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A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Philosophy

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AN ETHICAL JUSTIFICATION FOR RESEARCH WITH CHILDREN

(Thesis format: Monograph)

by

Ariella Binik

Graduate Program in Philosophy

A thesis submitted in partial fulfilment
of the requirements for the degree of
Doctor of Philosophy

The School of Graduate and Postdoctoral Studies
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Abstract

This thesis is a contribution to the ethical justification for clinical research with children. A research subject's participation in a trial is usually justified, in part, by informed consent. Informed consent helps to uphold the moral principle of respect for persons. But children's limited ability to make informed choices gives rise to a problem. It is unclear what, if anything, justifies their participation in research.

Some research ethicists propose to resolve this problem by appealing to social utility, proxy consent, arguments explaining why it is permissible to expose children to some harm, and an argument concerning the appropriate balance between research harms and benefits. I argue that each of these is a necessary part of the justification for research with children, but that the argument concerning harms and benefits is under-developed. It relies on the concept of minimal risk, but minimal risk is inadequately justified.

I propose an interpretation of minimal risk. I defend the idea that minimal risk should be interpreted according to the risks of daily life. I reject the most prominent defense of daily life, which claims that daily risks are morally relevant because they replace, rather than add to, the risks a child would ordinarily face. Instead, I propose that these risks are part of a reasonable trade-off between personal safety and our ability to pursue meaningful lives. I then examine whose daily life should be captured in the concept of minimal risk. I reject arguments that minimal risk should refer to healthy children or the subjects of the research (including healthy and sick children) and propose instead that the referent should be children who are not unduly burdened by their lives. I argue that children are not unduly burdened when they fare well and defend the idea that children fare well when they possess sufficiently high degrees of the substantive goods of childhood. I conclude by analyzing a controversial case study using my interpretation of minimal risk. I draw on this case to argue that my interpretation offers clear guidance for research ethics review and contributes to a determination that is more plausible than its rivals.

Keywords: minimal risk, research with children, ethics, research ethics, clinical trials

Co-Authorship Statement

A version of Chapter 3 of this thesis will be published in the Journal of Medicine and Philosophy under the title “Why the debate over minimal risk needs to be reconsidered”. This paper is co-authored with Charles Weijer. Ariella Binik took the lead on the paper’s conceptualization, drafting and revision. Charles Weijer contributed to the paper’s conceptualization and revision.

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Chapter 1

Children and clinical research

Clinical research that examines the safe and effective treatment of diseases, disorders, and conditions affecting children offers one of the best prospects for improving the medical treatment of children. But the ethical justification for the inclusion of children in research raises difficulties. Generally, a research subject's participation in a trial is justified, in part, by informed consent. Informed consent helps to uphold the principle of respect for persons and their autonomous decisions. A research subject's understanding of the purpose, methods, risks, benefits, and alternatives to the research and subsequent consent to participate helps to ensure that people enrol in research trials only when participation is consistent with their values, preferences, and interests (Emanuel, Wendler, & Grady, 2000). Informed consent is often thought to be a necessary condition for the ethical conduct of most clinical research. But children's limited cognitive competencies and experience restrict their capacity to make informed choices about research participation, to understand the consent process, and their ability to withdraw (Thompson, 1990). This gives rise to a problem: If informed consent is a necessary component of the ethical justification for research with human subjects and children are unable to provide informed consent, then research with children seems to be impermissible.

Commentators have responded to this problem in a number of ways. Some have pointed out that informed consent by the child is not a necessary requirement for the ethical inclusion of children in research. It may be morally permissible instead for a parent or guardian to consent to enroll a child in research provided that a number of conditions obtain. One necessary requirement for the ethical inclusion of children in research—and the main focus of this thesis—is that a trial must offer a reasonable balance between research harms and benefits. For a trial involving children to have a reasonable balance between harms and benefits, the risks of non-therapeutic research procedures must be low. This much is uncontroversial. But it is unclear how much risk is

permissible and why a low degree of risk is justifiable. The aim of this thesis is to identify a justifiable threshold for the degree of risk permissible in research procedures that are not administered in the interests of a particular child subject. My main argument is that it is permissible to expose children to the risks of non-therapeutic research procedures when these procedures pose no more than ‘minimal risk’, understood as the daily risks faced by children who are not unduly burdened by their lives.

In this chapter, I will examine four arguments that aim to justify the inclusion of children in research. I will argue that each of these arguments is an essential part of the justification for research with children, but that the argument relying on the concept of minimal risk is under-developed. In the subsequent chapters, I will examine the explication and justification of minimal risk. In chapter 2, I will argue that minimal risk should be defined according to children’s daily lives and defend a novel interpretation of why the risks of daily life are morally relevant. In chapters 3 and 4, I will examine who should be the referent for minimal risk, that is, I will ask whose daily lives should be captured in the concept of minimal risk? In chapter 5, I will use my proposed interpretation of minimal risk to analyze a controversial trial that includes children as research subjects and assess the plausibility of my arguments.

I begin this chapter by elaborating on the ethical problem that complicates the inclusion of children in research. I then examine solutions offered to this problem in research ethics. I argue that one main strategy that aims to justify the inclusion of children in research is unsuccessful and then examine more promising strategies. I argue that the ethical inclusion of children in research depends on the success of four different arguments. The ethical justification depends on (1) arguments appealing to the concept of social utility, (2) arguments establishing that it is permissible to expose children to some degree of harm in the interest of others, (3) arguments establishing that informed consent is not a necessary condition for trial enrollment; at times, surrogate consent for children’s participation in research is consistent with respecting the moral worth of children, and (4) arguments proposing that it may be permissible to include children in a trial when the research offers subjects a reasonable balance between harms and benefits.

Each of these four arguments identifies a unique and necessary part of the justification for the inclusion of children in research. But one of these arguments—the

argument concerning harm benefit assessments—is under-developed. It relies on the minimal risk threshold, which constrains the degree of risk permissible in procedures on children that are not administered in the medical interests of a child research subject. But it does not adequately explicate and justify this concept. I conclude that a successful justification for the ethical inclusion of children in research depends on a better explanation of and justification for the concept of minimal risk.

Before elaborating on the problem concerning the inclusion of children in research, it is important to define the way in which I will use the term child throughout this thesis. The term ‘child’ is often used broadly to refer to all those below the age at which a person can provide legal consent to medical treatment (IOM, 2004; NIH, 1998). But a definition relying exclusively on age does not line up with our intuitions about how to treat children from a moral perspective. For example, on some occasions, it seems reasonable to respect a teenager’s decisions concerning medical treatment, irrespective of whether she is legally empowered to consent to medical treatment. Thus, what it means to be a child should refer to more than an age range.

While it seems clear that the concept of childhood should refer to more than an age, accurately capturing the meaning of childhood is complicated. Part of this difficulty is derived from the fact that children are not a homogeneous group. People commonly recognized as children possess varying and variable capacities. Further, it is difficult to specify an unambiguous and non-arbitrary threshold of capacities under which a person should be considered a child rather than an adult. Nonetheless, there are commonalities between the people commonly recognized as children. Schapiro summarizes these well. She writes:

Our basic concept of a child is that of a person who in some fundamental way is not yet developed, but who is in the process of developing. It is in virtue of children’s under-developed condition that we feel we have special obligations to them, obligations which are of a more paternalistic nature than are our obligations to other adults. These special obligations to children include duties to protect, nurture, discipline, and educate them....we feel bound to fulfill them regardless of whether the children in question consent to be protected, nurtured, disciplined,

and educated. Indeed, we think of children as people who have to be *raised*, whether they like it or not. (Schapiro, 1999, p. 716)

That is, part of what it means to be a child is to possess a developing, but not yet adequately developed ability to govern oneself. A child may be able to exercise some degree of autonomy in certain domains. For example, she might have the capacity to make decisions about preferred ice cream flavours or about which colour sweater to wear, but a child does not yet have the ability to make many important decisions, including decisions about medical treatment or participation in clinical research. I will use the term child to describe a person below the legal age of consent who does not pass the threshold of competency required to make autonomous decisions about important matters, including medical treatment or participation in clinical research. This interpretation is meant to capture infants as well as most young children and some adolescents. My definition falls short of offering a comprehensive analysis of what it means to be a child, but captures some common intuitions about childhood and about why children require additional protections in research. I will now turn to a consideration of the problem complicating the ethical justification for research with children.

1.1 The problem

Albert Jonsen writes that '[b]ioethical debates are often framed by dramatic events. Rational analysis and argument may be pushed aside by shocking stories. The history of the use of children as research subjects is a series of such shocking events' (Jonsen, 2006, p. s12). One event—Krugman and Giles's studies on infectious hepatitis (published in 1958)—triggered the controversy over the ethics of research with children in the latter half of the twentieth century. Krugman and Giles's research, which aimed to examine the natural progress of infectious hepatitis and eventually to develop a vaccine, involved the deliberate infection with hepatitis A of a cohort of children newly admitted to Willowbrook state hospital, an institution for disabled children in New York (Jonsen, 2006). Krugman and Giles argued that their research was ethically permissible because hepatitis was endemic at Willowbrook and the children admitted to the facility were very likely to contract the disease irrespective of their research participation (Krugman, 1986; Rothman, 1982). But newspapers and critics often describe the Willowbrook study as a

scandal that exploited especially vulnerable children (Jonsen, 2006). The Willowbrook study illustrates some of the unique features and difficulties of pediatric bioethics (Lantos, 2013) and is perhaps best understood as giving rise to a debate over what kind of research, if any, is justifiable with children as research subjects.

Inspired, in part, by the controversy over Willowbrook, Paul Ramsey and Richard McCormick initiated a debate about whether it is possible to morally justify research involving children. Some of McCormick's arguments were incorporated into the recommendations of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (henceforth, the National Commission), which served as the basis for the current U.S. Department of Health and Human Services (DHHS) regulations governing research with children (Jonsen, 2006). Moreover, the debate between Ramsey and McCormick raised difficult questions concerning the Willowbrook study, and research with children more generally, that remain unanswered. For example, they asked what, if anything justifies the inclusion of children in research? Is research that offers the child subject the prospect of direct benefit easier to justify than research that is not in the child's medical interests? Can the requirement for informed consent for research participation be replaced by a requirement for proxy consent?

Ramsey argued that the permissibility of all research involving human subjects depends on an absolute requirement to obtain informed consent. He claimed that the only way of respecting the moral value of human beings is by treating them as ends in themselves and never as mere means to other social goals. For Ramsey, a researcher treats a subject as an end and not a mere means only if the researcher obtains informed consent. His idea is that through informed consent, a research subject adopts the goals of the research as her own and, at least to some extent, becomes a partner or "joint adventurer" in the investigation (Ramsey, 1970, p.5). Thus, any attempt to include a person in research without her consent violates the requirement to respect the moral worth of persons. Ramsey's adherence to an absolute requirement for obtaining informed consent combined with the inability of children to provide informed consent suggests that on Ramsey's view, children are unsuitable research subjects. He writes:

[T]o experiment on children in ways that are not related to them as patients is already a sanitized form of barbarism; it already removes

them from view and pays no attention to the faithfulness-claims which a child, simply by being a normal or a sick or dying child, places upon us and upon medical care. We should expect no morally significant exceptions for this canon of faithfulness to the child. (Ramsey, 1970, p.12-13)

That is, parents and doctors have certain obligations towards their children, including the obligation to protect their children from harm. To consent on behalf of a child for her participation in research that is not in her interests would be to treat the child as a mere object in medical experimentation, which is a clear failure of the duty to protect children from harm. Thus, children's inability to consent to research participation suggests that it is impermissible to include them in research that is not in their interests.

After describing what seems to be an absolute prohibition on research with children, Ramsey identifies one important exception to his argument. He claims that while research that is not in the medical interests of children is always impermissible, parents can consent on behalf of their children for participation in research that aims to offer a child the prospect of medical benefit. That is, when the research relates to a child's recovery, parents can provide legitimate proxy consent for their children's participation. Ramsey's reasoning is that sometimes a physician-investigator is charged with the medical treatment of a child suffering from a condition for which there is no available standard remedy. In these cases, enrollment in research seems to be in the child's best interest. It is the best available option for the child and preferable to the alternative, which involves withholding an experimental drug from a child who has no other medical options (Ramsey, 2002; Ramsey, 1976).

It is hard to reconcile Ramsey's exception with his absolute requirement to obtain informed consent for research participation. Ramsey clearly wants researchers to pursue experiments that are in children's medical interests and he also wants to permit parents to consent on behalf of their children for participation in this kind of research. But this seems incompatible with his claim that respecting the moral worth of children in research requires informed consent. Ramsey is aware of this tension in his argument; he struggles with the ethical justification of exceptional or "borderline situations" of legitimate proxy consent (Ramsey, 1976) and ultimately suggests that the potential knowledge to be

gained from such research is too valuable to prohibit. He exhorts researchers and parents submitting children to research that is in a child's medical interest to knowingly do wrong, or "sin bravely" for the sake of the public good (Ramsey, 1976, p.21). Ramsey's position is perhaps best understood as prohibiting the ethical inclusion of children in research that doesn't offer the prospect of medical benefit but (reluctantly) endorsing their inclusion in research that offers the prospect of medical benefit.

McCormick responds to Ramsey by arguing that research with children is morally permissible irrespective of whether it is in a child's interests (McCormick, 1974; McCormick, 1976). McCormick argues that it is impermissible to subject children to research risks for which they would not consent if they were capable of consenting. But he argues that we can reasonably presume what a child would decide for herself if she were capable of making her own decisions (McCormick, 1974). Given that we know what a child would consent to, it is reasonable for a parent to consent on her behalf for participation in these activities.

How can we know what a child would desire if she could make her own decisions? McCormick argues that there are certain objective values that are definitive of our well-being. Further, it is reasonable to presume that people's decisions will be based on their desire to realize the values that are definitive of their well-being (McCormick, 1974). The idea seems to be that we can establish what someone desires by assuming that she desires those things that contribute to her well-being and then examining which things do, in fact, contribute to her well-being. Once we've identified the goods and activities that promote a person's well-being, we know what she would choose if she could do so.

McCormick's argument applies directly to research that offers a child the prospect of direct medical benefit. Research involving the administration of medical interventions that are in a child's medical interest aims to improve a child's health. Health is one of the things that contributes to a child's well-being. A child should consent to research that contributes to her well-being. Thus, it is reasonable to presume that a child would consent to participation in research involving therapeutic interventions (McCormick, 1974). McCormick concludes that this is a reasonable construction of a child's wishes and

consequently, proxy consent is legitimate; it is an accurate reflection of what a child would decide, if she could decide for herself.

McCormick then extends his argument to research that is not in a child's interests. He argues:

To share in the general effort and burden of health maintenance and disease control is part of our flourishing and growth as humans. To the extent that it is good for all of us to share this burden, we all ought to do so. And to the extent that we ought to do so, it is a reasonable construction or presumption of our wishes to say that we would do so. The reasonableness of this presumption validates vicarious consent. (McCormick, 1974, p.12-13)

That is, participation in clinical research—even that which does not offer the subject the prospect of direct medical benefit—is a desirable activity; it contributes to human flourishing and wellbeing. Children, like adults, should participate in activities that contribute to the well-being of others. It is reasonable to presume that children and adults will seek to do what they ought to do. Thus, parents can provide proxy consent for children's participation in research that benefits others because it is a reasonable presumption of what the child ought to—and accordingly would—choose.

Ramsey responds by pointing out that McCormick's argument for a social obligation to participate in research is consistent with the legitimate enrollment of anyone—including adults—in compulsory research without that person's consent (Ramsey, 1976). That is, McCormick's argument endorses enforced altruism, which is a difficult requirement to accept. In response, McCormick acknowledges that his position requires a moral obligation to participate in research but defends the imperative to participate in research. He claims that Ramsey's understanding of human beings is overly individualistic. Insofar as humans are social beings they all—irrespective of age—have an obligation to seek the means to preserve the health of others. As long as the risks are not excessive, it is morally obligatory to contribute to the welfare of others (McCormick, 1976). Thus, children are morally obligated to participate in some clinical research for the benefit of others.

Ramsey's argument against the ethical permissibility of including children in research prevails over McCormick's defense of pediatric research. One problem with

McCormick's argument is his claim that a child would choose to participate because the child should choose to participate. This claim treats a child as a morally responsible agent. But children are not moral agents; they have the capacity to become moral agents but this capacity is not yet actualized. Consequently, their moral choices cannot be relied upon to diverge from their inclinations (Ramsey, 1976). Thus, McCormick's argument that a child would choose research participation if she could choose for herself misunderstands the nature of childhood; it treats the child "as only a little adult" (Ramsey, 1976, p. 22).

Further, even if a child were a fully formed moral agent, there is no obvious reason to think that she would be subject to a moral obligation to participate in research. McCormick argues from the idea that human beings are social to the conclusion that we have an obligation to further the interests of other human beings by participating in research. But it is not clear why the sociability of human beings contributes to a requirement to further the interests of similar beings. Nor is it clear how the obligation to participate in research accrues to any particular person or how a given person should fulfill this obligation. Further, McCormick's claim that people's decisions are based on their desire to realize the values that are definitive of their well-being is not persuasive. People often make choices that conflict with their objective well-being, including unhealthy life-style choices, for instance. But if identifying values that are definitive of well-being does not give us a reason to think that a person will pursue these values, then there is no clear reason to think we can accurately predict what a child would choose if she could make her own choices. Thus, a parent cannot legitimately consent on behalf of her child on the basis that she can presume what the child's wishes would be. As a result, McCormick's argument fails to justify proxy consent for children's participation in research. It follows that there seems to be no ethical justification for the inclusion of children, who cannot consent for themselves, in research that does not offer them the prospect of direct medical benefits.

Ramsey's position holds up well to McCormick's criticisms. But it is also problematic. Ramsey's argument relies on the belief that research that is not in the medical interests of children is especially problematic and that it is ethically permissible

to include children in research that is in their medical interests. McCormick shared this belief, as did his interlocutors. For example, William May argues:

There is no serious debate among authorities, medical, legal, or moral, when the experiment in question is therapeutic, that is, when it is designed to secure some benefit for the subject. In cases of this kind, consent to the experiment can be given by others (parents, guardians, etc.) on behalf of persons incapable of giving proxy consent for themselves...there is unanimity that in therapeutic situations such proxy consent is morally justifiable. (May, 1977, p. 21)

But this idea bears careful examination. Ramsey's defense of research that offers a child subject the prospect of medical benefit depends on the idea that in some cases, standard medical therapies are exhausted and experimental procedures offer a child the best remaining option for recovery. That is, the research is therapeutically warranted; it might be a child's best (or only) prospect for recovery. As Ramsey argues:

[Once] other remedies have failed to relieve their grave illness, it is reasonable to believe that the administration of a drug as yet untested or insufficiently tested on human beings, or the performance of an untried operation, may further the patient's own recovery. (Ramsey, 1970, p.11-12)

Ramsey's point is that there is no equally good or better alternative for the medical treatment of certain child patients. The experimental intervention administered in the context of an experiment is justifiable because the alternative, that is, withholding the experimental intervention from the child, would prevent her from receiving her best prospect of recovery. But Ramsey's claim that research is the only available alternative means of receiving the treatment is not persuasive. He neglects to consider an alternative: the experimental intervention could be administered to the child outside of the research context, that is, as part of the child's medical care. In this way, one could achieve the best therapeutic ends for the child outside of a trial. The child would receive the experimental intervention and she would do so without being volunteered for trial participation. Thus, on Ramsey's view, it seems that proxy consent for children's participation in research that is in their interests is not the best way to further the medical interests of a child. Consequently, it is unjustifiable.

