, "Would it be compatible with responsible parenting to allow one's children to undergo this level of risk for the sake of public benefit?" Under the current framework, decision-makers are encouraged to ask, in applying the minimal-risk standard, a question that is also vague: "Is the level of risk associated with the study within the range of risks that children face *in everyday life* and routine medical examinations?" (emphasis added). In applying the standard of a minor increment over minimal risk, one is asked to consider whether the level of risk associated with the study is within *a minor increase* over minimal risk—without guidance as to what counts as a minor increase. And, for studies reviewed under section 407, decision-makers are offered no heuristic at all for determining acceptable risk; by contrast, we offer a meaningful, if vague, heuristic. Thus, in comparison with the standards embodied in the current regulatory framework, the standard we propose does not seem to us embarrassingly vague or unhelpful.

Moreover, under our proposal, decision-makers involved in section 407 review could develop a set of case types or procedures that presumptively

fall within the range of "relatively minor risk." They could begin by bearing in mind the degree of risk featured in parenting scenarios such as those presented earlier: an array of cases of responsible parenting that allow some pediatric risk taking for altruistic purposes. With that approximate range of risk levels in mind, they could then consider what sorts of research procedures seem to fall within the same range of risk. Proceeding in this way, they might plausibly judge that within the range of acceptable risk are not only such procedures as blood draws (commonly thought to present minimal risk) and skin biopsies and chest x-rays (often thought to present a minor increase over minimal risk) but also—in some instances, depending on details—lumbar punctures and broncoscopies (often thought to exceed a minor increase over minimal risk). Thus, we have answered the charge of vagueness.

Is our proposal insufficiently *rigorous* due to its reliance on ethical intuitions or considered moral judgments? We think not. While our proposal does rely on such judgments, the case in its favor is not built on intuitive support alone. The judgments themselves cohere with the highly relevant norm of responsible parenting, a norm that we specify for present purposes in terms of an independently plausible assertion: children have a (negative) moral right to adequate protection from harm. This right, as we have seen, is correlative to parental obligations whose content can be clarified through intuitive judgments about cases. Importantly, the rights-claim offers explanatory power. It explains why pediatric studies approvable under sections 404, 405, 406, and—with our proposed ceiling—407 are all morally permissible: they are compatible with this right. Conversely, this rights-claim explains why proposed studies that are not approvable on account of their projected risk levels are not morally permissible: these studies fail to respect this right. Meanwhile, the intuitive judgments about responsible parenting in connection with accepted risks cohere with the considered moral judgment that it is impermissible to use persons merely as means or tools to societal ends, a judgment that helps to motivate the moral constraint embodied in the right to adequate protection. In sum, our proposal enjoys not only the support of considered moral judgments about particular cases but also extensive coherence with other highly credible moral norms and significant explanatory power across the domain of relevant norms.[15]

Varied Risk Levels in the Current Regulatory Framework

Our analysis raises a key question: If relatively minor risk (that exceeds the other risk standards) is acceptable in *some* instances—those exceptional ones that are appropriate candidates for section 407 review—why is this risk level not acceptable in pediatric research across the board?

One possible reply is that the current ethical and regulatory framework is, and always has been, overly protective and risk averse, for example, by

potentially "block[ing] important research that is needed to provide health care for all children" (Wendler, 2008). For this reason, it has long precluded pediatric research that would have been justified by the relatively minor risk standard. Accordingly, one might argue that the relatively minor risk standard should apply to all pediatric research. We disagree with this approach and suggest another way of understanding the matter that, in effect, invokes the distinction between ideal and nonideal moral theory.[16]

We believe that the relatively-minor-risk standard *would in certain ideal circumstances* be the appropriate standard for all pediatric research that does not offer the prospect of direct benefit to participants. These would be circumstances in which research institutions and investigators were not biased in favor of conducting research, the federal government and its officials reliably treated individual children with as much care and protection as responsible parents typically treat their children, and prospective participants and their proxies never felt intimidated and pressured by biomedical personnel into joining particular studies. Given that these ideal circumstances *do not* obtain, it is appropriate that in most instances children receive more protection than they would need in ideal circumstances. In this light, the more restrictive standards of minimal risk and of a minor increase over minimal risk are very reasonable in their respective contexts.