A second problem with Ramsey's justification for research that offers medical benefit is that it relies on the problematic idea that some research is purely in the interests of the child research subjects. Ramsey's argument is based on the therapeutic benefit a child stands to receive from research participation and never on the likelihood of benefits that could flow from the experiment for other children. He thinks that justifiable proxy consent for children's participation in research is appropriate only when the research is in the interest of the children participating. He claims that "no parent is morally competent to consent that his child shall be submitted to hazardous or other experiments having no diagnostic or therapeutic significance for the child himself" (Ramsey, 1970, p.13). The idea that some research is conducted purely for the benefit of the research subject while other research is conducted for the sake of broader social goals is often referred to as the distinction between therapeutic and non-therapeutic research. Therapeutic research is understood as offering medical benefit to the subject whereas non-therapeutic research is designed to further biomedical and behavioural research: that is, to "advance the maladies that afflict mankind, and to enhance the human good" (May, 1977, p. 19). Ramsey's argument suggests that only therapeutic research can be permissible because it offers children direct benefits while non-therapeutic research is impermissible.

However, the distinction between therapeutic and non-therapeutic experiments is problematic (Levine, 1986, p.8-9; Levine, 1999). Clinical trials cannot be clearly divided into these two categories; most clinical research involves a combination of therapeutic and non-therapeutic procedures (Levine, 1986; Freedman, Fuks, & Weijer, 1992). Therapeutic procedures are those administered with therapeutic warrant. They often involve the same treatment or diagnostic interventions that a physician administers to her patient in the course of standard care. Non-therapeutic procedures, on the other hand, are administered in order to answer the study question. Clinical research that offers children the prospect of medical benefit also contains non-therapeutic procedures. For example, a study aiming to evaluate the efficacy of a new drug for the alleviation of pain in children with cancer involves some therapeutic procedures, such as the administration of a drug aimed to control pain. But this study will also involve non-therapeutic procedures carried out purely for research purposes such as the review of medical records for data collection, additional clinical examinations solely for data collection purposes, diagnostic

investigations such as blood tests or radiological investigations that have no bearing on clinical care (Weijer & Miller, 2004).

The insight that all therapeutic research involves non-therapeutic procedures has an important impact on Ramsey's justification for the inclusion of children in research that is in their interests. Ramsey's justification relies on the idea that some research is purely in the interests of children. It is permissible because it offers a child the best prospect for recovery and no aspect of it is administered to benefit other children. Research procedures that are not administered with therapeutic warrant are strictly prohibited (Ramey, 1970). Thus, on Ramsey's view, non-therapeutic research procedures—like data collection and extra examinations—are impermissible for those who cannot provide informed consent. Given that all therapeutic research—including research that aims to offer the child subjects the prospect of direct benefit—includes both kinds of procedures, Ramsey's argument suggests that it is never permissible to involve children in any research. If any kind of research with children is permissible, it would have to be because of the potential benefit the research can offer to future children or children suffering from the same conditions or disorders and not because of the potential benefit for a particular child. Thus, Ramsey's idea that research that is in the medical interests of children should be understood as a reasonable exception to the absolute requirement to obtain informed consent for all research participation is not persuasive. Insofar as children's participation in research that is in their medical interests also exposes them to research risks that are administered without therapeutic warrant, research that is in a child's medical interests also seems to violate Ramsey's requirement of moral respect for children. Thus, according to Ramsey's requirement for informed consent, research that offers children the prospect of medical benefit is ethically problematic, just like research that does not do so. It follows that the problem concerning the ethical inclusion of children in research is more pressing than Ramsey and his interlocutors realized. There seem to be no circumstances in which it is morally permissible to include children in research.

1.2 Can expanding the concept of benefit justify research with children?

The problem concerning the ethical inclusion of children in research is more pressing than Ramsey realized; all research, including research that is in the medical interests of children (i.e. that offers children the prospect of benefit), poses ethical challenges. But this has not been fully appreciated in the literature concerning the ethics of research with children. Following Ramsey's lead, some commentators assume that research that offers children the prospect of direct medical benefit is ethically permissible. Accordingly, some seek to justify the ethical inclusion of children in research by expanding the concept of benefit. Proponents of this kind of argument claim that our common understanding of benefit is overly narrow. While children may not derive medical benefits, their participation may benefit them in other ways. I will argue that this strategy is not successful. Identifying new sources of benefit incurred by research participation does not justify children's exposure to research risks.

Some commentators argue that research that is not in the medical interests of children may be permissible because it contributes to a child's moral education (Beecher, 1970; Bartholome, 1977; Ackerman, 1979). That is, the concept of benefit should be broadened to include the benefits of moral education. For example, Bartholome argues that research participation may help children to "become sensitive to moral obligations"; it can help to foster in children a disposition towards choosing that which is good (Bartholome, 1977, p.17). Further, a trial's potential to steer a child's development into a socially responsible adult justifies her participation in "no risk clinical research" (Bartholome, 1977, p.17). More generally, these arguments conclude that children's participation in some research is justifiable because it provides them with educational—if not medical—benefit.

While it seems reasonable to conclude that some children may derive educational benefit from research participation, this potential benefit cannot justify research with all children. As proponents of this argument recognize, identifying moral education as a benefit of research participation excludes some groups of children from research participation. Any child lacking the cognitive capacities necessary to learn the value of

altruism is unable to benefit from research participation. It follows that she is an inappropriate research subject (Ackerman, 1980). But this means that infants and some very young children cannot be research participants. Consequently, expanding the concept of benefit to include educational benefits does not provide an ethical justification for research with all children.

David Wendler proposes a different way of broadening the notion of benefit that aims to justify research with children of all ages; he argues that benefit should refer not only to medical benefits but also to benefits derived from contributing to a valuable project (Wendler, 2010;Wendler, 2012). Wendler's idea is that children's contributions to valuable projects, even when they are too young to take moral responsibility for these contributions, have the ability to improve their lives. That is, the fact of having participated in a valuable project makes one's life better. Research with children is permissible because it is a valuable project that can offer child participants the prospect of benefit. He concludes that children's participation in research that does not offer them the prospect of direct clinical benefit is permissible because it does offer them some prospect of non-clinical benefit, that is, the benefit derived from their contribution to a valuable project. His argument improves upon Bartholome and Ackerman's by suggesting a reason why it is permissible to include all children, including infants and very young children, in clinical research. Given that Wendler's is the most recent justification for research with children, I will examine it in more detail than the previous arguments.

Wendler's argument that contributions to a valuable project have the ability to improve the lives of human beings is derived from his account of human interests. Wendler identifies five things that are in our interests: (1) It is in our interest to fulfill our biological needs. That is, a person's biological needs, including food, water, and sufficient sleep, are necessary for a child to fare well (Wendler, 2010, p. 130). (2) It is in our interest to achieve our experiential preferences (Wendler, 2010, p.130). Wendler provides no precise definition of what he means by experiential preferences, but claims that it is in our interest to experience certain states of mind and to avoiding others. For example, he claims that it is in everyone's interest to be content with oneself and the world (Wendler 2010, p.130). (3) It is in our interests to be involved in meaningful

relationships. For Wendler, meaningful relationships can occur between people, animals, the environment or with particular projects (Wendler, 2010, p. 130). For example, an individual may have a meaningful relationship with a worthwhile project such as building homes for the homeless or performing in a symphony (Wendler 2010, p.130). These relationships are meaningful because they give people an opportunity to make contributions to a worthwhile outcome. (4) We have an interest in achieving worthwhile personal goals. According to Wendler, a person's personal goals should be understood broadly as including her preferences, desires, hopes, dreams, and projects (Wendler 2010, p.131). For Wendler, the success of one's life depends to a great extent to how well one pursues one's personal goals, and the extent to which one achieves them (Wendler, 2010, p. 131).¹ (5) Our lives are improved by human achievements, which are "accomplishments and contributions that are valuable for us given the kinds of beings we are" (Wendler, 2010, p.133). For example, contributing to a project that saves many lives is important, irrespective of whether it is in line with a person's personal goals and preferences. Wendler's point is that what is valuable for a person is not necessarily exhausted by what she wants, prefers or strives to accomplish in her life. A good life is one that involves good accomplishments, which may or may not be preferred accomplishments.

Wendler's main innovation is to argue that worthwhile projects can benefit a person in more ways than are commonly recognized. He points out that in general, commentators think the value a person derives from her participation in a project is thought to derive from the active contribution she makes to that project. For example, the value derived from participation in a project aiming to build homes for the homeless is thought to lie in understanding the project, embracing its goals, and contributing in some way to its realization (perhaps by fundraising, bricklaying or locating a place for the new construction). This belief is based on the idea that our experiences and (worthwhile) personal goals are primarily responsible for advancing or thwarting our interests (Wendler, 2010) and it follows that only autonomous people can derive value from their

¹ Wendler acknowledges that some personal goals are not valuable and that pursuing these goals will not lead to an improvement in one's overall life but says little about how to parse the worthwhile from the non-worthwhile goals.

participation in a worthwhile project.

However, Wendler argues that this understanding of benefit is too narrow; it is not uniquely one's contribution to a project that matters. Instead, "the mere fact of being part of a worthwhile effort is valuable, connecting one with others and with a project of significance and meaning" (Wendler, 2010, p.130). His idea seems to be that involvement in worthwhile projects is valuable in and of itself. Our physical participation in valuable projects has the ability to improve our lives. It follows that contributions to a project can improve lives even if they are undertaken by people who are unable to take moral responsibility for their choices (or other's choices on their behalf), such as children (Wendler, 2012; Wender, 2010). Wendler writes:

It seems clear that making a contribution can be in an individual's interests even when it does not have a positive impact on him; for instance, even when he does not enjoy making the contribution and does not learn from it. Making a contribution can be in an individual's interests when it represents an important accomplishment for him. Put in terms of the five categories of human interests, making a contribution to a valuable project can be in an individual's interests when it represents a valuable human achievement or involves a meaningful relationship, even when making the contribution does not satisfy the individual's experiential preferences or realize her personal goals. (Wendler, 2010, p.178)

His reasoning seems to be that a person need not become a "joint adventurer" to benefit from a project. That is, she need not understand, embrace, and actively contribute to a project to benefit from it. She must simply be physically involved in it. As long as the project is a valuable human project, achieving it improves the quality of a person's life.

Wendler makes his case by drawing on the intuition that a life involving contributions to valuable projects seems more valuable than a similar life involving fewer or no contributions. He offers several case examples to support this idea. He begins with cases in which someone's life is made worse by her participation in a negative project even though she was too young to take moral responsibility for her actions. Wendler asks us to consider a two year old who finds a loaded gun in her parents' house and innocently hits the shiny trigger, which discharges a bullet that kills the child's nearby companion (Wendler, 2012). Wendler claims that this experience is bad for the child, even if he is

not morally responsible and is not affected physically or emotionally by the experience itself or its later consequences. He writes:

We prefer for our children, for their own sakes, that they not kill an innocent person... It would be very bad for an individual to willingly kill a friend as an autonomous adult. It is less bad for the individual innocently to kill a friend as a 2-year-old. However, it would be even better, for the individual's own sake, to never kill a friend. (Wendler, 2012, p.27)

Wendler also asks us to consider Irmgard Hunt who—while out on a walk with her mother at age three—is photographed sitting on Hitler's knees. At the time of the photos Irmgard is too young to resist or understand the Nazi cause but as an adult, Irmgard worries that the pictures may have been used by Nazi propagandists to increase Hitler's popularity. Further, she worries that her appearance in these pictures may count as a small contribution towards furthering the horrors of the Second World War (Wendler, 2010, p.205). As Wendler understands it, Irmgard's concern is reasonable; she “recognizes that it would be worse for her if she” made this passive contribution to a horrific cause (Wendler, 2010, p.205). He concludes that these examples serve as evidence that passive contributions to projects can have negative effects on our interests.

Wendler then claims that in the same way that negative contributions, active or passive, can make a person's life worse, positive contributions can improve someone's life, even if these contributions were undertaken non-autonomously. In the same way that a life that includes the accidental killing of a friend seems worse than a life without an accidental killing, a life that includes a positive contribution, like contributing to the civil rights movement of the 1960s, seems better than the same life absent that contribution (Wendler, 2012, p.28). He argues:

[T]he contributions we make as children, whether we harm or help others, are things that we do. They become part of our lives. This suggests that such contributions can benefit children by promoting their interests in having a better life overall. This is true independent of the extent to which the children learn from making the contribution. The fact of making a causal contribution is an independent source of benefit for the participating children. (Wendler, 2012, p.28)

For Wendler, the causal contributions we make become part of our life's narrative and

influence how well our lives go (Wendler, 2012). Thus, contributions to valuable projects are good for us independent of a person's goals or preferences; they make our lives better overall (Wendler, 2010).

Wendler then applies this argument to the justification of pediatric research that doesn't offer children the prospect of direct medical benefit. He argues that pediatric clinical research is a valuable project; it is vital to improving the medical care of children (Wendler, 2012). There are at least two ways in which a child may derive benefit from her participation in this valuable project: First, the child may come to embrace the contribution as an adult, which would improve her life by increasing the number of personal worthwhile goals she has achieved. Second, the contribution a child makes to clinical research can improve her life—even if she never comes to embrace the goal of the research—by adding to her life the fact of having made a contribution to a valuable project (Wendler, 2012). The fact of making a causal contribution is an independent source of benefit for the participating children (Wendler, 2012). Thus, while some research does not offer child subjects the prospect of medical benefit, it can improve their overall lives by providing them with the fact of having participated in a valuable project.

For example, a child's non-autonomous participation in the trials that developed a safe and effective vaccine for rotavirus is permissible because it improves her life; her non-autonomous contribution becomes part of her life's narrative and makes her life better (Wendler, 2012). If we evaluate the quality of two similar lives, one that involves a contribution to the development of the rotavirus vaccine and one that does not, Wendler thinks that we would clearly prefer the former. Thus, helping others through research participation can be in children's interests, and consequently, can justify the exposure of children to some non-therapeutic research risks, even for very young children who are not autonomous.

Wendler does not think that the benefits derived from a child's participation in valuable projects justify their participation in any trial. His justification is subject to at least two important constraints: the "risk allowance" requirement and the "risk ceiling" requirement (Wendler, 2010; Wendler, 2012). The risk allowance requirement only permits children to be enrolled in research that doesn't offer clinical benefit "when the risks are low" (Wendler, 2012, p.24). The risk ceiling requirement prevents children from

being enrolled in research that doesn't offer them the prospect of direct medical benefit "when the risks are high, no matter how much the research might benefit others" (Wendler 2012, p.24). Thus, Wendler's argument is meant to justify pediatric research that involves only low and never high non-therapeutic risks.

Wendler's claim that there are a series of goods that contribute to our interests is plausible. Some of the items on his list, including biological needs and meaningful relationships, seem to be important parts of our welfare. But his claim that physical contributions to valuable projects—even those that have no effect on a person—make her better off, is not persuasive. Consider the following example. Suppose that a sleeping infant carried by her parent is photographed in a 'Take Back the Night' rally protesting violence against women. This photograph appears on the front page of a major newspaper, makes the public more sympathetic, and helps the rally to achieve its aims. Nonetheless, the infant's parent never notices the photograph and the infant never comes to learn of her passive contribution to the rally or its goals. It seems clear that the infant participated non-autonomously in a project with the valuable goal of reducing violence towards women, but it is hard to believe that the physical contribution alone, without the infant ever coming to know of the event or embracing its goals would have any impact at all on the photographed infant's life. But Wendler's claim is that this kind of passive involvement makes the infant's life better, irrespective of whether she later learns about or embraces her involvement.

Further, one can make sense of some of Wendler's examples without accepting the idea that physical contributions to projects impact our lives. Wendler argues that Irmgard Hunt's life would be better if she could be certain that she had not contributed to Nazi propaganda. I agree, but for a different reason. The negative impact on Irmgard's life seems to be derived from the fact that she may have been connected to Nazi propaganda while she prefers to have had no connection to Hitler. That is, discomfort about Irmgard's case can be captured by the idea that her involvement conflicted with one of her preferences. But if we can make sense of this case with reference to the notion of preference satisfaction, then it offers no clear reason to support Wendler's claim that causal contributions to projects affect our interests.

Wendler's examples aiming to establish that non-autonomous participation in clinical research improve someone's life are also problematic. He draws on the example of a successful clinical trial to make his case, but once we consider trials with inconclusive or negative outcomes (which account for a significant number of clinical trials), Wendler's argument is less plausible.

Wendler uses the example of trials that helped to identify safe and effective vaccines for rotavirus, which kills thousands of children each year (Wendler, 2012). He argues that the vaccines developed in these trials have the ability to yield enormous benefits and to save many children's lives (Wendler, 2012). He then asks us to put ourselves in the shoes of a parent faced with the following choice for their child: their child might have (1) a good and decent life or (2) a good and decent life that also includes participation in one of the rotavirus vaccine trials. Wendler thinks that it would be reasonable for a parent to prefer life 2 for her child, even if this choice also involved exposing her child to some research risks, because "[a] life that includes a contribution to such valuable studies seems better for the individual whose life it is compared to the same life absent that contribution" (Wendler, 2012, p.29). He concludes that a life involving a purely physical contribution to the valuable cause of clinical research is better than one without this contribution because it promotes a child's interests.

This claim is unpersuasive if we take into account clinical trials that are not successful. Consider, for example, a study examining the efficacy of hypothermia therapy in children who have suffered traumatic brain injury (Hutchison, et al., 2008). Hypothermia therapy has been shown to significantly improve survival and neurological outcomes in rodent models of traumatic brain injury. Consequently, researchers conducted a randomized controlled trial including 225 children to assess whether hypothermia therapy started within 8 hours of injury may help children who have severe traumatic brain injury (Hutchison et al., 2008, p.2448). The trial found that hypothermia therapy in children with severe traumatic brain injury does not improve the neurological outcome and may increase mortality (Hutchison et al., 2008, p.2454).

The hypothermia therapy trial is valuable because it yields some evidence that in spite of evidence from animal models and some evidence from trials with small sample groups of children, hypothermia therapy for children may not be a useful intervention for

children with brain injury. This information may become instrumental in the improved medical treatment of other children with traumatic brain injury. It may also help to prevent additional harm to future children who suffer a similar injury. But if we analyze this example according to Wendler's calculus, that is, if we consider the overall value of a life involving participation in this study and the overall value of a second similar life absent this contribution, it seems reasonable to conclude that the life without this contribution seems preferable or at least equivalent. In other words, when considering purely physical contributions to a valuable clinical trial with negative outcomes, there is no reason to think that a life involving trial participation is better than one that does not.

Wendler's argument relies on the claims (1) that clinical research is a valuable project and (2) that a child's non-autonomous participation in clinical research improves her life overall. The first claim is convincing. Even trials that yield negative results or harm children have the ability to generate results that will improve the medical care of children. And as long as these trials are well-designed, meet ethical constraints, and seem reasonably promising *ex-ante*, the fact that they yield negative consequences does not render them impermissible. Wendler agrees with this insight (2012). But Wendler's second claim that non-autonomous participation is in a child's interests seems to rely on the research having a successful outcome. When we consider examples of unsuccessful research or research that harms child subjects common moral intuitions do not line up with Wendler's. Lives that do not involve some contribution, even non-autonomous, to a project that harms children, even if this harm contributes to improved care for future children, are arguably better than lives that do not. Thus, Wendler's claim that participation in the valuable project of clinical research adds an objective good to a child's overall life is not convincing.

Peter Singer also objects to Wendler's claim that children's lives are improved by contributions to worthwhile endeavours for which they have no moral accountability. He argues that our reactions to acts for which we are morally responsible can be felt appropriately. But the "moral sensitivity" we might experience for actions undertaken in situations in which we were not morally responsible (including childhood) is inappropriate (Singer, 2011). That is, our lives do not go better "if, without any moral responsibility on our part, we contribute to a beneficial project" (Singer, 2011, p.115) and

to think that our lives to go better is to allow “moral sensitivity” to “spill over into an area where it does not belong” (Singer, 2011, p.115). His claim suggests that non-autonomous participation in clinical research is not liable to make a life better or worse. It simply has no bearing on the quality of one’s life. It follows that Wendler’s claim that non-autonomous participation in a clinical trial is an objective good that improves a child’s life is not convincing. A life involving non-autonomous participation in some trials seems less desirable than one absent this contribution or perhaps most plausibly, non-autonomous participation has no necessary bearing on one’s life.

Moreover, even if Wendler’s argument that purely physical contributions to a valuable project are objective goods, this would be insufficient to justify children’s inclusion in research. More generally, arguments aiming to establish that research participation offers children benefits other than medical benefits do not offer a persuasive ethical justification for research with children. Clinical trials are not rendered uncontroversial by virtue of offering the prospect of benefit, medical or otherwise. Some trials that offer the prospect of medical benefit are ethically impermissible. For example, a trial offering subjects the prospect of medical benefit that is significantly lower than the benefit they would receive during the course of standard care is unethical; it unfairly deprives research subjects of competent medical care. In addition, a trial offering child subjects the prospect of some medical benefit in addition to highly invasive interventions administered without therapeutic warrant is ethically impermissible. It exploits the vulnerability of children by exposing them to high degrees of research risk purely in the interest of others. The ethical permissibility of a trial seems to depend on more than benefit. The morally relevant consideration is not uniquely whether a trial offers some prospect of benefit but whether the potential benefit of a trial stands in reasonable relation to the trial’s risks. That is, the moral justification of a trial depends on establishing that its harms and benefits are appropriately balanced.

At times, commentators seem to recognize that benefit alone does not justify a trial. Bartholome argues that educational benefit justifies only “no risk” research (Bartholome, 1977, p.17) and Wendler writes that enrolling children is consistent with their interests only “when the risk/benefit ratio of the research is at least as favorable as that of available alternatives” (Wendler, 2012, p.24). Further, he recognizes the

constraints of the risk ceiling and risk allowance conditions. But commentators don't seem to recognize the implications of these comments. If the potential benefit of a trial is only a morally relevant part of the justification for children's inclusion in research when this benefit is reasonably balanced with research risks, then the justification of research with children depends on an explanation of how harm-benefit assessments in research involving children should proceed. Identifying new sources of benefit does not, on its own, facilitate this assessment in any obvious way. For instance, Wendler does not explain how to assess the degree of benefit derived from non-autonomous participation in clinical research. Further, he does not explain how to measure these potential benefits against the risks involved in research participation. Thus, it is not clear whether, and if so how, the benefits derived from non-autonomous participation in clinical research offers a favourable risk/benefit ratio. While understanding what counts as a benefit may be important, Wendler's argument is, at best, incomplete. The ethical justification of research with children depends not only on identifying a potential source of benefit from research participation, but also on a more fundamental question, that is, when do research risks stand in reasonable relation to their potential benefits. Consequently, even if commentators could successfully establish that benefit should be broad enough to account for non-medical benefits, these arguments would not offer a moral justification for children's inclusion in research.

Unlike Ramsey, current commentators do not think that research can be purely in the interests of children. In other words, most recognize that no clear distinction can be drawn between therapeutic and non-therapeutic research. But they do assume that identifying benefit in a trial goes a long way towards justifying the enrollment of children as research subjects. This assumption diverts attention from morally relevant considerations about whether research risks are reasonable in relation to potential benefits to be gained from a trial that proposes to include children as research subjects.

1.3 Four solutions

Expanding the concept of benefit may not help to justify the inclusion of children in medical research, but four arguments in research ethics do contribute to an ethical justification for research with children (irrespective of whether it offers the prospect of

medical benefit). These arguments aim to explain why, and under what conditions, it is morally permissible to include children in research. Commentators aim to justify the inclusion of children in research (1) by appealing to social utility, (2) by arguing that it is permissible to expose children to some degree of risk in the interest of others, (3) by arguing that informed consent is not always a necessary ethical condition; proxy consent for children's participation is consistent with respecting the moral worth of children, and (4) by arguing that the inclusion of children in research is permissible when the research offers a favourable balance between research risks and benefits.

In the following, I explain how each argument identifies a unique and necessary component of the justification for the inclusion of children in research. Moreover, I will point out that one argument—the argument concerning harm-benefit calculations—is under-developed. It relies on the concept of “minimal risk” but does not adequately justify its interpretation or application. A convincing justification for research with children requires the clarification of the minimal risk concept and the combination of this concept with successful aspects of the other arguments aiming to justify pediatric research.

(1) The first argument aims to justify the inclusion of children in research by appealing to social utility. The argument proceeds as follows: the inclusion of children in research is in the interests of children as a group; it helps to establish the safety and efficacy of standard interventions for use in children and to work towards the treatment of diseases and disorders that are unique to children. Excluding children from research will compromise the progress of information about the medical treatment of children in general. Thus, it is in the long-term interests of children as a group not to exclude them from research participation. For example, Capron argues that excluding children from research comes at the expense of understudying children's responses to standard drugs. In the absence of research with children, drugs used and tested in adults would simply be prescribed to children with lowered dosages. This is problematic because children are not simply “little people” (Capron, 1971); they differ from adults in various ways, including metabolic response, enzymatic and excretory systems, and skeletal development. These differences contribute to variations in the ways in which adults and children respond to drugs and medical treatments. Thus, generalizable knowledge about the safety and

efficacy of medical treatments for children cannot be obtained uniquely through extrapolation from studies conducted with adults (Shirkey, 1999; Ackerman, 2001; Spriggs & Caldwell, 2011; IOM, 2004; Laventhal, Tarini, & Lantos, 2012).

Levine elaborates by emphasizing the risks involved in treating children without the knowledge derived from trials. He argues that in the absence of trials, doctors would have to distribute the unknown risks of drugs in children unsystematically. This practice increases the frequency of the occurrence of risks and minimizes the probability of their detection (Levine, 1986). He proposes that conducting trials with children is preferable because it allows the first administration of drugs in children to be conducted under conditions more controlled and carefully monitored than is customary in medicine. Under these conditions, it is likely that adverse drug reactions unique to children would be identified earlier and drugs either discontinued for use in children or involve appropriate warnings (Levine, 1986). Levine concludes that excluding children from research unjustly deprives children as a class of the benefit of safe and effective drugs (Levine, 1986). The common thread in these arguments is that excluding children from clinical research would, in the long run, leave them “therapeutic orphans”, that is, children as a group would be rendered orphans of proper therapy (Shirkey, 1968), which is an even greater risk than the research risks faced by individual child research subjects.

The idea that research participation contributes to children’s well-being generally, and reduces children’s exposure to risks that arise from the off-label prescription of medications tested only in adults, is essential to the justification of research with children. It helps to explain why clinical research is important and why parents and researchers might want to subject their children to research risks that do not necessarily offer the prospect of corresponding medical benefit. Arguments from social utility emphasize that clinical research is a valuable project and that children who participate in it are not subjected to risks simply because it is easy to exploit those who are unable to protect their own interests but because their participation—and its accompanying exposure to risks—has the ability to produce significant social value. For example, children’s participation in trials aiming to develop a vaccine preventing rotavirus contributed to the development of knowledge that can help to save thousands of lives a year.

However, appeals to social utility can offer only a partial justification for research with children. Arguments from social utility suggest that as long as the social value of the research is sufficiently important, it is permissible to expose child research subjects to any degree of risk. That is, there is no upper limit on the degree of risk that might be found permissible. Thus, these arguments seem to legitimize high degrees of risk to particular children on the basis of the benefits research may confer to others. And this kind of reasoning neglects researchers' and parents' obligations to particular children. It is also vulnerable to Ramsey's criticism that including children in research fails to respect the moral worth of a child. Thus, the social utility of clinical research is not a sufficient condition for the justification of a trial involving children. It does not explain the conditions under which one can, consistent with respect for the moral worth of children, expose any particular child to research risks for the benefit of others.

(2) A second kind of argument fills in part of this gap by explaining why it may be permissible, at times, to expose a particular child to risk purely in the interest of others. One need not always act in a child's best interests. At times, it is permissible to expose a particular child to risks purely in the interest of others. There are at least two such occasions: when the risks to a child are counterbalanced by the benefits offered to another family member or to the family as a whole and when the risks to a child are undertaken in the interest of important social goals, like the success of a social community.

This argument of social communities is derived from the recognition that children are often members of intimate families. Families have goals and interests that cannot be reduced to those of one member and to which the interests of an individual child are inextricably bound. At times, the intricacies of family life require that a certain member's interests be compromised in the interests of another member or in the interest of the group as a whole (Ross, 1998, p.43). It follows that decision making should take into account not only the individual's interests but her interests as part of a family. To this end, it may be permissible for parents to make intra-familial trade-offs that benefit the family unit as a whole (Ross, 1998). For example, it may be reasonable for parents to move a child away from established social relationships to take up a new job in a different country or to force a child to wait long hours in an emergency room while her

sibling receives medical treatment (Ackerman, 1980, p.96). Thus, it may be permissible to expose children to risks when it is beneficial for another family member or for the family as a whole.

It may also be permissible to make decisions that are not in the interests of a child and expose her to risk because it helps to promote important social goals, like communal living. The success of social life depends, in part, on the existence of a community that adheres to a common set of moral principles, that is, a moral code (Ackerman, 1980). To contribute to the continued success of social living, parents should educate and habituate children to share in the moral principles of the common code. To this end, it may be reasonable for a parent to teach her child about common moral principles (such as showing respect for others and keeping promises), encourage her to follow these principles, and scold her if she fails to do so. These interventions are not justifiable because they benefit a particular child (although they might). Instead, they are permissible because of their ability to inculcate in a child adherence to sound moral principles that contribute to her development into an adult with sound moral behaviours, which promotes the successful future of a moral community (Ackerman, 1980). In both of the above cases, there are limits on the extent to which a child's interests may be sacrificed for other ends. But it is important to recognize that under certain circumstances, it is permissible to include children in activities that are not in their interests for the sake of others.

These insights about the permissible treatment of children have important implications for the justification for research with children. Ackerman and Ross point out that certain kinds of interventions that are not in a child's interests are morally legitimate in the context of family life or for the benefit of communal living. More generally, their argument suggests that, at times, it is permissible to submit children to activities that are not in the child's best interests and may expose them to harm because these activities contribute to important social goals. This point has important implications for the justification of non-therapeutic research procedures on children. Clinical research is an important social goal; it contributes to the success of a community by improving the health of its members. Given that clinical research is a valuable social endeavour and that children may be exposed to some harm to promote social ends, it may be permissible to

expose children to research risks that are not in their interests but help to promote the health of the broader community.

These arguments successfully establish that at times, it may be permissible to expose children to risk for the sake of others and that it is in the medical interests of children as a group to participate in research. But they do not provide a successful justification for research with children. These arguments do not explain why it is permissible to expose a child, who cannot consent for herself, to research participation. Further, the above considerations do not adequately explain the conditions under which it is permissible to expose a child to risk in the interest of others. The next two arguments take up these tasks.

(3) A third kind of argument fills in another component of the justification for research with children by explaining that informed consent is not a necessary condition for the ethical inclusion of children in research; at times, it may be permissible for parents to provide surrogate consent for their children's enrollment. Proponents of this argument claim that Ramsey's absolute requirement for informed consent for research participation is inappropriate in the case of children. The requirement to obtain informed consent arises from the requirement to respect a person's capacity for self-determination. But children are not capable of autonomous decision-making. Consequently, they are not subject to an absolute requirement to obtain informed consent. It follows that including children in research does not necessarily fail to respect them as morally valuable beings (Ross, 1998; Levine, 1986; Ackerman, 1979; Freedman, 1975).

Freedman points out that the requirement to obtain informed consent does not seem to apply to children. In the case of adults, informed consent serves to respect the autonomy and dignity of the individual. But "a child is (morally) a different sort of thing than is an adult; we must adjust our relations with them according to their claims upon us" (Freedman, 1975, p.38). That is, children are not autonomous; they cannot express autonomy and dignity through choices. It follows that there is no reason to think that a child should decide whether to participate in research. Freedman thinks that children do have rights but that these differ significantly from the rights of adults. Unlike adults, children have no right to liberty. They do, however, have a right to custody (Freedman, 1975). Children's right to custody incurs an obligation from a parent or guardian to

protect and aid in a child's development but not to respect her uninformed and non-autonomous decisions. Freedman writes: "[I]n consequence of this right [to custody] we must do what we may to promote the welfare of the child; we must abstain from doing what will injure the child, physically or otherwise; and, as far as this right goes, we are at liberty to deal with the child in ways which neither help nor hurt" (Freedman, 1975, p.38). On this view, it is legitimate for parents to provide surrogate consent for "harmless experiments on children" as long as they are well-designed, involve highly trained experimenters, and meet the other canons of medical ethics (Freedman, 1975, p.38). Restricting a child's ability to make the decision is permissible because it does not infringe on the child's right to welfare.

Ackerman agrees with Freedman that respecting children does not involve a requirement to respect their autonomous decisions. He points out that the decisions children make are not autonomous choices. Instead, children's "choices" can reasonably be expected to mirror the suggestions made to them by parents and others. To respect children, it is the moral duty of people in positions of authority to guide children. They must "encourage, direct, advise, and even sometimes coerce" children to engage in activities that will contribute to their becoming the right kind of persons (Ackerman, 1979, p.346). Ackerman understands the idea of moral guidance as involving emotive appeals, speaking of what good persons do, and giving praise. But it does not involve leaving decisions in the hands of children. He concludes that "we fool ourselves if we think we fulfill our moral duties by standing aside and asking the child to decide. Our duty is to guide or direct the child to make the best choice" (Ackerman, 1979, p.346). On both these views, a parent can, consistent with respecting the moral worth of a child, provide surrogate consent for that child's participation in research. Enrolling a child is a reasonable way to guide a child's moral education or a reasonable decision for a parent to make on behalf of her child.

Lainie Ross offers another argument for why surrogate consent for children's research participation is ethically permissible. Ross proposes that children should be subject to a modified principle of respect for persons that applies to children rather than adults. Her proposed principle of respect is derived from Kant's second formulation of the categorical imperative. It states that "[c]hildren should never be treated solely as

means, but always at the same time, as developing persons and as individuals who have actualized some of the characteristics associated with personhood” (Ross, 1998, p.47). Ross understands this principle as giving rise to two requirements: (1) a negative requirement that prohibits the abuse, neglect, and exploitation of all children. For Ross, what counts as abuse or neglect depends on the relationship between a child and an adult. For example, it may be neglectful for a parent to fail to provide her child with lunch, but it is not neglectful for a teacher to fail to do so (Ross, 1997, p.48). (2) Ross’s principle also involves a positive requirement which compels particular individuals to “provide particular children with the goods, skills, liberties, and opportunities necessary to become autonomous adults capable of devising and implementing their own life plans” (Ross, 1998, p.47). The positive component applies only to particular relationships. For instance, a parent is obligated to provide for her child’s basic needs. This positive component recognizes obligations on behalf of parents to their children, but it provides wide discretion to parents to direct their child’s future according to the parent’s own conception of what is good (Ross, 1997, p.48). The positive obligation is met when parents provide their children “with the goods, skills, liberties, and opportunities necessary to devise and implement particular life plans” (Ross, 1997, p. 49). The goods in question may include the opportunity to receive a formal education at an exclusive boarding school or an Amish family’s decision to remove a child from school at a young age.

Ross’s modified principle aims to respect children’s developing capacity by protecting them from harm and by providing them with the goods and opportunities that promote a child’s development into an autonomous adult. But her principle does not require informed consent or assent for participation in research. Her analysis assumes that children are incompetent to make their own decisions about health care and “that they should not have presumptive decision-making autonomy” (Ross, 1997, p.7). She argues that parents have presumptive decision-making authority for their children and that parental decisions are binding unless they are disrespectful of a child’s developing personhood (Ross, 1998).

With respect to participation in clinical research, Ross argues that parents may legitimately provide surrogate consent for their children’s participation as long as the

risks of the research are low enough; decisions about a child's research participation fall within the purview of parental autonomy because they do not disrespect a child's developing personhood. She writes:

Parental authorization or prohibition of their child's participation in minimal-risk research is not abusive or neglectful, even if the child is forced to participate against his will. Rather, it is one way in which parents can attempt to steer their child's development into a socially responsible adult. They may or may not succeed, but it is reasonable for them to try and guide his development in this way. (Ross, 1998, p.92-93)

That is, research participation is a socially responsible activity. It is reasonable for parents to try and inculcate values that they themselves cherish in their children. One way to try and inculcate this value in a child is by authorizing her participation in clinical research. A child can reasonably be expected to come to share some of her parent's social goals. Thus, through exposure and participation, a child is reasonably likely to come to view clinical research as a socially responsible activity. And even if the child does not come to embrace the same value as his parent, authorizing a child's participation is one reasonable way to try and guide a child's development into a socially responsible adult. Thus, it is permissible for parents who value research participation to try and inculcate this same value in their children by providing surrogate consent for their children's enrollment in research that poses minimal degrees of risk (Ross, 1998, p.92).

This argument successfully establishes that there is no absolute ethical requirement to obtain informed consent from children. Insofar as children lack the capacity to make autonomous choices, respecting them as persons should not involve respecting their non-autonomous choices. To do so would be to the detriment of a child. It might prevent her from receiving the moral and educational guidance she is owed by her parents. Thus, it can be permissible for a parent, guardian or legally authorized representative to provide surrogate consent for a child's research participation.

Arguments for the moral legitimacy of surrogate consent are an essential part of the justification for research with children. These arguments explain why a parent can fulfill her duty to protect a child and respect her moral worth but still enroll her in clinical research. But these arguments do not adequately explain the conditions under which a

parent or guardian may provide surrogate consent for her child's research participation. Freedman's argument identifies "harmless" research as permissible, but this threshold seems overly restrictive. Most research procedures pose some risk of harm, and many pose a slight risk of serious harm. If parental proxy consent is only legitimate when research is harmless, then it seems impermissible to include children in most kinds of clinical research.

Ross identifies "minimal risk" as a threshold of permissible risk to which parents should be permitted to expose children in research that is not in their medical interests. But this threshold requires further examination. Ross endorses Ackerman's definition of minimal risk, which recognizes minimal risk procedures as those that pose no more risk than activities to which parents typically expose their children for educational purposes (Ackerman, 1980). But she does not adequately justify this threshold. Ross claims that the "development of autonomy requires that children be allowed to take some risks" and that it is both impossible to live in a risk free world and "contrary to the pursuit of a meaningful life plan" (Ross, 1998, p.92). That is, the pursuit of almost any life plan will necessarily involve exposure to some risk. These claims are convincing. But they do not explain why minimal risk is the right level of risk to which it is permissible to expose children in research. Further, it is not clear what kind of risks parents typically expose their children to for educational purposes or whether these risks are justifiable. Consequently, this risk threshold does not necessarily protect children from ill-intentioned or ill-informed parental decisions.