Occasionally, however, this additional downward (protective) pressure on permitted risk levels may appropriately be relaxed due to extraordinary circumstances and the exceptional promise of a proposed pediatric study. In these instances, permissible risk may—if necessary—rise to the "top" of the relatively-minor-risk standard. But, in these instances, as the regulations stipulate, national expert review is necessary. Thus, while the *substantive* protection is slightly relaxed with an increased level of permissible risk, the *procedural* protection increases to ensure adequate subject protection. In our view, adoption of the relatively-minor-risk standard as the risk ceiling for section 407 review would constitute a helpful revision of current regulations. With this modification, we believe, children's right to adequate protection from harm would be respected within all categories of permitted pediatric research.

IV. IMPLICATIONS FOR THE BEST INTERESTS STANDARD

Traditionally, the best interests standard has been cited as the decisive guidepost for making decisions for those who lack the ability to make decisions themselves, such as children (Buchanan and Brock, 1989; Kopelman, 2005; Salter, 2012). Yet, many scholars, for example, Ross (1998), Kopelman (2005), and Salter (2012), have criticized the best interests standard for its ambiguity and strained applicability in many contexts. We do not offer a full analysis of the best interests standard here, but examining its relationship to our framework can illuminate the scholarly discussion of best interests.

How should we understand the best interests standard? An overly literal interpretation of best interests could support the prohibition of *all* pediatric research that entails any risk at all without the prospect of direct benefit to participants. That is, it would (arguably) be in any child's individual best interest not to take on the marginal additional risks of research participation. Such a position is implausibly strict.

We often say that adults have an obligation to promote their children's best interests, a morally serious-sounding claim that is unlikely to be challenged in everyday life. Yet, taken literally and examined carefully, this claim represents an exaggeration. Although parents have obligations to secure their children's welfare, or essential interests, they are not obligated to *maximize* the promotion of their children's interests—for example, when doing so would be highly deleterious to the parents' or others' interests. Supposing it is greatly in a particular stay-at-home parent's personal or professional interest to return to the workforce yet slightly suboptimal for one of the family's children, we cannot judge on this basis alone that it would be wrong for the parent to do so. Parents are not obligated to maximize their children's welfare, to strive obsessively for their (literally) best interests. Rather, they are obligated to make every reasonable effort to secure their *essential interests* or *basic needs*—and perhaps to do more for them when they can *without undue sacrifice*.[17] This standard is far more in keeping with considered moral judgments about parental responsibilities than a standard that requires literally maximizing a child's interests.

A small minority of commentators (e.g., Ramsey, 1976) has argued, contrary to our position, that we should not allow *any* research risks at all for children whose participation in research includes no prospect of direct benefit. It is true that the anticipated risks are no greater than those encountered in the everyday lives of healthy, well-situated children, so these risks are perfectly ordinary and minimal. But, by involving children in this research, we are *adding* a small set of risks to the small set of risks they would undergo anyway.[18] From this standpoint, it may seem that to impose even minimal (nonzero) risk on pediatric subjects—who, once again, cannot provide informed consent—is to use them as mere means to the ends of research. To those who do not hold this view (including the vast majority of scholars who consider the matter), however, rejecting minimal-risk research on these grounds just seems contrary to good sense and extreme in its protectiveness.

Our position supports the latter judgment. When parents act responsibly as parents, they treat their children in morally appropriate ways. They do not, for example, violate their rights, including their right to adequate protection. But, we already noted the considered moral judgment that responsible parenting and adequate protection of one's children are compatible with allowing them to take relatively minor (yet sometimes more than a minor increment over minimal) risks in efforts to help others or society at large. This suggests that one who rejects even minimal (nonzero) risk in pediatric research with no prospect for direct benefit has an overly restrictive view.

Our rejection of a highly literal interpretation of best interests leads naturally to the question of how we think best interests ought to be understood. We suggest understanding a child's best interests in the context of pediatric research—that is, if we retain the concept of best interests in this context at all[19]—simply as his *essential interests* or the *satisfaction of his basic needs*. The essential interest or basic need on which we have focused in this paper is adequate protection from harm (to which every child has a moral right). To protect a child's essential interest in adequate protection, we maintain, is to provide him with adequate—not necessarily perfect—protection from harm. This entails keeping risk levels *acceptably low*, not eliminating them altogether in the absence of a prospect for compensating direct medical benefit. Our earlier discussion of risk levels associated with sections 404–407 provides details of what constitutes acceptably low risks to pediatric research participants (in non-ideal circumstances).

Thus, in addition to illuminating what we believe to be the error in rejecting even minimal risk for pediatric research participants, our comments about essential interests are intended to help clarify the concept of best interests as it is often used in pediatric research ethics.[20] This obviates the dispute between those who reject the child's best interests as an appropriate standard in pediatric research—because the standard seems too restrictive—and those who insist on this standard—because it seems so commonsensical. If understood in terms of essential interests, the best interests standard *is* commonsensical without being overly restrictive.