(4) A fourth argument proposes to fill in this missing gap by arguing that it is permissible to include children—as well as adults—in research when an ethics review committee determines that the research offers subjects a reasonable balance between harms and benefits. Commentators then suggest a mechanism by which to assess whether a trial protocol offers a reasonable balance between harms and benefits.

One such mechanism, called component analysis, offers a persuasive system for assessing harms and benefits (Weijer, 2000; Weijer & Miller, 2004; Miller & Weijer, 2006; Freedman, Fuks, & Weijer, 1992).² Component analysis is based on Levine's

² The most prominent competing system for harm-benefit assessment is Wendler's net-risks test (Wendler & Miller, 2007; Wendler, 2006; Rid & Miller, 2011). A critical

insight that clinical research involves both therapeutic and non-therapeutic procedures. That is, all trials that aim to offer research subjects the prospect of some direct medical benefit also involve non-therapeutic procedures that are administered solely in the interests of gaining generalizable knowledge. Proponents of component analysis argue that there is a morally relevant distinction between these two kinds of procedures and that the justification for exposing research subjects to risks differs for each kind of procedure. That is, there should be separate moral rules for the evaluation of therapeutic and non-therapeutic procedures.

Only therapeutic procedures can be understood as advancing a subject's interest in receiving medical treatment. As a result, the benefits and harms associated with therapeutic procedures may be justified by means of a comparison with the benefits and harms of available treatments (Weijer & Miller, 2004; Miller & Weijer, 2006). The moral rules governing therapeutic procedures are intended to protect subjects from receiving substandard medical care. On the other hand, non-therapeutic procedures do not advance the welfare interests of patient-subjects. Given that they are administered in the interests of the study and not to benefit a particular subject, these risks should not be balanced against the potential medical benefit a subject may receive from them (for there is none). Instead, moral rules governing the use of non-therapeutic procedures should protect subjects from unreasonable risks administered solely in the interests of others (Weijer & Miller, 2004).

Component analysis specifies distinct rules for each kind of procedure. To be permissible, therapeutic procedures must meet the requirement of clinical equipoise (Weijer & Miller, 2004). Clinical equipoise is one of the conditions that legitimizes the randomization of research subjects to various treatments that offer some prospect of medical benefit. It aims to explain when a researcher can, consistent with her duty of care to a subject, offer her enrollment in a clinical trial. Clinical equipoise exists when there is an honest professional disagreement among the community of experts about the preferred treatment (Freedman, 1987). That is, it is permissible to offer a subject enrollment in a

exchange about the merits and drawbacks of each approach can be found elsewhere in the literature (Weijer and Miller, 2007). Examining the implications of each approach on the assessment of harms and benefits in research with children is a future project of mine. But it is beyond the scope of this chapter.

trial when there is disagreement among expert practitioners about the relative merits of various treatment alternatives.

Clinical equipoise provides researchers and research ethics committees with procedural and substantive guidelines to help with their determinations. Procedurally, an ethics committee examines whether clinical equipoise obtains by analyzing a study's protocol and justification, reviewing relevant literature, and, when necessary, by consulting with experts (Weijer & Miller, 2004). Further, meeting the requirement of clinical equipoise helps ethics committees to establish that all arms of a trial are consistent with competent medical care (Weijer, 2000). The existence of clinical equipoise suggests (1) that there is sufficient warrant to expose people to an experimental intervention and (2) that research subjects in the control arm of a trial are not being subjected to the risks of substandard intervention. Clinical equipoise is met if the ethics committee finds that the evidence supporting the various treatment options is sufficient that, were it widely known, expert practitioners would disagree about the preferred treatment (Weijer & Miller, 2004).

The moral requirements governing the permissibility of therapeutic procedures are the same for both adults and children. When considering which therapeutic research procedures are permissible, children—like adults—must be protected from receiving substandard care. The existence of clinical equipoise helps to ensure that children's participation in research will not knowingly place them at a disadvantage compared with children who receive standard medical care. It follows that surrogate consent for children's exposure to therapeutic research procedures is justifiable if clinical equipoise obtains.

Component analysis provides a separate set of rules for assessing the moral permissibility of non-therapeutic procedures. Non-therapeutic procedures do not advance the interests a patient-subject has in receiving medical care. As a result, moral rules governing the use of non-therapeutic procedures are intended to prevent people from undergoing unreasonable risks that are solely in the interests of others (Miller & Weijer, 2006). To be permissible, the risks associated with non-therapeutic procedures must be (a) minimized consistent with sound scientific design and (b) reasonable in relation to the knowledge to be gained (Weijer & Miller, 2004). For both adults and children, an ethics

review committee can establish whether non-therapeutic risks are minimized consistent with sound scientific design by requiring, where possible, that a study involves no additional procedures above and beyond those required to answer the study question and by requiring the substitution of procedures that are already performed for treatment purposes (Weijer & Miller, 2004). For example, during a clinical blood draw, additional blood may be drawn for research purposes to spare the subject an additional venipuncture.

The second requirement—that non-therapeutic risks should be reasonable in relation to the knowledge to be gained—requires that a research ethics board determine that the study’s scientific value is sufficient to justify the risks to subjects. This is a determination about social priorities and accordingly, should rely on the judgment of professional members of a research ethics board as well as community representatives (Weijer & Miller, 2004). When the research proposes to involve a vulnerable population, such as children, additional protection is required. To protect children from the risks of non-therapeutic research procedures, a threshold may be invoked limiting the non-therapeutic risks (Weijer & Miller, 2004). Following the U.S. Department of Health and Human Services regulations (DHHS regulations), component analysis restricts the non-therapeutic risks on children to a standard of a “minor increase over minimal risk” (45 CFR 46(a)). The DHHS regulations define minimal risk procedures as those in which “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” (45 CFR 46.102(i)). That is, minimal risk procedures pose no more risks than those encountered in “daily life”. This restriction is meant to help protect children from overly high levels of risk that do not offer a corresponding potential for medical benefit. It aims to do so by limiting non-therapeutic risks to the same degree of risk or a sufficiently similar degree of risk that a child faces daily (Weijer & Miller 2004). Limiting the degree of research risks in research with a vulnerable population is understood to be “one of the core protections that children receive” (President’s Commission, 2013, p.29). Limiting these risks according to a minimal risk threshold appears not only in component analysis but also in

other guidelines, international regulations, and ethical commentary on the ethical inclusion of children in research (CIOMS, 2002; TCPS, 2010; Council of Europe, 2005).

To summarize, according to component analysis, the justification for research with children, like the justification for research with adults, depends on two different sets of moral rules governing therapeutic and non-therapeutic procedures. For therapeutic procedures to be permissible, they must meet the requirement of clinical equipoise. On the other hand, the risks of non-therapeutic procedures must be minimized consistent with sound scientific design, reasonable in relation to the knowledge to be gained, and in the case of children pose no more than a minor increase over minimal risk. To be found permissible, a trial protocol must meet the requirements for both its therapeutic procedures and non-therapeutic procedures.

Component analysis fills in some of the missing components of a successful justification for research with children. By requiring independent review of the harms and benefits of research participation by an ethics review committee, component analysis provides an additional level of protection above and beyond that afforded by parents and researchers. Requiring a research ethics board to determine that a given protocol is permissible helps to ensure that researchers and parents will be offered the opportunity to enroll their children in a trial only when a committee of experts has determined that trial enrollment is a reasonable option. Consequently, independent ethics review helps to protect children from uninformed or ill-intentioned parental decisions to enroll their children in clinical trials.

Further, the claim that therapeutic research procedures are only permissible when the requirement for clinical equipoise is met improves upon arguments aiming to justify the inclusion of children in research by broadening the concept of benefit. Rather than identifying some benefit that accrues to research participation and then arguing that the existence of this potential for benefit justifies children's inclusion in research (Wendler, 2010; Wendler, 2012; Bartholome ,1976), clinical equipoise provides clear answers about how much benefit is sufficient to justify a child's participation. According to the requirement of clinical equipoise, a therapeutic research procedure provides adequate benefit to justify enrollment when it is consistent with competent medical care. Thus, component analysis's requirement for therapeutic procedures helps to resolve questions

about when the potential for benefit is sufficient to outweigh the risks of research participation and how to assess the permissibility of therapeutic risks.

1.4 The missing argument

Component analysis provides resolutions to some of the problems complicating research with children. But it does not provide an adequate analysis of the concept of minimal risk, which is central to the justification of non-therapeutic procedures with children. That is, the concept of minimal risk is not adequately justified or explicated. The idea that the risks of non-therapeutic research procedures on vulnerable populations should be constrained is persuasive. Children are vulnerable; they cannot protect their own interests and are dependent on adults for the satisfaction of their basic needs and wants.

Accordingly, they require more protections in research. While it may be permissible to expose them to some risk in the interest of others, restricting the permissible degree of risk helps to ensure that children's interests will not be sacrificed for the benefit of others.

Further, it seems reasonably uncontroversial that the permissible degree of non-therapeutic risk to which they may be exposed should be low. Undertaking a high degree of risk purely in the interest of others requires an understanding of the nature of this risk and autonomous decision to take it on. Thus, restricting the risks of non-therapeutic procedures on children to a low degree helps to ensure that they will be respected as persons and not exploited for the sake of society. One way of operationalizing the 'low' or defensible degree of risk requirement is by measuring risks according to the concept of 'minimal risk'. The concept of minimal risk offers a threshold according to which to assess the permissibility of non-therapeutic risks. That is, it provides a measure by which to determine the kinds of risks that are low enough to protect children's interests in research. But what degree of risk is low enough to prevent exploitation? What should minimal risk mean? And how should we determine when it is surpassed?

Commentators endorsing a minimal risk threshold sometimes suggest that it is reasonable to measure non-therapeutic research risks according to the risks of daily life because these risks replace or are sufficiently similar to the risks a child would otherwise undergo in the pursuit of her normal risky daily life (Freedman, Fuks, & Weijer, 1993). But how can we know when the risks of research actually replace and do not add to the

risks a child would otherwise face? In addition, what makes the risks of daily life morally relevant or permissible? And how do we ensure that these risks are “sufficiently similar” to the risks of daily life? Further, if minimal risk should be defined according to the risks of daily life, then whose daily life should be used as the reference point? That is, who should be the referent for minimal risk? Without convincing answers to these questions, the minimal risk concept remains unclear. Moreover, without an adequate analysis of the concept of minimal risk, Ramsey’s challenge remains unanswered. That is, it is not clear whether, and if so under what conditions, children can justifiably be included in research. Thus, the next chapters aim to explicate and justify the concept of minimal risk.

In this chapter, I have argued that the justification for research with children depends on several important insights. First, it depends on an argument about social utility. Research with children is permissible, in part, because it is the source of a critical public health benefit: it improves medical practice on the basis of scientific evidence. Consequently, it is justifiable because of its ability to improve the medical care of children. But this justification is insufficient. It does not provide a persuasive reason why it is permissible to expose particular children, who cannot consent for themselves, to research risks for the benefit of others. Second, commentators argue that at times, it may be permissible to expose children to risk purely for the sake of others. This argument successfully establishes that it might be permissible to expose children to harm, but it leaves other important questions unanswered. It does not explain why it is permissible to enroll children who cannot consent to a trial and it does not explain the degree of risk to which a child can be exposed in the interest of others.

Two additional arguments provide partial answers to these questions. One claims that the requirement to obtain informed consent applies only to people who can make autonomous choices. Given that children are not autonomous, respecting their moral worth in research is not subject to the requirement to obtain informed consent. Instead, parents or guardians can provide surrogate consent for children’s participation in research. This argument successfully establishes that children can participate in some research but it does not explain when a parent can, consistent with her parental duty to respect and protect her child, enroll that child in a clinical trial.

One promising way of establishing the conditions under which it is permissible to enroll a child in a trial is to derive insights from the conditions that legitimize the inclusion of adults in research. Adults can enrol in research when an ethics review committee has determined that a research protocol is ethically permissible. Requiring independent review by an ethics committee helps to ensure that a group of experts finds a particular research protocol valuable and permissible, which helps to ensure that parents are given the option to consent on behalf of their children only when enrollment in the trial is a reasonable option. Further, the justification for research with children depends on ethics review committees making reasonable determinations about whether a trial is permissible. Component analysis is a useful mechanism that helps to guide ethics review committees in their harm benefit determinations. Component analysis provides a convincing explanation of when it is permissible to expose children to therapeutic research procedures. But it does not provide a sufficient explanation of the conditions under which non-therapeutic procedures are permissible for children. It relies on—but does not adequately explicate and justify—the concept of minimal risk. It follows that a successful justification for research with children depends on a more persuasive justification for minimal risk. As noted above, the remaining chapters of my thesis will analyze this concept.

Chapter 2

The risks of daily life

The ethical inclusion of children in research requires a number of protective measures, including the restriction of research procedures that are not administered in the medical interests of a child, that is, non-therapeutic research procedures. Most agree that the risks of these procedures should be low. But what degree of risk, if any, is low enough?

Research ethics guidelines and commentary often measure non-therapeutic risks with children according to the concept of minimal risk. That is, they limit the risks of non-therapeutic research procedures to those that pose less than minimal risk, minimal risk or a minor increase over minimal risk. No matter where the line is drawn, the justification for research with children ultimately relies on an explanation of why it is permissible to expose children to a given degree of risk purely in the interest of others. There are two main challenges: (1) explaining what is meant by minimal risk and (2) explaining why this kind of risk is morally relevant, that is, why is it an appropriate comparator for the risks of non-therapeutic research procedures with children.

In this chapter, I defend the idea that minimal risk should be interpreted as the risks of daily life. I reject the most prominent defense of this interpretation, which relies on the idea that the risks of daily life are a morally relevant comparator for the risks of non-therapeutic research procedures because they substitute, without adding to, the risks a child would otherwise face. I then propose a different defense, according to which daily life is morally relevant because our daily activities involve risks that are, and should be, considered socially permissible. That is, people have good reasons to accept daily risks because they are part of a reasonable trade-off between personal safety and the ability to pursue the kinds of lives they find valuable. Insofar as reasonable people have good reason to deem daily risks socially acceptable, they serve as a justifiable measure for the kinds of risks that should be permitted in non-therapeutic research procedures with children.

Defending a daily life interpretation of minimal risk raises two difficult questions: What, if anything, is morally relevant about daily life? And whose daily life is morally relevant? A persuasive defense of a daily life interpretation must answer both questions. But identifying a referent for daily life presupposes that there is something morally relevant about some people's daily experiences. To put it another way, an examination of whose daily life is morally relevant is only useful provided that we have some idea about why the concept of daily life carries moral force. Consequently, I will first examine whether there are good reasons to think that daily life is a useful measure for minimal risk and I will then identify a referent for daily life. In this chapter, the discussion of daily life should be understood as referring to the daily lives of those who fare well. That is, daily life does not refer to the daily lives of people who are significantly disadvantaged but to the daily experiences of people who are well off. This is an oversimplification. In subsequent chapters, I will examine in detail whose daily life is morally relevant and what it means for a child to fare well.

This chapter proceeds as follows. First, I explain why it is permissible to expose children to a minimal degree of risk in the interest of others. Second, I propose four criteria required for a successful interpretation of minimal risk. Third, I argue that the main competing interpretations of minimal risk fail to meet the necessary criteria. Fourth, I examine the idea that minimal risk should be interpreted as the risks of daily life. I draw attention to a problem with the most prominent defense of this interpretation and propose a new justification for why the risks of daily life are morally relevant. Fifth, I offer a few final thoughts on how my interpretation fares with respect to its rivals.

2.1 Risks for the sake of others

As noted in chapter 1, the moral principle of respect for persons generally requires a prospective research subject to provide autonomous consent to enroll in a trial. Her informed decision to enroll, based on an understanding of the purposes, methods, risks, and benefits of the research, legitimizes her inclusion and subsequent exposure to research risks. But children are unable to make an informed decision to enroll. Consequently, it is not clear what, if anything, legitimizes their exposure to risks administered in the interest of others.

In the previous chapter, I argued that part of the justification for the inclusion of children in research is that it is sometimes permissible to expose a particular child to risks purely in the interests of others. There are at least two such occasions: (1) when the risks to a child are counterbalanced by the benefits offered to another family member or to the family as a whole and (2) when the risks to a child are undertaken in the interest of important social goals, such as the success of a social community.

However, in both family life situations and in research, interventions that expose children to risk without the prospect of direct benefit must be limited. And it is important to limit these interventions to a defensible degree. What degree of risk is defensible? It seems reasonably uncontroversial that a defensible degree of risk should be low. This is because children are vulnerable; they cannot protect their own interests and are dependent on adults for the satisfaction of basic needs and wants. Accordingly, they require additional protections. While it may be permissible to expose them to some risk in the interest of others, restricting the permissible degree of risk to a low degree helps to ensure that children's interests will not be sacrificed for the benefit of others. In other words, restricting the degree of non-therapeutic risks on children to a low degree helps to ensure that they will be respected and not exploited for the sake of others.

How should this low degree of risk be understood? And how should we determine when it is surpassed? One way of operationalizing the 'low' or defensible degree of risk requirement is by measuring risks according to the concept of 'minimal risk'. The concept of minimal risk offers a threshold by which to assess the permissibility of non-therapeutic risks. That is, it provides a measure by which to determine the kinds of risks that are low enough to protect children's interests in research. In the following sections, I examine how minimal risk should be understood.

2.2 The requirements for a successful account of minimal risk

A variety of interpretations of minimal risk have been proposed; one suggests interpreting minimal risk according to the interventions parents deem permissible for children, another proposes to understand minimal risk as the degree of risk faced in medical procedures undertaken during a routine examination, while still another defines it in terms of the risks people take when participating in charitable activities. These proposals

seem to be motivated by different factors, including clarity, intuitive plausibility, and breadth. Each of these factors seems important, but the competing proposals' diverging goals complicates their evaluation; one interpretation's ability to apply to children of all ages seems desirable while another's intuitive plausibility gives it a different kind of edge. It is not immediately obvious whether meeting any particular goal makes an interpretation more successful than its competitors. To resolve this difficulty, I will begin by proposing a set of requirements that must be met by a successful interpretation of minimal risk. With this foundation in place, I will examine which, if any, of the competing interpretations of minimal risk meet these requirements.

A successful interpretation of minimal risk should fulfill four criteria. First, an interpretation must meet the requirement of practicality. To fulfill this criterion, an interpretation must give sufficient guidance to make it possible to assess the degree of risk posed by various procedures. This requirement aims to ensure that an interpretation is acceptable only if it can be implemented in practice. Second, a successful interpretation must meet the requirement of generality. To meet this requirement, an interpretation must apply to children of all ages (e.g. infants through non-autonomous teenagers). Requiring that an interpretation holds true for a range of children aims to ensure that a successful interpretation takes into account the differences among children of different ages and provides a way in which to accommodate these differences.

Third, a successful interpretation should meet the requirement of fidelity. That is, it must be consistent with common moral intuitions about the permissible treatment of children (such as the intuition that children should be nurtured). This criterion aims to establish that a successful interpretation of minimal risk will expose children to a degree of non-therapeutic research risk that corresponds to commonly held ideas about the morally appropriate treatment of children, which, in turn, may facilitate the recruitment of parents willing to consent for their children's research participation. Fourth, a successful interpretation must meet the requirement of defensibility. It must constrain the degree of non-therapeutic research risks that are permissible to a non-arbitrary degree. Limiting the risks of non-therapeutic research procedures to a defensible degree helps to ensure that the moral principle of respect for persons is upheld and that clinical research will not sacrifice any particular child's interests unduly for the sake of other children or

the social good. Further, a defensible standard helps to ensure that a successful interpretation will provide convincing reasons for why a given standard is a good comparator for non-therapeutic research procedures. Finally, for an interpretation of minimal risk to be found acceptable, it must fulfill all four criteria; they are individually necessary and jointly sufficient.

2.3 Competing interpretations

The set of criteria developed above provides the foundation for a successful interpretation of minimal risk. These criteria also facilitate the examination of diverse interpretations of minimal risk. In this section I examine whether some of the most prominent interpretations of minimal risk meet the necessary requirements for a successful interpretation.

2.3.1 Common usage

One way to interpret minimal risk is to examine its use by the community of clinical researchers and research ethics boards. If the community of practitioners generally deems certain procedures as involving minimal risk, then this common usage might inform an interpretation of minimal risk. This kind of interpretation would have the advantage of being familiar to experts and might line up well with their intuitions about what minimal risk means.

Unfortunately, there seems to be little agreement within the community of experts about the meaning of minimal risk. Janofsky and Starfield's survey of pediatric department chairs and pediatric clinical research center directors found wide disagreement in the way that risk levels of various procedures were assessed (Janofsky & Starfield, 1981). While most respondents agreed that one venipuncture or hospitalization for observation (for 24 hours) posed less than minimal risk for newborns to children age 18, there was no consensus about the degree of risk involved in any given procedure, and there was significant disagreement about the degree of risk posed by most of the procedures surveyed (Janofsky & Sarfield, 1982). For example, when asked to ascertain the degree of risk posed by a puncturing of the ear drum to withdraw fluid (tympanocentesis) for children between 1 and 4 years old, responses were almost equally

split among three different risk assessments; 35% of respondents deemed the procedure minimal risk, 34% thought it posed a minor increase over minimal risk, and the remaining 31% believed the procedure involved more than a minor increase over minimal risk (Janofsky & Starfield, 1981, p.844). Chairs responses also varied over the degree of risk involved in procedures such as arterial punctures, skin biopsy, bone scans, and gastric or intestinal intubation (Janofsky & Starfield, 1982).

A study conducted in 2004 obtained similar results. Shah and colleagues' telephone survey of ethics committee chairs across the U.S. found that while the majority of respondents agreed that a single blood draw posed no more than minimal risk (81%) and that a lumbar puncture with conscious sedation in healthy children involved more than a minor increase over minimal risk (82%) (Shah, et al., 2004, p.479), chairs' risk perceptions differed widely about the majority of procedures surveyed. With respect to some procedures, including a confidential survey of sexual activity or allergy testing, responses were almost evenly split among the three risk categories (Shah, et al., 2004). These surveys suggest that common judgments by experts about the meaning of minimal risk are insufficient. While some procedures clearly pose very low or high degrees of risk, many, if not most, resist obvious categorization by experts.

While an interpretation informed by common usage might have the merit of intuitive plausibility, this interpretation does not meet the requirements of a successful minimal risk standard. It fails the criterion of offering useful practical guidance. Given that even within a circumscribed community of expert practitioners there was little agreement, appealing to common usage would not provide a consistent and useful standard. Further, the differences between different ethics committees common usage of minimal risk may pose particularly difficult complications for investigators carrying out multicenter trials (Lantos, 2004).

Interpreting minimal risk according to common usage also fails to meet the requirement of a defensible standard. Even if the expert community used minimal risk in the same way and to refer to the same kinds of procedures, it is not clear whether, and if so why, these particular procedures are appropriate kinds of risks for non-therapeutic research procedures. Insofar as this standard does not offer a justified defense or useful

guidance for ethics review, minimal risk should not be interpreted in terms of common usage.

2.3.2 Quantitative interpretation

Given that there seems to be no consensus at least among experts about the meaning of minimal risk, some have proposed quantitative strategies for assessing permissible risks.

Nicholson argues:

The evidence presented of the inaccuracies in investigators' perceptions of risk suggests that it is important to work towards an arithmetical categorization of risk and away from such categories as negligible, minimal, minor increase over minimal, and so forth, which are impossible to define and rely heavily on perceptions of risk, particularly those of the professionals involved. (Nicholson, 1986, p.118)

That is, one might reduce variability and ambiguity in risk determination with the help of a quantitative interpretation of the permissible degree of risk.

How would this work? Nicholson proposes that the worthiness of a given trial be assessed by appealing to a complex arithmetical formula that proceeds as follows: one multiplies the length of time for which each harm potentially caused by a research procedure would last by its valuation on the Rosser scale (Rosser & Kind, 1978), which assigns a numerical value to different states of illness. The product is then multiplied by the probability that the harm will occur. This preliminary result represents the disutility score for each harm that an individual might face in the trial. The disutility scores are then multiplied by the number of subjects in a trial and then added together which results in a final disutility score for the whole project (Nicholson, 1986, p.108-110).

Once the final disutility score of a trial is calculated, it is evaluated by reference to a second set of numerical values that prescribe permissible levels of risk for non-therapeutic procedures. For Nicholson, minimal risks are those that pose less than 1 per million risk of death, less than 10 per million risk of major complication, and less than 1 per thousand risk of minor complication (Nicholson, 1986, p.119). Nicholson claims that these values represent permissible degrees of risk because they correspond to the degree of risk that is generally considered negligible in medicine (Nicholson, 1986).

Nicholson's system for risk evaluation is not purely arithmetic or purely quantitative. It relies on the judgment that negligible risks in medical practice are a morally appropriate comparator for risks in research as well as the idea that the risks considered negligible in medicine can be represented quantitatively. While Nicholson recognizes that values will inevitably enter into judgments about risk (Nicholson, 1986, p.81), he endorses the use of quantitative calculations whenever possible to reduce the ambiguity and variability generated by intuitive risk assessments. Thus, for Nicholson, the appropriate ethical assessment of clinical research—and non-therapeutic research procedures—depends on a quantitative calculation that is then assessed by comparison to the degree of risk that is considered acceptable in medical practice.

Nicholson's quantitative strategy is unsuccessful. It relies on at least two problematic claims. First, it is not clear that the degree of risk considered negligible in medicine can be reflected quantitatively. Nicholson arrives at his calculations by examining statistics collected about the risks of certain medical procedures and doctors' as well as the general public's reactions to these risks. For example, he appeals to the research of the Committee on Safety of Medicines to find statistical information about the risks of taking medications. The Committee on Safety of Medicines examined data about the number of deaths reported as being caused by a particular drug during a given period and the number of prescriptions for the drug in the same period; they found that 22 drugs produced a risk of death per prescription no greater than 1 per million, 6 drugs produced a risk greater than 10 per million, and 1 drug produced a risk of 160 per million (Nicholson, 1986, p.89).

Nicholson claims that these statistics serve as some evidence that both doctors and the general public deem a risk of death of one per million as negligible in medical practice (Nicholson, 1986, p.89). But this conclusion is unwarranted. It is not clear whether doctors prescribe drugs that cause a risk of 1 per million of death because they deem this degree of risk negligible or whether they are simply unaware of the risks of certain prescriptions. The results of the Committee on Safety of Medicines may well contribute to changes in prescribing practices. Further, this example cites evidence based on an examination of 29 medications, which is a very small subset of the medications prescribed by physicians on a regular basis. Even if evidence about these 29 medications

revealed that physicians deem negligible a 1 per million risk of death per prescription, it is not clear whether, and if so why, these statistics can be generalized to broader prescribing practices. Consequently, it is hard to see how the Committee on Safety of Medicines' report translates into statistics about the degree of risk generally considered negligible in medical practice.

Moreover, while a doctor's decision to prescribe a medication may well take into account the statistical likelihood of a medication resulting in death, her prescribing habits are likely influenced by different or multiple factors. A physician's judgment also depends on particularities of the situation, including a given patient's risk factors, allergies, and circumstantial or environmental factors that make a given medication a better choice for her. The physician's subsequent judgment about what medication to prescribe is a qualitative judgment based on a consideration of the various benefits and harms of various medical options. It is problematic to appeal to a quantitative calculation that would exclude these considerations in medical practice. Doing so would result in poorer medical care. If the degree of risk considered permissible in clinical research is based on the degree of risk considered negligible in practice, then it should be calculated using more than statistics about risks of death and injury. Making risk assessments based on these factors alone runs the risk of neglecting other important features of a trial. Thus, it is difficult, at best, to accurately reflect the risks considered negligible in medicine quantitatively and even if one could, doing so is undesirable.

Second, Nicholson's proposal depends on the problematic idea that the degree of risk considered negligible in medical practice is a morally relevant comparator for permissible risks in research. The goal of clinical practice is to treat patients; accordingly, the interventions prescribed and administered in practice aim to offer a patient the prospect of direct benefit. It follows that some risks may be deemed negligible in clinical medicine not because there is something inherently acceptable about this degree of risk but because the risk is far outweighed by the potential benefit of a treatment. But this is not necessarily the case in clinical research. Some research procedures are administered exclusively in the interest of answering the scientific question and do not aim to offer a subject the prospect of direct benefit. Given that risks associated with procedures administered in clinical practice may be considered negligible because of the benefits

these procedures offer and that some research procedures do not offer the prospect of benefit, the degree of risk considered negligible in medicine is not an appropriate comparator for the degree of risk that is considered ethically permissible in research.

More generally, quantitative interpretations for minimal risk must either arbitrarily choose a number to represent morally permissible degrees of risk or they must appeal to another kind of justification about what serves as a useful comparator for morally permissible risks in research. The former option is unjustifiable and in the latter, it is the second comparative judgment that serves as the moral foundation for the interpretation. That is, the success of the proposal ultimately depends on the strength of the moral comparator chosen for permissible risks in research, which is a qualitative judgment. Thus, quantitative strategies are ill-equipped to serve as interpretations for minimal risk. Insofar as Nicholson's proposal fails to offer a convincing reason why the risks deemed negligible in medicine (were it possible to reflect these quantitatively) serve as a useful comparator for morally permissible risks in research and there are good reasons to think that it should not be the appropriate comparator, his proposal fails to meet the requirement that an interpretation limit risks to a defensible degree. Consequently, it is not a successful interpretation of minimal risk.

2.3.3 Routine examination

Another possible interpretation of minimal risk suggests that the threshold for permissible non-therapeutic research procedures on children should be the degree of risk a child faces during the performance of routine physical or psychological examinations or tests. This interpretation is endorsed by the Council for International Organizations of Medical Sciences' *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (CIOMS, 2002, Guideline 9, p.48) and Kenya's National Council for Science and Technology's *Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya* (Kenya's National Council for Science and Technology, 2004, Guideline 6, p.11). The procedures performed during a healthy child's routine physician visit are reasonably well-characterized; they include routine age-appropriate physical and psychological examinations or tests, guidance and education, and immunizations (IOM, 2004, p.124).

One advantage of this interpretation is that it offers clear procedural guidance about the kinds of procedures that pose no more than minimal risk. But this interpretation is not persuasive. First, it is not consistent with common moral intuitions about the permissible treatment of children. The risks of routine examinations in countries with reasonably well-developed health care systems pose almost no risks (Wendler, 2005). The Institute of Medicine claims that a healthy child's doctor's visit often involves a history, physical exams (including height, weight and head circumference measurements, collection of blood, measurement of heart rate and blood pressure), psychological exams, guidance or education, and immunizations (IOM, 2004, p.124). These procedures involve very few risks. Consequently, implementing this interpretation would prevent children from facing most risks that offer them no prospect of direct benefit. But this seems overly restrictive. As discussed earlier, parents should have broad discretion over the kinds of risks that their children should face. And at times, it is permissible for parents to expose their children to some risk for the benefit of the family or for unrelated others. Restricting minimal risk to the procedures administered during a routine examination prevents many non-therapeutic research procedures. It also restricts a parent's ability to exercise discretion about the kinds of risks their children should face that do not aim to offer their children the prospect of direct benefit. Consequently, this interpretation does not meet the requirement of fidelity.

Further, the routine examination interpretation does not limit risk to a defensible degree. No argument is provided about why the degree of risk faced in a child's routine physical or psychological examination is a morally relevant threshold. In the absence of this kind of argument, there is no obvious reason to accept that the risks of routine examinations should be the basis of comparison for minimal risk. In fact, there are good reasons to think these risks are the wrong comparators. The procedures administered during a well-child visit offer children the prospect of direct benefit. They track children's development and seek to identify any problems in need of treatment (Wendler, 2005). Given that they involve risks undertaken with the prospect of direct medical benefit and not for the benefit of others, they are not an appropriate baseline according to which to measure the permissibility of non-therapeutic research procedures. Given that

the routine examination interpretation fails to meet the requirement of fidelity and the requirement of defensibility, it does not offer a persuasive interpretation for minimal risk.

2.3.4 Charitable participation

Wendler defends the “charitable participation” standard (Wendler, 2005; Wendler & Glantz, 2007; Wendler, 2010) according to which risks are considered minimal when they do not “exceed the risks of charitable activities deemed acceptable...in daily life” (Wendler, 2005, p.40). That is, children should be enrolled in research that does not aim to offer them the prospect of direct benefit only when the research poses no more risk than society would deem permissible for a child to face while she participates in charitable activities. For example, minimal risks should be understood as those faced by children participating in Global Youth Service Day, during which children across the world carry out local community improvement projects including crop planting, visiting the sick, digging wells, and collecting donations (Wendler & Glantz, 2007).

Wendler makes his case by drawing parallels between research and charitable activities and then appealing to our intuitions about the permissibility (or desirability) of volunteering children to participate in charitable activities. He argues that both charitable activities and nonbeneficial pediatric research are designed to help unrelated and unidentified others (Wendler & Glantz, 2007). And neither activity is able to predict with certainty that it will benefit others; the benefits of a clinical trial, like those of a charitable fund raiser, may not materialize. But both are valuable endeavours that offer a reasonable prospect of helping others (Wendler & Glantz, 2007).

Next, Wendler argues that participation in charitable activities is socially endorsed. He writes:

Parents may reasonably instruct their children to mow the lawns of infirm neighbors, and they may allow their children to participate in car washes and go door to door collecting money for charitable organizations, even though these activities pose some risks to their children. Further, society not only implicitly accepts such charitable activities but in many cases actively endorses them. Schools and local governments often support them, and respected organizations like the Red Cross and Habitat for Humanity encourage children to participate in

them. Presumably, if society considered it outright exploitation in every case to expose children to risks for the benefit of others, the public would not, through the government, give them a special tax status. (Wendler, 2005, p.40)

That is, society endorses parent's decisions to volunteer their children's help in charitable activities that pose some risks to children but also offer the possibility of helping unidentified and unrelated others. This suggests that it may also be permissible for children to participate in clinical research involving similar degrees of risk without direct medical benefit but with the ability to benefit others.

The charitable activity interpretation lines up well with the common moral intuition that parents should encourage children to learn the value of charity and of helping others. In addition, charitable organizations often have strict rules about what kinds of charitable activities children of different ages may undertake, which offer clear guidance about what kinds of risks may be permissible in research (Wendler & Glantz, 2007). For example, Habitat for Humanity reaches out to children as young as 5 years old to help contribute towards their goal of providing every person with a safe, decent, and affordable place to live. But children's participation is carefully constrained to age-appropriate activities. Children between 5-8 years old are encouraged to help build piggy banks for fundraisers, construct welcome baskets for homeowners, and help with landscaping (Habitat for Humanity). But to be permitted on construction sites, one must be over 16 years old (Habitat for Humanity). Thus, some charitable organizations offer clear guidance about what kinds of risks are appropriate for children of different ages.

However, Wendler's charitable participation standard fails to meet other necessary criteria of a successful interpretation. Wendler's standard does not clearly limit risks to a defensible degree. Wendler successfully points out that charitable activities help to teach children socially and morally valuable traits. He also points out that the risks of participating in charitable activities are risks and burdens to which society is willing to expose individuals for the benefit of others (Wendler, 2005, p.40). These claims are compelling. But it is not clear that charitable activities are the only kinds of valuable activities in which society is willing to expose children to risk for the sake of others.

Wendler does not offer a strict definition of what he means by charitable participation and the scope and range of activities that should count as charitable is not

entirely clear. But his examples, including American Red Cross, Habitat for Humanity, UNICEF, and Global Youth Service Day (Wendler & Glantz, 2007) refer mostly to the works of charitable organizations. He also raises the example of helping out infirm neighbours (Wendler, 2005). There is little question that these are valuable activities. But there are other valuable activities in which it may be permissible to undertake, or to expose children to risks for the sake of others, that do not clearly fit within Wendler's charitable activities standard. Consider, for example, valuable social goals such as reducing poverty, promoting public health, promoting democracy, reducing pollution, reducing traffic accidents, and promoting racial tolerance, to name a few. It is desirable for people to be involved in, and in some instances, to involve their children in activities that involve risk but help contribute to these valuable goals. But constraining the degree of risk to which it is permissible to expose children in research to the degree of risk involved in charitable activities does not capture the permissibility of involving children in these other kinds of valuable activities. In other words, Wendler's interpretation is overly narrow. He identifies a set of clear cases in which one exposes oneself or one's child to risks in order to benefit another, often a complete stranger, but it is not clear why we should limit permissible risks to the risks involved in charitable activities. These are only one example of the kinds of valuable activities society promotes.

Further, Wendler's charitable activity standard fails to meet the requirement of generality. That is, it does not apply to children of all ages. As Wendler recognizes, interpreting minimal risk according to charitable activities does not seem to support research on infants or very young children. Socially endorsed charitable organizations, like Habitat for Humanity, do not endorse the inclusion of children under five years old in charitable activities (Wendler & Glantz, 2007). If minimal risk is to be compared to the degree of risk socially permissible in charitable activities, then infants and young children cannot face any risks without the prospect of corresponding benefits. This is not simply a disadvantage of the argument (Wendler & Glantz 2007, p.580) but a serious problem; a convincing interpretation of minimal risk must explain the permissibility of research risks for children of all ages. Insofar as the charitable activity interpretation bars infants and young children from facing any degree of risk, it is not a persuasive definition of minimal risk. Applying it would prohibit the progress of research that investigates the medical

treatment of infants and young children. Thus, Wendler's charitable participation interpretation should be rejected.