V. CONCLUDING REFLECTIONS

It is a laudable goal to promote children's health and well-being through research. Not all pediatric research, however, is permissible. Because children are unable to give informed consent to participate in research, the risks to which children may be exposed in research are strictly limited to accord with their moral right to adequate protection from harm.

The rights framework that we have recommended as a conceptual lens provides a unifying rationale for current ethical and regulatory pediatric research protections by accounting for the differing permissible levels of research risk (in nonideal circumstances). In doing so, it explains why it is permissible to impose any risks on pediatric participants who do not stand to benefit directly from enrollment in research. Our framework further illuminates section 407 as more than a "catch-all" for important, but otherwise unapprovable, research by suggesting a risk ceiling that respects children's right to adequate protection from harm—an interpretation more in line with section 407's original intent (PCSBI, 2013, 43–6). Finally, our analysis illuminates the best interests standard, suggesting a plausible interpretation in terms of essential interests and vindicating its central place in pediatric research ethics.

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NOTES

1. The U.S. Food and Drug Administration (FDA) has codified substantively identical regulations at 21 Code of Federal Regulations Part 50 Subpart D (FDA, 2014, § 50.50, et seq).

2. We do not deny that there may be some mature minors who are capable of genuine informed consent. Our analysis is intended to apply to the vast majority of minors who are presumed to be incapable of informed consent.

3. The slightly stronger thesis that this right is *implicit* in the current ethical and regulatory framework is made by DeGrazia (2001).

4. Relevant differences among research contexts are indicated in sections 404–407. We refer to 45 C.F.R. § 46.404 (HHS, 2014) as "section 404," 45 C.F.R. § 46.405 (HHS, 2014) as "section 405," and the like.

5. Relatively disadvantaged people might live in unsafe neighborhoods or in circumstances that pose a higher degree of risk in their everyday lives. In that case, the degree of risk that they ordinarily face would be unsuitable as a baseline for what constitutes "minimal risk" in research (Institute of Medicine, 2004; Secretary's Advisory Committee on Human Research Protections, 2005).

6. Or at least this judgment seems commonsensical. Later, we will consider a skeptical challenge regarding minimal-risk research that offers no prospect of direct benefit.

7. Some commentators, for example, Brown (1988, 183–93), assert that the slightly higher level of risk accepted in this category of research is justified, because children may be presumed to *identify* with other children who share the medical condition relevant to the study or in some important sense to be *in the same community* as other children with the condition. We reject this justification. While it is true that child participants in a study of this kind are members of a class of children who share a particular medical condition, it is also true that the children are members of any number of classes of individuals. Indeed, they are members of the broad class of human beings. If membership in a class were a basis for presuming significant identification with other members of the class (or the sense of being in the same community), we could presume that any human being identifies with human beings as such *and for this reason should be permitted to accept a higher level of risk than would otherwise be justified*. If this were correct, then it would be permissible—not just in highly exceptional cases but routinely—to subject healthy child participants to more-than-minimal risk research that has no particular medical relevance to them. This seems wrong (we explain why it is wrong later), as does the appeal to presumed identification, which generated this implication.

8. The negative rights/positive rights distinction is highly imperfect. For one thing, negative rights such as the right to free speech cannot be reliably enjoyed without the (positive) provision of enforcement measures and a criminal justice system.

9. For a discussion that takes this approach, see Brody (1988, 22–32).

10. Responsible parents are presumably *reasonable* in their parenting, so one might wonder about the relationship between our standard and the reasonable person standard in the law. The latter standard is often invoked in criminal and tort law to refer to an imaginary person who exercises average or reasonable care, skill, and judgment in his conduct, thereby providing a standard for assessing liability. The responsible parenting standard, by comparison, is more specific insofar as it focuses on behaviors that are consistent with morally responsible parenting. Also, while some (not all) appeals to the reasonable person standard speak of what an *average* person would do in a particular set of circumstances, our approach takes no interest in what average or typical parents would do; our approach is explicitly normative, invoking considered moral judgments about responsible parenting.

11. By contrast, the National Commission was more explicit. Rather than referring to "sound ethical principles," it stated, in Recommendation (6), the requirement that "THE CONDUCT OF RESEARCH WOULD NOT VIOLATE THE PRINCIPLES OF RESPECT FOR PERSONS, BENEFICENCE AND [sic] JUSTICE." (National Commission, 1977, 10, capitals in original). The National Commission elaborated as follows:

> The Commission believes that only research of major significance, in the presence of a serious health problem, would justify the approval of research under Recommendation (6) (B). The problem

> addressed must be a grave one, the expected benefit should be significant, the hypothesis regarding the expected benefit must be scientifically sound, and an equitable method should be used for selecting subjects who will be invited to participate. Finally, appropriate provisions should be made for assent of the subjects and permission and participation of parents or guardians (National Commission, 1977, 12).