2.3.5 Socially allowable risks

A fifth possibility interprets minimal risk as the risks to which it is socially permissible for parents to expose children. Some of the comments of the National Human Research Protections Advisory Committee (NHRPAC) suggest this kind of interpretation (NHRPAC, 2002). Specifically, NHRPAC interprets minimal risk according to the daily life of a "normal, healthy, average child" but also endorses a socially allowable risk standard. They write: "Conceptually, the minimal risk standard defines a permissible level of risk in research as the socially allowable risks which parents generally permit their children to be exposed to in non-research situations" (NHRPAC, 2002, p. 1). NHRPAC do not explain how their endorsement of a daily life and a socially allowable risk interpretation can be reconciled. That is, it is not clear whether they think that minimal risks should be assessed by considering the risks of daily life or by considering whether a particular risk is socially allowable. And some have argued that the conceptual link between the two is unsuccessful (Kopelman, 2004b, p.364). Nonetheless, the socially allowable risks interpretation receives some support. When examining what is meant by a "minor increase over minimal risk", Wendler and Emanuel endorse a socially acceptable risk standard (Wendler & Emanuel, 2005, p.577).³ They argue that a minor increase over minimal risk refers to the level of risk in the lives of children who face greater than average, yet socially acceptable risks. He writes:

[In some cases,] society not only permits children to be exposed to greater risks, but also deems the related activities to be acceptable for children. For instance, children who assist their families on working farms face greater risks than the

³ Wendler's interpretation is surprising. Given that he defends a charitable activities interpretation of minimal risk (Wendler, 2005) and also endorses the need for empirical data about the quantitative degree of risk posed by daily life and charitable activities (Wendler et al., 2005), it seems reasonable to conclude that he would interpret a minor increase over minimal risk as some fixed degree of risk higher than that encountered in charitable activities. But Wendler does not explain how (or whether) his endorsement of the socially allowable interpretation is to be understood in light of the charitable interpretations standard and his emphasis on quantification.

risks ordinarily encountered by healthy children; children who take frequent car trips and children who go on mountain climbing trips with their parents face greater risks than other children...Society accepts children facing these risks and, in some cases, even explicitly endorses them.

At the same time, society often places additional restrictions on these riskier activities. Society requires that infants be placed in car seats, and younger children to work on family farms only. Furthermore, society does not accept all of the risks associated with family farms, such as the risks posed by unsafe machinery, even when these risks might be deemed acceptable by some parents. (Wendler & Emanuel, 2005, p. 577-578)

This interpretation aims to identify the degree of risk that is permissible in research as the risks that are deemed socially permissible by a society. When a society deems some risks, such as the risks faced by children who live in housing projects as unacceptable, then these risks are also assumed to be unacceptable in non-therapeutic research procedures. This position has some appeal. It draws on intuitions that social mores help to determine how children should be treated in research. And it seems plausible to draw on collective insights to help determine what kinds of activities or research procedures are permissible for children.

Nonetheless, the socially allowable threshold is ultimately unsuccessful. It is not clear how to determine whether something is considered socially allowable. Identifying something as socially allowable might mean that it is legal or it might mean that it is approved by most people (Kopelman, 2004b, 364). The former does not necessarily dictate what is morally justifiable and the latter standard is hard to gauge. Consequently, this interpretation does not meet the criterion of practical guidance. Further, requiring that an action be permitted by society does not ensure that it is an appropriate comparator for non-therapeutic research procedures. That is, it is not a defensible risk standard. The IOM point out that this interpretation suggests that if public opinion polls showed majority support for spanking, then hitting a child during an experiment would pose no more than minimal risk, which seems wrong (IOM, 2004, p.123). To put the point more generally, identifying socially acceptable risks does not explain whether or why these risks are morally permissible. And in the absence of a persuasive reason to think that a set of

actions should be socially permissible, measuring these actions against minimal risk, so defined, does not offer adequate protections for children in research.

2.3.6 Risks in family life

Ackerman defends another interpretation according to which “[a] research procedure involving minimal risk is one in which the probability of physical and psychological harm is no more than that to which it is appropriate to intentionally expose a child for educational purposes in family life situations” (Ackerman, 1980, p.106). That is, the degree of risk permissible in non-therapeutic research procedures should be restricted to the degree of risk to which parents are willing to expose their children for the purposes of their education.

Ackerman arrives at this interpretation through an examination of family life. His idea is that exploring the duties and privileges of parents can tell us about the appropriate treatment of children in research. Specifically, he argues that identifying the kinds of interventions that are commonly thought to be morally justified in family situations should inform determinations about permissible interventions in medical research (Ackerman, 1980). He then identifies three kinds of legitimate parental interventions into the lives of their children. First, parents should intervene to contribute to a child’s physical and personal development. Such interventions include the provision of food, shelter, and medical care as well as contributions to her personality development, learning, and skill acquisition. In addition, parents must take steps to limit children’s exposure to dangers that threaten their well-being (Ackerman, 1980, p.95).

Ackerman’s second and third kinds of justifiable interventions serve different goals. They represent interventions that are not merely in a child’s direct interests but are undertaken to promote the interests of others. The second permissible kind of intervention permits parents to intervene in the lives of their children so as to inculcate in their children traits of character that contribute to a child’s development into a morally acceptable adult (Ackerman, 1980, p.95-96). Ackerman’s idea is that social life depends on the existence of a community that adheres to a moral code and that parents can and should contribute to this moral community by educating their children about and habituating children to shared moral duties, including respecting others, keeping

promises, and avoiding harm. Third, parents can intervene in the lives of children to promote the interests of others, especially family members. For example, it may be reasonable for parents to move a child away from established social relationships to take up a new job in a different country or to force a child to wait long hours in an emergency room while her sibling's broken bone is attended to (Ackerman, 1980, p.96).

It is an important feature of Ackerman's account that morally justifiable interventions into the lives of children do not need to be in a child's direct or best interests (Ackerman, 1980, p.101). These interventions educate the child, but not exclusively for her own sake. But these interventions are subject to limitations: they must not frustrate or threaten a child's development, the risks associated with these interventions must be minimized, and the burdens incurred from these interventions must be fairly distributed (Ackerman, 1980, p.96).

Ackerman extends this analysis of family life to non-therapeutic research procedures with children. He writes:

[S]ociety may expect that parents will impose risks and discomforts upon children in order to inculcate dispositions of character which assure their acknowledgement of the publicly recognized moral code. Similarly, parents may impose upon a child to enhance the well-being of others, particularly family members. In each case, pursuit of the direct interests of the child may be circumscribed by goals related to the welfare of society and its other members. (Ackerman, 1980, p.101)

That is, if certain kinds of interventions that are not in a child's direct interests are morally legitimate in family life then they can, by analogy, also be morally justified in the context of research with children. But, in both family life situations and in non-therapeutic research procedures, limits must be placed on interventions that expose children to risk without the prospect of direct benefit.

What is the appropriate limit for the risks of non-therapeutic research procedures? Ackerman's answer is that given that it seems reasonable to permit children's moral education to involve some degree of risk to serve a socially worthy goal and that clinical research involving non-therapeutic research procedures also contributes to a socially worthy goal, it seems reasonable to conclude that non-therapeutic research procedures are

permissible if they pose no more harm than parental interventions do that contribute to a child's moral education (Ackerman, 1980, p.106). Interventions in the family setting that promote a child's moral education include chores such as washing the dinner dishes, which involves some risk of cuts and the discomfort of not doing other things during that time, and participating in an outing that is not of immediate interest to a child, such as a trip to the grocery store. Ackerman claims that the risks posed by these interventions are comparable to the risks posed by non-therapeutic research procedures such as weighing, aspirating bone marrow, needle biopsies, and lumbar punctures (Ackerman, 1980, p.107).

Ackerman's analogy—that is, between clinical research and family life as two situations in which it is permissible to expose children to risks for the benefit of others—is plausible. As with Wendler's charitable interpretation standard, Ackerman's proposal persuasively identifies an area in which it is permissible to expose children to some risks for the sake of others. And Ackerman's proposal is more convincing than Wendler's. The risks to which it is permissible to expose children for educational purposes in family life likely includes the risks of participation in charitable activities but in addition to a broader range of valuable activities. That is, given that many parents think it is appropriate to encourage their children to help unrelated others, Ackerman's interpretation of permissible risks includes the risks of charitable activities such as helping neighbours. But it also has a broader scope. The risks to which it is permissible to include children in family life for educational purposes also include different risks undertaken for the purposes of a child's moral education, such as teaching children to keep promises. Thus, this interpretation offers a persuasive account of many risks to which it is appropriate to expose a child in the interest of others.

However, there are difficulties with Ackerman's argument. First, his standard does not adequately constrain the degree of risks that children may face in research. Some parents' systems of moral education expose their children to risks that would be inappropriately high in the context of non-therapeutic research procedures. For example, James Mill—following the principles of Bentham's associationist psychology—required John Stuart Mill to learn Greek by the age of three, Latin by age eight, and master the basics of economic theory complemented by extensive work in logic and mathematics by age fourteen. Acquiring this knowledge is admirable, but Mill complained that his

father's rigorous training led to the intense depression he suffered by age twenty (Wilson, 2007). Non-therapeutic research procedures dangerous enough to cause severe depression seems to pose too much risk. More generally, it seems impermissible to permit non-therapeutic research risks that are equivalent to those imposed by a heavily burdensome program of study on a young child. But given that some parents find high risks appropriate during a child's education in family life, they might be deemed minimal on Ackerman's account. More generally, it is not clear that this interpretation can distinguish between malicious, mistaken or ill-informed parental treatment and consequently, does not meet the requirement that a successful account must be subject to adequate constraints.

One might respond to this objection by pointing out that Ackerman's interpretation indexes permissible risks to those to which parents *should* expose children (and not as the risks to which some parents do expose children), which would reflect a social judgment about the kinds of risks that are permissible in family life situations (Nelson & Ross, 2005, p.565). But this response is not persuasive. First, it is not clear that such an interpretation could be implemented in practice. There is no unambiguous body of risks to which it is socially permissible to expose children for educational purposes in family life. There is little doubt that James Mill's methods were severe but they contributed to his son's becoming the most influential English-speaking philosopher of the nineteenth century. Should the risks of this kind of training be appropriate for educational training in family life? If not, where should the line be drawn within the spectrum of risks to which parents intentionally expose children for the purposes of their education? In short, it is not clear that there exists one common social judgment about permissible educational interventions, which complicates efforts to operationalize this interpretation. But this suggests that Ackerman's interpretation does not meet the requirement of practicality.

In addition, Ackerman's interpretation does not meet the requirement of generality. Parents do not generally morally educate infants or very young children. It follows that this interpretation offers no persuasive reason why it is permissible to include infants and very young children in research that exposes them to risks for the benefit of others. Ultimately, the success of Ackerman's interpretation depends on the development of an account of the risks to which parents should expose children for the purposes of their

education, an explanation of the ways in which we morally educate very young children, and practical guidance. As it currently stands, Ackerman's interpretation does not constrain non-therapeutic risks adequately or provide adequately clear or general guidance for ethics review.

2.3.7 The risks of daily life

The National Commission defends the idea that “minimal risk is the probability and magnitude of physical or psychological harm that is normally encountered in the daily life, or in the routine medical or psychological examination, of healthy children” (National Commission, 1977, xx). The current U.S. DHHS regulations also interpret minimal risk according to the risks of daily life (although they omit the phrase “healthy children”) (45 CFR 46.102(i)). The daily life interpretation draws on the fact that, no matter how careful a person is, carrying out her usual daily activities—such as eating a meal or crossing the street—involves exposure to some risk. This inevitable degree of risk should be understood as minimal risk (Ackerman, 2001, p.32).

There is little question that our daily activities expose us to risks but measuring minimal risk according to daily life gives rise to at least two difficult questions: (1) what, if anything, is morally relevant about the risks of daily life? That is, why is it a justifiable measure for minimal risk? And (2) whose daily life do we have in mind? In the rest of this chapter I examine whether there are good reasons to think that daily life should serve as a measure for minimal risk. Specifically, I will offer an account of why the risks of daily life are morally acceptable and serve as a justifiable measure for the risks of non-therapeutic research procedures with children. In subsequent chapters, I take up the second question of whose daily life is morally relevant.

One reason to think that the risks of daily life are morally relevant is that they replace (and do not add to) the risks a child faces in her usual activities. Commentators argue:

The risks of research are to a degree substitutive, rather than additive: research risks are undergone, but the risks of alternative activities are foregone. Normal, healthy subjects of research would otherwise be pursuing their normally risky daily lives.... (Freedman, Fuks, & Weijer, 1993, p.17)

Similarly, McMillan and Hope write:

[R]esearch which is no more harmful than activities that an individual takes part in during everyday life is not harming that individual in a way that he would not have been harmed had he not taken part in the research. In other words a research participant is not worse off by taking part in the research than he would have been if he got on with his life in other ways. (McMillan & Hope, 2004, p.112)

The moral rationale in these passages is that restricting the risks of non-therapeutic research procedures to the same degree of risk a child would otherwise be facing in her normal risky daily activities helps to ensure that research risks substitute and do not add to the amount of risk a child will face at any given time (Ackerman, 2001, p.32; McMillan & Hope, 2004). A child may have different kinds of experiences (and their accompanying risks) in research, but what is important is that these risks replace her usual and comparably risky daily experiences. If the risks of research replace the risks of daily life, then children's participation in a trial does not expose them to any additional harm. Understood in this way, daily life is a justifiable interpretation not because of any morally salient features about the risks of daily life but because it helps to ensure that participation in research will not unjustifiably sacrifice children's interests for the sake of others.

However, the argument for risk substitution is not successful. It is based on the idea that one cannot literally be in more than one place at one time. That is, a child cannot simultaneously undergo a non-therapeutic blood draw in a research setting and ride her bicycle on the street. This is true, but it does not necessarily prevent a child from undergoing additional risks as the result of her research participation. That is, while one activity may substitute the other, the risks of non-therapeutic procedures do not necessarily substitute the risks of daily life. The risks of non-therapeutic procedures are not constrained to the period of time during which the procedure is administered (or even to the duration of the study). For example, the risks of injection with an investigational drug are likely to persist after a child leaves the hospital or clinic. It follows that the activities she undertakes post-procedure but while the effects of the intervention persist are subject to two sets of risks: those incurred as the result of the research intervention as well as those incurred as the result of her usual daily activities. To carry normative force,

the argument for risk substitution must establish that one cannot simultaneously be exposed to the risks of non-therapeutic procedures at the same time as one is exposed to the risks of daily life. But the risks of research procedures can increase a child's risks. It follows that the argument for risk substitution is unsuccessful. If daily life is a useful comparator for minimal risk, it requires a different justification.

2.4 A new justification for daily life

Is there a different reason that daily life is a morally justified comparator for minimal risk? I will defend the thesis that daily life is morally relevant because it involves risks that most reasonable people undertake without much thought, concern, and irrespective of whether they offer the prospect of corresponding benefit. That is, these risks are socially acceptable risks. Moreover, the acceptance of these risks is not the result of mistaken or ill-informed judgment. They are risks that most reasonable people have good reasons to deem safe enough for themselves, their children, and for unrelated others even when they do not offer the prospect of corresponding benefit. Insofar as people have good reasons to deem these risks acceptable for the benefit of others, they serve as a justifiable measure for the kinds of risks that are morally permissible in non-therapeutic research procedures with children. In the first section, I will argue that the risks of daily life represent the kind of risks that most reasonable people accept as socially permissible and then, I will argue that there are good reasons for people to deem these risks socially permissible.

Theoretically, one can always make efforts to reduce the risks associated with an activity. But at a certain point, most reasonable people stop trying to reduce the risks of their activities. They make trade-offs between safety and the pursuit of other goals or goods. The kind of risks that most reasonable people are willing to accept as part of this trade-off—that is, the risks that are deemed 'safe enough'—are morally relevant. They are the socially acceptable risks in a given time and place. To put it another way, identifying some risks as 'safe enough' reflects a normative judgment about risks that reasonable people should undertake without significant calculation and irrespective of whether they offer the prospect of direct benefit. Further, identifying what kinds of risks, if any, are socially acceptable can guide decisions about the kinds of risks that are

permissible in non-therapeutic research procedures on children. The main tasks then are to say what risks are considered safe enough and why they should be deemed socially acceptable.

How safe is safe enough? People's attitudes towards risk vary. As Altham writes:

To some people, in some circumstances, the consciousness of risk has positive value. To others in the same circumstances, the consciousness of risk may be unpleasant. What gives one some pleasurable excitement gives another the pain of anxiety. A person may be temperamentally risk-averse or risk-loving.

Similarly a person may relish or detest the experience of uncertainty, where objective probabilities are not assignable. (Altham, 1984, p.24)

But then how do we identify risks that both the skydiving enthusiast and the couch potato think are safe enough? One promising option is to identify 'acceptable risk' as a point on the lower end of the risk spectrum. Freedman and colleagues write:

[B]y specifying the threshold [of acceptable risks] at or near the risks of everyday life we approximate a lowest common denominator of risk, the level at which most reasonable people feel 'safe enough' so that their choices can be made without considering the small risk repercussions. (Freedman, Fuks, & Weijer, 1993, p.17)

That is, socially acceptable risks should be chosen as a minimal level that most reasonable people accept as permissible for all. The idea that there is something socially acceptable about the risks of daily life is well reflected in our behaviour. Most reasonable people—irrespective of whether they are risk-averse or risk-takers—undertake the risks of daily life without much thought or calculation. Further, we identify those who disagree with this judgment, that is, people who try and avoid daily risks are considered deviant. For example, we understand agoraphobes—who experience anxiety about being in situations or places that make escape difficult (DSM IV, 2000), including normal experiences of daily life such as riding in an elevator, travelling in a bus, car or plane or walking through crowded public places—as suffering from a disorder (DSM IV, 2000). We classify their behaviour as unusual or problematic and recommend therapies to help them face everyday experiences without panicking. This suggests that daily risks—including crossing the street, riding in public transportation, eating a meal, and entering public areas—are generally thought to be safe enough. Further, this judgment applies

broadly; we think that these daily risks should be acceptable for members of a given society.

However, identifying the kinds of risks reasonable people treat as safe enough is not, on its own, a sufficient justification. A successful interpretation of minimal risk must also explain why people should accept these risks. That is, it should explain whether there are good reasons to accept the risks of daily life. Moreover, it must explain why there are good reasons to accept these risks for the benefit of others. This analysis is more complex. A substantial body of evidence from cognitive psychology suggests that people are notoriously poor judges of risk (Tversky & Kahneman, 1981; Tversky & Kahneman, 1974; Slovic, Fischhoff, & Lichtenstein, 1982; Teuber, 1990). We assess risks by appealing to a series of common heuristics that lead to systematic errors of judgment.

We tend to judge the likelihood of an event based on whether it is available to us, that is, based on whether instances of this event can be easily recalled or imagined. For example, people often guess the likelihood of heart attacks in middle-aged men based on their recollection of these occurrences amongst acquaintances (Tversky & Kahneman, 1982; Slovic et al., 1982). But this kind of judgment is problematic; it ignores the fact that proximate or recent instances of events are not always good indicators of the most pressing dangers (Slovic et al., 1982). Another common error arises in our estimation of probabilities. We tend to begin with an initial value and then adjust this value to yield a final answer. But these adjustments are insufficient; different starting points—that are generally the result of a particular formulation of a problem or the result of a partial computation—yield different estimates that are biased toward the initial values. Consequently, our estimations of probabilities often contribute to distorted risk perceptions (Tversky & Kahneman, 1982).

Further, we overestimate rare cases of death and underestimate common causes of death (Slovic et al., 1982), we undervalue outcomes that are probable in comparison with outcomes that are obtained with certainty (Kahneman & Tversky, 1982; Tversky & Kahneman, 1981), we are biased to think bad things will happen to others but not to us (Slovic et al., 1982) and we fall prey to the gambler's fallacy, that is, the belief that chance is a self-correcting process in which a deviation in one direction leads to a deviation in the opposite direction in order to maintain an equilibrium (Teuber, 1990;

Tversky & Kahneman, 1982). Research shows that even people with extensive training in statistics are prone to intuitive biases of risk perception (Kahneman & Tversky, 1982).

One might understand this evidence as suggesting that we make poor and incoherent decisions about probabilities that fail to match up with the actual dangers that risks pose. This interpretation suggests that we do not have good reasons to accept the risks of daily life. We mistakenly think these risks are low but if we understood the dangers posed by our usual activities properly, we would deem them unacceptably high. This is how Wendler and colleagues interpret the evidence (Wendler, Belsky, Thompson, & Emanuel, 2005; Wendler, 2010, p.66-67). They argue that ignoring the risks of daily life is not rational; these risks are higher than we realize, and much higher than most ethics committees think are allowable (Wendler et al., 2005). Wendler writes:

[T]he extent to which we ignore the risks of daily life is not a fully rational process. In many cases, our attitude regarding risks has to do with features of the situation that are not correlated directly with risk levels, such as our perceived level of control and our familiarity with the activity...Recognizing the different factors that influence our perception of risks undercuts the attempt to ascribe moral significance to the threshold for which risks we attend to. (Wendler, 2010, p.66-67)

Wendler also suggests that providing more empirical evidence about the risks of daily life is likely to convince ethics committees to reject these risks as excessively risky and a poor comparator for risks in research with children (Wendler et al., 2005).

However, this is not a persuasive interpretation of the evidence. It is true that we assess risks in ways that are predictably problematic and lead to systematic errors. But it is unlikely that our perceptions of the risks of daily life are flawed in the way Wendler suggests. That is, it is unlikely that knowing empirical statistics about the likelihood and magnitude of the risks of daily life would convince us that our risk judgments are ineffectual and that our usual activities are too risky. For example, upon learning the risks of crossing a busy street, a person seems unlikely to decide that this activity is less acceptable than she originally thought and to attempt to limit her street crossings in the future. This suggests that our acceptance of the risks of daily life may not be the result of our propensity to misjudge risks and deem risky situations safer than they actually are.

Instead, it is an indication that our risk perceptions may also be influenced by another, non-empirical kind of mechanism.

A better way of understanding the way in which we perceive risks is that we are not uniquely or primarily motivated by empirical evidence, that is, we do not seek to limit risks to the lowest possible degree or even to a consistent degree. Instead, we construct and manipulate our understandings of risk to conform with a society's broader values. The main idea is that as a society or a given group, we value certain projects, goals or ways of life. These projects, goals or ways of life are valued for the benefit of society as a whole and not uniquely for a particular individual. Further, our decisions to focus on some risks and to disregard others reflect the things and ways of life cherished by the group.

We perceive risks as acceptable not because they pose less than a particular statistical degree of death or injury. Instead, they are acceptable because they conform to a society's social values and commitments. By the same token, we ignore or manipulate perceptions of risk that threaten the ways of life valued by the aggregate. Understanding risk perceptions as a social construct and a meaningful representation of the things we value suggests that statistics estimating the likelihood of death or disability associated with various actions will not necessarily motivate changes in our behaviours or attitudes. We may simply manipulate the empirical evidence in order to pursue chosen ways of life.

The idea that our risk perceptions are, at least in part, a reflection of societal values helps to explain why we have good reasons to perceive the risks of daily life as socially permissible. We deem these risks acceptable because they are a reasonable sacrifice to make in the interests of pursuing the kinds of lives we want to live as a society. That is, our acceptance of daily risks as permissible reflects the group's conception of the kinds of projects and institutions that help to uphold and promote meaningful ways of life. For example, as a society, we value pollution reduction. Thus, we undertake activities such as community clean up days and weekly recycling that contribute to this goal. Recycling will (hopefully) limit and reduce the amount of waste added to landfills, which, in turn, aims to contribute to a better world for future people. Recycling involves some degree of risk, such as the risks of being cut by tin, glass or paper goods while sorting recyclables and the risks of moving a recycling box to and from the street for a roadside pick up. But

we accept these risks as safe enough because they contribute to a valuable cause. More generally, daily risks should be understood as an acceptable range of risks that a society as a whole has undertaken to promote a certain form of social life.

An important point arising from this analysis bears further clarification. Many of the risks of daily life are accepted because they offer corresponding personal benefit. For example, the risks of driving to work may be undertaken because they offer the benefit of a convenient and timely arrival. But understanding the permissibility of daily risks as a reflection of a group's values (rather than an individual's values) helps to explain why daily risks are permissible not only for personal benefit but also for the sake of others. Recycling aims to limit environmental harms for future people, but it is unlikely to have any immediate effect on the quality of the air that we currently breathe. Nonetheless, we accept the risks of recycling because they are part of an environmentally responsible and valuable social goal that is widely endorsed. That is, they are risks that are permissible and desirable for the benefit of others.

One might respond to this by pointing out that not everyone embraces the same goals or undertakes efforts to promote valuable social goals. That is, there is rarely complete agreement about the projects, goals, and ways of life that are meaningful to every member of a group. This is true. But for a daily activity to be 'safe enough' in the way suggested above, it need not be the case that every member of society endorse a given activity as a useful contribution to a meaningful way of life. Instead, it is sufficient that it is widely recognized that the kinds of activities, projects, and social organizations that impact our lives, and the kinds of risks that we face daily as a consequence of these organizations and projects, are considered acceptable by most reasonable people. Thus, the fact that society offers regular recycling pick-ups and sanctions the use of plastic bags to carry groceries might be taken as evidence that environmental consciousness is socially endorsed way of life. And daily risks undertaken to promote this goal are considered acceptable, in part, because they contribute to valuable ways of life.

The idea that our risk perceptions reflect our values is well-illustrated by research in anthropology. One of the basic claims of cultural theory is that there is an important relationship between various ways of life and risk perceptions. Proponents argue that people organize their perceptions of risk to support and advance the way of life to which

they are committed (Douglas, 1985; Douglas & Wildavsky, 1982; Wildavsky & Dake, 1990). For example, we link ideas of risk with deviancy. In primitive religions, people's perceptions of the risks of pollution were constructed in conformity with and in order to maintain the dominant religious order. To this end, acts that violated the code—like adultery or political disloyalty— were understood not only as impious but also as the causes of the outbreak of contagious diseases or the cause of natural disasters (Kahan & Braman, 2006; Douglas, 1966). Further, we continue to link ideas of risk with deviancy (Kahan & Braman, 2006). Modern conceptions of dirt, and the revulsion we feel towards dirty things, is linked to the violation of ordered relations in modern societies. Douglas writes:

Shoes are not dirty in themselves, but it is dirty to place them on the dining-table; food is not dirty in itself, but it is dirty to leave cooking utensils in the bedroom, or food bespattered on clothing; similarly, bathroom equipment in the drawing room clothing lying on chairs out-door things in-doors; upstairs things downstairs; under-clothing appearing where over-clothing should be... (Douglas, 1966, p.35-36)

Her idea is that our assessment of something as a source of dangerous contamination can be understood as an effort to condemn “any object or idea likely to confuse or contradict cherished classifications” (Douglas, 1966, p.36; Kahan & Braman, 2006, p.152). That is, we deem things dangerous when they threaten social relations and institutions that we value.

It follows that our seemingly peculiar tendencies to focus on some risks and to disregard others can be understood as an attempt to accommodate and to reinforce various ways of life. As Douglas writes:

Persistent shortsightedness, selectivity, and tolerated contradiction are usually not so much signs of perceptual weakness as signs of strong intention to protect certain values and their accompanying institutional forms...Gaps and contradictions in a system of thought are a good guide to the institutional fabric which supports it and to which it gives life. (Douglas, 1985, p.3)

Understood in this way, people's risk perceptions and disagreements about risk are neither ill-informed nor incoherent but part of an “ongoing debate about the ideal society” (Douglas & Wildavsky, 1982, p.36). They reflect the kinds of risks we think

should be socially acceptable in order to pursue meaningful lives and to uphold the institutions that contribute to these ways of life.

Research in social psychology also suggests that psychological mechanisms induce people to form beliefs about the risks of activities that conform with their cultural evaluations of those activities (Kahan & Braman, 2006). One such mechanism, called cognitive-dissonance avoidance, explains that dissonance—that is, the existence of non-fitting relations among cognitions (beliefs and knowledge)—motivates our beliefs and perceptions (Festinger, 1957, p.3). It is comforting to think that what is cherished is harmless and what is vulgar is dangerous. Further, it is psychologically uncomfortable to discover the existence of dangers that threaten our commitments or affiliations (Kahan & Braman, 2006). Consequently, we try to reduce dissonance and to avoid information that is likely to increase dissonance (Festinger, 1957, p.3). In short, we focus on certain risks and disregard others in order to avoid the discomfort arising from risk judgments that threaten our commitments and our adherence to ways of life that we find meaningful.

A set of dynamics known as “in-group/out-group” dynamics also harness risk perceptions to cultural values (Kahan & Braman, 2006, p.155). These dynamics explain that our commitments influence the way we assess conflicting claims about risk. Specifically, when we encounter conflicting claims about risks that we are ill-equipped to assess—such as claims about the likelihood of a terrorist anthrax attack or the risks of salmonella poisoning from spinach purchased at the grocery store—we rely on experts that we trust to differentiate between serious and specious risks (Kahan & Braman, 2006, p.155-156). But we tend to trust those whose viewpoints are similar to our own and are consequently biased towards some conclusion by mechanisms like cognitive-dissonance avoidance (Kahan & Braman, 2006, p.155-156). Thus, our commitments or worldviews are at play even when we mediate between conflicting evidence by turning to experts.

Evidence for a strong connection between risk perceptions and worldviews is also corroborated by studies. For example, one study found that cultural worldviews exert stronger influence over our perceptions of environmental and technological risk than all other factors, including gender, race, income, education, and political ideology (Kahan, Braman, Gastil, Slovic, & Mertz, 2005). Other studies generalize the impact of worldviews on risk perceptions to people’s beliefs about the efficacy of various public

policies. For example, a survey of 1800 people demonstrated that respondents' beliefs about whether increasing restrictions over gun control will (a) promote public safety by reducing gun violence and accidents or (b) reduce public safety by restricting the ability of innocent people to protect themselves against violent crime were best determined by their worldviews. People who tended towards a hierarchical and individualistic worldview believe that increasing gun control is unreasonable while more egalitarian and solidaristic people trust that gun control will enhance safety (Kahan & Braman, 2006). Researchers have also replicated these results with reference to attitudes towards the death penalty, drug criminalization, and abortion (Kahan & Braman, 2006).

These studies offer general lessons that help to explain why daily life is morally relevant. Research from anthropology and social psychology indicates that our risk perceptions are intertwined with our values. These perceptions reflect and reinforce the kinds of activities and the ways of life that we cherish. We downplay the risks of walking, crossing busy streets, driving in cars, and riding in public transportation because these actions facilitate mobility and we value our ability to get from place to place. Similarly, we emphasize the positive aspects of living in communities—like help from neighbours, support from friends, and easier access to various goods and services—and downplay the risks of doing so—such as increased likelihood of encountering violent crimes and the easier spread of contagious diseases—because we value social life, bonds with other people, as well as access to goods and services. More generally, our judgments about what is risky or not reflect the activities, projects and ways of life that we find desirable. They are part of our conception of what makes a life meaningful and which kinds of institutions help to uphold and promote meaningful ways of life.

It follows that the failure of our risk judgments at times to line up with empirical evidence about the risk of death or injury incurred by an activity does not threaten attempts to ascribe moral significance to the risks of daily life. We ignore the risks of daily activities not because we mistakenly think they involve only low risks but instead because it is necessary to undertake these risks in order to promote ways of life we find desirable. To put this another way, these risks are part of an acceptable trade-off between personal safety and being able to live the kinds of lives valued by a group.

I am not suggesting that each morning, or before undertaking any particular daily activity, we pause and calculate whether the risk of the activity (or the risks for the day) are necessary or worthy aspects of an institution that contributes to our chosen way of life. Instead, the risks of daily life should be understood as a background set of risks that most reasonable people accept implicitly. That is, the risks of daily life are part of a range of risks that a society as a whole has undertaken to promote a certain form of social life. Consequently, we accept these risks (and undertake them automatically) as part of a reasonable trade off between our personal safety and our ability to pursue the kinds of lives we value.

Further, it need not be the case that a daily risk is one that is literally encountered by most or all people everyday. Daily risks should be understood as risks comparable to or of the same magnitude as those encountered in daily life; they are part of a background range of risks that form part of an acceptable trade-off between personal safety and valued ways of life. They are the kinds of risks that reasonable people should deem socially acceptable. That is, people have good reason to consider these risks socially acceptable; undertaking these risks helps to promote the kinds of lives they want to live.

Ascribing moral significance to the risks of daily life has important implications for research with children. Socially acceptable risks (that is, risks that people have good reasons to accept) strike a reasonable balance between individual safety and the pursuit of valuable goals. That is, they are the kinds of risks that are acceptable to undertake in the interests of permitting valuable social pursuits to continue. Further, these risks are permissible not only for ourselves but for a broad range of members of a group and they are permissible irrespective of whether they offer direct corresponding benefit. Clinical research with children is a valuable social endeavour; it promotes improved care for current and future children. Accordingly, it should be permissible for clinical research to expose subjects to some kinds of risk. To how much risk should we expose children in research procedures that do not aim to offer them direct medical benefit? Children should be exposed to the same kinds of risks that are acceptable in the pursuit of other valuable social endeavours, that is, to socially acceptable risks or the risks of daily life. Thus, it seems reasonable to measure the risks of non-therapeutic procedures according to the risks of daily life.

Three points raised by the comparison of minimal risks to the risks of daily life merit further consideration. First, the idea that our risk perceptions are linked with and formed by our values and the ways of life we cherish does not suggest that we should disregard empirical evidence. I've argued that Wendler's statistics about the risks of death or injury incurred during everyday activities do not necessarily indicate—as he suggests—that daily life poses unacceptably high risks about which we are unaware. Further, I've argued that Nicholson's quantitative account of risks is unsuccessful. But the main problem with these proposals is not that they invoke empirical evidence. The problem is that they try and constrain the permissibility of risk according to a particular empirical degree of death or injury. And there is no clear and non-arbitrary way of drawing a normative line at some particular degree of risk of death or injury. To put it another way, it is, at best, hard to see why we should recognize a 1 in 1,000,000 risk of death, for example, as negligible.

Nonetheless, any successful account of minimal risk should be open to empirical evidence. Statistics about the risks of death or injury of daily activities may draw public attention to serious and unanticipated problems generated by commonly undertaken activities. This evidence could influence our assessments of permissible risk. When empirical evidence about the risks of an activity is strong enough to persuade people in a society that a given activity is overly risky, that is, that it is not a reasonable trade-off between personal safety and valuable social goals, then this risk should no longer be accepted as part of the background range of risks considered to be morally acceptable daily risks. Understood in this way, my account of minimal risk as the risks of daily life may be informed, but not primarily guided by empirical evidence about the risks of our common activities.

A second point to consider is how minimal risk should be understood with respect to daily life. Should minimal risk activities be understood as posing no more than the risks of daily life? Is it permissible for the risks of non-therapeutic procedures to pose a minor increase over the risks of daily life? To recall, component analysis limits the risks of non-therapeutic procedures to a *minor increase over* minimal risk. The logic is as follows: the kind of risk identified as socially acceptable was chosen as a point on the lower end of the spectrum of risks, which reflects the risks most reasonable people

already do find acceptable. But if the threshold for acceptable risk permitted only the risks of daily life or risks of the same magnitude, and never anything more, then no new experiences could be enjoyed. And this would not be in a child's best interests (Freedman, Fuks, & Weijer, 1993, p.16).

The argument draws on ways in which responsible parents make decisions in family life. When a parent considers whether a child should participate in a new kind of activity, she asks whether the risks of the new activity are sufficiently similar to those in the child's usual life that the experience should be permitted at a given time. It follows that a parent's decision about whether to permit a new experience and its risks is anchored to and not governed by the risks of daily life (Freedman, Fuks, & Weijer, 1993, p.16-17). Similarly, when standing in for the scrupulous parent, a research ethics board should use similar logic, that is, they should set the upper threshold for the risks of non-therapeutic research procedures as a minor increase over minimal risk or a minor increase over the risks of daily life.

According to my analysis, acceptable risks are daily risks because these risks reflect ways of life that a society supports as valuable for the benefit of the group. The assessment of permissibility is not made on behalf of a particular child. Instead, it is made by a research ethics board on behalf of a reference class of children and by appeal to a common set of risks that are deemed permissible in order to pursue valuable projects or ways of life. Given that it does not focus on the potential benefit of a new experience to a particular child, there is no clear reason to permit a minor increment over the degree of risk that is acceptable in order to promote valued ways of life. It follows that according to my interpretation, the risks of non-therapeutic research procedures should pose no more than minimal risk, understood as the risks of daily life.

A third point raised by the above analysis threatens the success of ascribing moral significance to the risks of daily life. I've argued that daily life is morally relevant because it involves risks that people have good reason to accept as socially permissible. That is, daily risks are part of an acceptable trade-off between personal safety and the pursuit of cherished ways of life. But this analysis does not apply to all people's daily risks. The daily lives of different people involve different degrees of risk, some of which do not seem to be socially endorsed. For example, daily life in a war zone or a resource

scarce setting may pose high degrees of risk that are inevitable or the consequence of injustice rather than risks that reasonable people have good reasons to accept. Identifying daily life as morally relevant opens my argument to a serious problem: it permits the differences between the risks of different people's daily lives to be used to exploit them in research. As Evans and Evans point out:

A problem with [the daily life] interpretation of 'minimal risk' is that different people's daily lives vary enormously; are the relevant clinical risks to be compared with the typical daily life of a schoolteacher, or of a long-distance lorry-driver, or of a steelworker, or of a librarian? (If a schoolteacher, then in an urban secondary school or in a rural primary school? And so on). (Evans & Evans, 1996, p.66)

That is, people's daily lives vary significantly, and if we allow these differences to influence the degree of risk that a child may face in non-therapeutic research procedures, then children who face higher daily risks will be at a disadvantage. They will be permitted to face higher risks than their counterparts who live safer lives. And there is no obvious reason to permit this variation in treatment; it may contribute to the exploitation of unfortunate children in research.

This objection is on solid ground. Indexing minimal risk to the risks of daily life without specifying a particular reference group of children whose daily lives are morally relevant opens the possibility of unjustified or unjustifiable treatment between children in research. To prevent the exploitation of children in research it is necessary not only to explain why the risks of daily life are morally relevant but also to say whose daily life, in particular, should be morally relevant. This analysis must constrain the referent for minimal risk in such a way that daily risks imposed by background conditions of injustice are not used to justify the permissibility of non-therapeutic research procedures. I take up this task in the following chapters; I propose a framework by which to assess which children should be the referent for minimal risk.

2.5 Further reflections

Understanding minimal risk as the risks of daily life retains some of the advantages of the other interpretations while avoiding their pitfalls. There is something appealing in Wendler's account of charitable activities and in Ackerman's account of children's

education in family life. These proposals draw on social mores about what is permissible and desirable; each refers to an activity or goal that reasonable people would identify as socially valuable. Further, they both involve activities that involve risks for the benefit of others. These are desirable features for a morally relevant comparator for minimal risk. But these accounts require further examination. Neither meets the requirement of generality; we do not tend to morally educate infants and very young children and this group does not participate in charitable activities. Consequently, it is not clear whether, and if so why, they can participate in research. Further, Wendler's account fails to explain why charitable activities are the only valuable social goals that should serve as moral comparators for risks in non-therapeutic research procedures. And Ackerman's account doesn't adequately explain how to operationalize the degree of risk to which it is appropriate to intentionally expose a child for educational purposes in family life.