12. One recent analysis (Wendler, 2013) suggests that a minor increase over minimal risk be adopted as the limit on pediatric research risk, with some exceptions. Our reasoning takes us to a different approach.

13. A reviewer thought that our present claim was an overgeneralization and suggested, as a counterexample, "savior siblings": children conceived, possibly through selective in vitro fertilization, and brought to term in order to be a source of organs or cells for an older sibling with a life-threatening medical condition. We believe that bringing into existence a savior sibling *can* be morally justified but that, when it is justified, it is not a case of using the new child as a *mere* means to the sibling's ends. Rather, in such cases, the new child is also loved and respected as an individual human being—he *is* used as a means but is also treated as someone with full moral status and therefore is not reduced to a *mere* means.

14. This point is insightfully developed in Wendler (2012). We focus our discussion here on the "ordinary life" or "daily life" aspect of the definition of minimal risk. The "routine examination" aspect of that definition is not relevant because routine medical or psychological examinations are undertaken for the benefit of the child, not for the benefit of others or the public good. A reviewer raised the possibility that responsible parents might allow their children to take on relatively minor risks for the public good because children, all of whom benefit from risks other children took in participating in past pediatric research, *have an obligation* to do the same so as to do their share and not "free ride." We find it plausible that all persons have an obligation to contribute to the public good (assuming they are capable of doing so), but we also believe that this obligation can be discharged in innumerable ways. Participating in pediatric research with no prospect of direct benefit would be one way of discharging, or partly discharging, this obligation. But, it would not be the only way—and there is no requirement that persons discharge this obligation while they are minors.

15. For an insightful discussion of some of the theoretical virtues discussed in this paragraph, see Kagan (1989, 11–5).

16. For helpful discussions of the distinction between ideal and nonideal theory, see Nielsen (1985), Sher (1997), and Murphy (2000).

17. Other candidates for the essential interests or basic needs of children include the following: nutritious food, clean water, safe shelter, protective clothing, and competent medical care when medical care is needed; freedom from slavery, other forms of wrongful coercion, and physical abuse; education and adequate stimulation; opportunities to play and experience enjoyment; the opportunity to develop independent interests and gradually find their own path; and the love, kindness, and attention of at least one committed, reasonably competent parent (DeGrazia, 2012, chap. 6). Lainie Friedman Ross has argued against the best interests standard in favor of a "constrained parental autonomy" decision-making model (Ross, 1998, 3). She explains that "a modified principle of respect allows parents to make intrafamilial trade-offs according to their own conception of the good[,] provided that each child's basic needs are procured" (Ross, 1998, 51). Although we similarly make reference to a child's "basic needs," we approach the concept differently. Rather than defining a baseline beyond which trade-offs among siblings and other family members are allowed, we discuss basic needs—or essential interests—to clarify how the best interests standard ought to be understood and to relate our discussion of a right to adequate protection to the best interests standard.

18. A reviewer asserted that we are mistaken to think of minimal risk in such an "additive" way (that the risks of minimal risk research could be added to those of everyday life). That reviewer states, plausibly, that "doing 'one more' activity doesn't increase risk to that person in a meaningful way. If the concept of minimal risk were used additively, it would make a lot of human subjects research impermissible." But surely small risks *can*—indeed, at some point *must*—be considered additively, explaining why the risk of a simple blood draw on a given day imposes minimal risk while the risk of 100 blood draws (on the same person) on a given day is much greater. We concur with the reviewer's implication in the second quoted sentence that it would be mistaken to regard minimal-risk research as impermissible. But, the basis of our agreement is not the claim that we cannot think additively about small risks but rather that a child's right to adequate protection from harm is compatible with the taking of relatively minor risks for the sake of public benefit.

19. Another option is to jettison the concept of best interests in the pediatric research context, an option that could be motivated by (1) appreciation that a literal interpretation of "best" suggests an implausibly strict protective standard and (2) an expectation that retaining the language of "best interests" will invite precisely this implausible understanding.

20. For authors who defend "best interests" as an appropriate standard for pediatric research ethics while also accepting the minimal risk standard, see, for example, Brock (1994), National Bioethics Advisory Commission (1998), Shore and Hyman (1999).

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