My interpretation also measures risks according to activities and projects that are deemed socially valuable. Further, it also identifies a group of risks that may be permissible for the benefit of others. Specifically, it identifies the morally relevant risks as those involved in projects and activities that contribute to ways of life that society finds valuable. But it does not constrain permissible risks to certain kinds of valuable projects; it is a broader standard, which accounts for the many and varied projects and activities that we value, including charitable activity and moral education as well as other important social goals such as reducing pollution, promoting peace, promoting democracy, and fighting for human rights. Further, it offers a standard that applies to children of all ages, including infants and very young children. Thus, it has an advantage over the others.

Nonetheless, it is worth emphasizing that my interpretation is consistent with and aims to build on Wendler and Ackerman's proposals. The moral education of children in family life and participation in charitable activities are likely to be two instances of the activities of daily life. They are examples of activities or projects that are, and should be, deemed socially permissible; people have good reasons to accept these activities, and their accompanying risks, as part of a reasonable trade-off between personal safety and cherished ways of life. Consequently, the risks of charitable activities and moral

education are examples of the kinds of morally relevant activities that might also be found permissible according to a daily life interpretation.

Is the daily life interpretation successful? At the beginning of this chapter, I proposed that a successful interpretation must meet four criteria; it must meet the requirements of practicality, generality, fidelity, and defensibility. The analysis in this chapter offers a preliminary account of a general and defensible interpretation. But it is incomplete. It has not adequately constrained the interpretation of minimal risk to the daily lives of a particular group of children. Further, it has not explained how the daily life interpretation may be implemented in practice. In the following chapters, I will refine my proposal. In chapters three and four, I will constrain my interpretation of minimal risk to the daily lives of children who do not face undue burdens and in chapter 5, I will examine a case study to demonstrate how my proposal may be implemented by an ethics committee. After elaborating on these aspects of my interpretation, I will assess my proposal's success by examining whether it meets the necessary criteria for a successful justification.

Finally, I've argued that the main challenges involved in identifying which degree of risk is low enough to be permissible in non-therapeutic research procedures with children lie in defining what is meant by minimal risk and explaining why this kind of risk is morally relevant. I've defended the idea that minimal risk should be understood as the risks of daily life and sketched a new justification for why daily risks are morally important. Our daily activities involve risks that are, and should be, treated as socially permissible. The following chapters will focus on whose daily life should be morally relevant, that is, who should be the referent for minimal risk.

Chapter 3

The uniform and relative interpretations⁴

I've argued that the concept of daily life has some normative force; it identifies the kinds of risks that should be treated as socially permissible. Daily risks are part of a reasonable trade-off between personal safety and the ability to pursue meaningful lives. But this analysis is incomplete. A persuasive defense of a daily life interpretation must also specify whose daily life is morally relevant. The daily lives of some groups of people seem to involve risks that are not socially permissible. Thus, the success of the daily life interpretation of minimal risk relies on answering an additional question: who should be the referent for minimal risk?

Commentators in research ethics recognize that this ambiguity must be addressed. But their arguments aiming to identify the referent for minimal risk are often unclear. When examining who should be the referent, commentators also ask a second question: does a uniform standard or a relative standard governing research with children meet the moral requirements of justice? That is, should minimal risk apply to all children in the same way or are there morally relevant differences between children that justify differential treatment in research? This second question is important; it asks what kinds of moral rules are justifiable in research with children, but it is separable from the identification of a group of children whose daily lives should serve as the morally relevant comparator for minimal risk. Nonetheless, the two questions have become intertwined.

In this chapter, I argue that progress on the identification of a morally justifiable referent for minimal risk requires that we separate examinations about what kind of standard is morally appropriate from attempts to identify a group of children who should be the referent for minimal risk. I argue that focusing on the uniform and relative interpretations gives rise to two main problems: (1) these interpretations misconstrue the

⁴ A version of this chapter has been accepted for publication in the *Journal of Medicine and Philosophy* (Binik & Weijer, forthcoming).

most fundamental difference between proposals for who should be the referent for minimal risk and (2) the uniform interpretation fails to identify one distinct and consistent group of children as the referent for minimal risk; different descriptions of this position identify unique, and, sometimes conflicting groups of children as the referent. I conclude that progress on the identification of a justifiable referent for minimal risk requires that we stop focusing on the uniform or relative standards and address a more fundamental question: should healthy children or the subjects of the research—including both healthy and sick children—be the referent for minimal risk?

My argument is divided into the following sections: I begin by describing the debate over minimal risk as it traditionally appears in the research ethics literature, that is, as a debate between the uniform and relative interpretations. I then clarify misconceptions and construct the strongest version of each interpretation. Next, I identify two problems that arise when commentary focuses on the uniform and relative interpretations. In the final section, I argue that identifying the referent for minimal risk requires that we focus on whether healthy children or the subjects of the research should be the referent for minimal risk.

3.1 The traditional formulation of the debate

Ambiguities concerning the identification of the referent for minimal risk receive attention in the research ethics literature. Many commentators describe the debate over the referent for minimal risk in similar terms. They frequently describe the debate as a choice between two interpretations, (a) the uniform interpretation (also known as the absolute interpretation) and (b) the relative interpretation (Wendler, 2009; Reid & Krahn, 2007; Kopelman, 2002b; Fisher, Kornetsky, & Prentice, 2007; IOM, 2004; Snyder, Gray, & Miller, 2011).

The uniform interpretation attributes the same degree of risk to all children irrespective of their health status (Ross, 2003). Thus, risks cannot be minimal for some children but more than minimal for other children. While the uniform interpretation applies one standard to all children, the competing interpretation, the relative interpretation, permits higher risks to count as minimal for some. The relative interpretation permits higher risks to be classified as minimal if they are comparable with

the risks experienced by that individual in her daily life (Freedman, Fuks, & Weijer, 1993).

3.2 Clarifying the uniform and relative interpretations

To determine whether either the uniform or relative interpretation can help to identify the referent for minimal risk it will be useful to clarify what is meant by each interpretation. In this section, I will construct the strongest version of each interpretation and dispel common misconceptions before subjecting each to critical scrutiny.

The uniform interpretation of minimal risk is also known as the absolute interpretation. That is, some commentators use the term absolute (Wendler, 2009; Reid & Krahn, 2007; Snyder et al., 2011; Kopelman, 2004; Westra et al., 2011) while others use the term uniform (Fisher et al., 2007; SACHRP, 2005) to describe the same interpretation of minimal risk. The terms absolute and uniform have different meanings. Which one do commentators have in mind? The term absolute refers to something objective or universal. It follows that one could understand an absolute interpretation of minimal risk as referring to a universal set of risks experienced by all children in their daily lives. This kind of interpretation would suggest that there is some fact of the matter concerning the risks children face in daily life. That is, that some fixed group of risks faced daily by all children could be identified as minimal risk. Further, this kind of interpretation would permit moral judgments about what kinds of risks count as minimal to be made by appealing to evidence about the “absolute risks” experienced by all children in daily life; if non-therapeutic research procedures pose risks that are comparable to the fixed group of risks faced daily by all children, then they could be deemed permissible.

This interpretation of minimal risk is implausible. There is no objective degree of risk that all children face in daily life; the risks children face in daily life differ according to a child’s age, environment, and health status. It follows that determinations about what degree of risk should be deemed minimal require that some person or group of people’s daily lives, in some particular place, and at some given time be chosen as a reference point. As Prentice and Gordon point out, “there is nothing absolute about ‘daily life,’ and the risks inherent in the daily life of a person from rural Iowa are not the same, quantitatively or qualitatively, as those inherent in a person from inner city New York”

(Prentice & Gordon, 2001, p.L-7). Kopelman agrees. She points out that minimal risk has multiple meanings and not one objective meaning. It might refer to “all the ordinary risks encountered in daily life by any of us or all of us” (Kopelman, 2000a, p.3-6). Further, it is this very ambiguity that motivates the debate over the referent for minimal risk. If there were one uncontroversial degree of risk faced by all children in their daily lives, then there would be no need to identify the referent for minimal risk. Thus, the absolute interpretation of minimal risk should not be understood as reflecting the literal meaning of the term “absolute”.

A more plausible understanding of the absolute interpretation of minimal risk, and the one reflected in the literature, understands minimal risk as giving rise to a uniform standard. The term ‘uniform’ describes something that is unchanging, unvarying, consistent or non-fluctuating. Thus, rather than suggesting the existence of a set of universal risks encountered in the daily lives of all children, a uniform interpretation of minimal risk chooses one degree of risk as the morally relevant type and applies this degree of risk to all children involved in research. The idea this interpretation is meant to capture is that no matter what kinds of differences children face in their respective daily lives, minimal risk must be measured according to one fixed level of risk, faced by some particular group of children. That is, something cannot be assessed as minimal risk for some people but not for others.

Commentators in the research ethics literature understand minimal risk in this way. For example, Kopelman argues that the “absolute interpretation of the ‘everyday-risks’ standard...does not permit reviewers to assess something as minimal risk for some people but not others” (Kopelman, 2004b, p.361). Similarly, Snyder and colleagues write:

[T]he federal guidelines are understood as setting a single standard for the risk found in the ordinary lives of a certain class or set of children. This standard class of children would then set the baseline for risk against which the actual risk found in proposed clinical trials would be measured. Even if the risks faced in the daily lives of the potential research subjects are different from those faced in the daily lives of the members of the standard class, it is the risks faced by the standard class that will be used as a basis of comparison. (Snyder et al., 2011, p.7)

Thus, both the absolute and uniform interpretations of minimal risk seem to refer to the same idea: that some particular level of risk faced by children in a society (regardless of their socio-economic or health status) should be identified as minimal and this basic shared level of risk should then be recognized as the baseline for measuring minimal risk.

The competing interpretation, the relative interpretation, permits risks to be considered minimal for one person but more than minimal for another; on this interpretation, risk determinations are made based on whether the degree of risk posed by some procedure is comparable with the risks experienced by a particular individual in her daily life. Insofar as children's daily experiences expose them to varying degrees of risk, what counts as a minimal degree of risk might vary between different children. Thus, unlike the uniform interpretation, the relative interpretation sometimes permits the degree of risk that counts as minimal to differ.

One common misconception about the relative interpretation bears clarification. The relative interpretation is often understood as justifying almost any degree of non-therapeutic risk with children just as long as we can identify a group of children who are unlucky enough to already face this degree of risk in their daily lives. Thus, the relative interpretation is commonly described as permitting the inclusion of children in high risk environments, including geographically unstable areas or war torn countries, in higher risk research. Commentators who understand the relative interpretation of minimal risk in this way reject it as unjust. They claim that this interpretation exploits the unfair circumstances of certain children. For example, Wendler claims that the problem with the relative interpretation is that "it would allow researchers to expose children who live in violent neighborhoods or who face greater than average environmental health hazards to greater risks in research that does not offer a prospect of direct benefit" (Wendler, 2009, p.116). Elsewhere, he argues that "[c]hildren who live in violent neighborhoods or who face greater than average environmental health hazards could thereby be exposed to greater research risks simply because they face greater risks in their daily lives. This result seems unjust, a kind of societally induced double jeopardy" (Wendler, 2005, p.827). Similarly, the IOM rejected the relative interpretation of minimal risk because it permits "greater research risk for children exposed to higher than average risk of harm in their personal lives (e.g., because they are ill or live in unsafe neighborhoods)" (IOM,

2004, p.5).⁵ Thus, the relative interpretation is understood as permitting a flexible standard, which allows children who face higher risks as a result of their illness or dangerous living environments to be exposed to higher degrees of risk than children facing lower degrees of daily risk.

However, according to the most plausible interpretation of the relative standard, children's dangerous living conditions do not justify their exposure to higher risk research. The relative interpretation does permit the meaning of minimal risk to vary, but not without constraints; the minimal risk standard operates within a broader framework of research ethics principles, which prohibit the inclusion of children in dangerous living conditions in any research, much less higher risk research. In the Belmont Report, the National Commission did not consider the ethical permissibility of including children in unsafe societies in research explicitly, but the report's emphasis on the importance of fairness in the selection of research subjects suggests that children in unstable societies should not be research subjects. It explains that "the selection of research subjects ... needs to be scrutinized in order to determine whether some classes are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied" (Belmont Report, 1979). The National Commission developed this argument with welfare patients, racial and ethnic minorities, and institutionalized people in mind. But it can be extended to the case of children living in unsafe environments. These children are more vulnerable than children living in safe environments and accordingly, their situation merits careful attention. If these children are selected because their compromised situation makes them readily available and easy to manipulate, then including them in research violates the principle of fairness in subject selection.

The prohibition on the inclusion of groups such as children who live in dangerous locations as research subjects is even clearer in the National Commission's procedural guidance for assessing the fairness of subject selection. They argue that particularly vulnerable individuals may need to be excluded from all types of research. They write:

⁵ See also Kopelman, 2000, p.750; Kopelman, 2004b, p.363; Wendler, 2004, p.191; Wendler, 2009, p.116; Shah et al., 2004.

[S]ocial justice requires that a distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons. (Belmont Report, 1979, p.18)

Insofar as children in unsafe environments are “doubly vulnerable”, both from their status as minors and from their higher risk living conditions, it seems reasonable to infer that they are precisely the type of group that the National Commission would exclude from research. Thus, one of the principles of research ethics—the requirement for fair selection of research subjects—prohibits the inclusion of children in dangerous living conditions from facing higher risks in research. Insofar as the minimal risk rule operates within and in conjunction with these moral rules, the most plausible understanding of the relative interpretation does not legitimize the exposure of children in dangerous living conditions to higher risk research.

A careful reading of commentary on the relative interpretation of minimal risk reveals that—in keeping with the moral principle of justice as it is described in the Belmont Report—proponents of the relative interpretation aim to exclude children in dangerous environments as the referent for minimal risk. In the original argument, Freedman, Fuks, and Weijer argue that “[b]ecause children and their situations differ, a judgment anchored to the risks of everyday life, whether arrived at by parent or ethics committee, must be made relative to the child's actual situation” (Freedman, Fuks, & Weijer, 1993, p.17). That is, they interpret the referent for minimal risk as the subject of the research and not children in dangerous environments. When discussing the “subject of the research”, the authors refer explicitly to healthy children as well as children with a disease or disorder. However, no mention is made of children living in unsafe environments. Although the language in the original formulation does not explicitly exclude the possibility of interpreting the subjects of the research as including children living in dangerous environments, the most plausible interpretation understands the authors as identifying the referent for minimal risk as the subjects of the research—including healthy, sick children and dying children—but rejecting the claim that children living in unsafe environments can be included in higher risk research.

Elsewhere, Miller and Weijer make this point explicitly. They reject the idea that measuring minimal risk against the daily life of the subjects of the research facilitates the exploitation of children who live in dangerous environments in research. They write:

... [M]inimal risk does not exist in a vacuum. It functions in conjunction with the fundamental principles of research ethics enunciated by the National Commission and the regulatory protections derived therefrom... [t]o remain consistent with the moral and regulatory framework of which it is part, minimal risk cannot be used to justify the exploitation of vulnerable populations. (Miller & Weijer, 2000, p. 9)⁶

That is, minimal risk is not the only moral requirement that must be met for research with children to be permissible. It exists in combination with other foundational principles of research with humans—such as the moral requirement not to burden an already burdened population—that prohibit the exploitation of particularly vulnerable children living in dangerous locations. Thus, the relative interpretation is best understood as permitting variable treatment of children within some constraints; this interpretation, in combination with the broader rules of research ethics, excludes children living in dangerous environments but does permit higher non-therapeutic research risks on some sick children or dying children. It follows that rejections of the relative interpretation should not be based on whether this standard permits children in dangerous environments to be the referent for minimal risk but on whether a child's health status justifies differential treatment. Thus, the relative interpretation is best understood as permitting variable treatment within constraints; it permits the degree of risk that counts as minimal to vary according to a child's health status.

3.3 Problems with the traditional formulation

Even the most plausible readings of the uniform and relative interpretation generate problems for the identification of a justified referent for minimal risk. (1) The uniform and relative interpretations misconstrue the most fundamental difference between

⁶ Other arguments that endorse the relative interpretation without endorsing the inclusion of children in dangerous environments in higher risk research include Freeman, 1994, p.1-5; Noel & Birnie, 2010, p.18-22; Snyder, Gray, & Miller, 2011, p.5-13.

proposals for who should be the referent for minimal risk and (2) the uniform interpretation does not identify a clear and consistent group of children as the referent for minimal risk; it follows that it does not identify a justifiable referent for minimal risk.

The main difference concerning the identification of a referent for minimal risk is not about uniformity and relativity. Some commentators who endorse a uniform interpretation think that unequal treatment between children in research is, at times, legitimate and necessary. For example, Wendler points out that the fact that the degree of risk children face daily varies according to age suggests that researchers and IRBs should implement two different minimal risk thresholds, one for research with younger children and a second for research with older children (Wendler, 2009). Kopelman also explains this point well: she argues that justice does not require equal treatment for all children in research, it requires that “similarly situated individuals be treated similarly, different situated people differently, and that the differences and similarities are relevant” (Kopelman, 2004c, p.752). Thus, the disagreement does not seem to be over whether there should be any differences in the ways that different children are treated in research but instead about which kinds of differences justify a departure from equal treatment between children in research.

The main question concerning the identification of a referent for minimal risk is: which property should justify unequal treatment between children in research? Only the relative interpretation permits determinations about what should count as minimal risk to change based on a child’s health status.⁷ The uniform interpretation, on the other hand, does not permit a child’s health to play a role in determining what kinds of risks count as minimal for her. To put it another way, the main difference seems to be that only one interpretation understands health as being a morally relevant property that justifies unequal treatment between children in research. This difference is important; it addresses a fundamental question about what is just in research with children, that is, can it be permissible to expose sick children to higher degrees of non-therapeutic research risks than would be permissible with healthy children? But this point is not well captured by the distinction between uniformity and relativity. Describing the debate over minimal risk

⁷ As mentioned above, all commentators agree, and for good reasons, that unequal treatment based on a child’s dangerous living conditions is unjust.

as a disagreement about whether a uniform or relative interpretation is appropriate suggests that the morally relevant question concerning research with children is whether a uniform or relative standard is morally permissible. But this obscures the idea that one might be able to consistently endorse a uniform interpretation and allow for some justified departures from equal treatment.

Describing the two competing interpretations as uniform or relative suggests that each interpretation involves either a distinctly uniform determination or a distinctly relative determination. But each interpretation seems to involve both a relativistic and a uniform judgment. The uniform interpretation of minimal risk—like the relative interpretation—requires a kind of relativistic judgment. Above, I explained that the main insight motivating a uniform interpretation is that some degree of risk should not be assessed as minimal risk for some children but not for others. That is, no matter what kinds of differences children face in their respective daily lives, minimal risk must be measured according to one fixed level of risk, faced by some particular group of children. For example, the group “healthy adolescents in Canada” may be chosen as the referent for minimal risk. In this case, minimal risk would be defined as the risks healthy Canadian adolescents face in daily life and this degree of risk would be applied uniformly to children worldwide as the risk threshold for research involving children that does not aim to offer direct benefit. But to choose one group of children (e.g. healthy Canadian adolescents) as the morally relevant group is to make a relativistic determination. That is, if a relativistic determination is understood as a judgment that permits differential treatment between children in research, then it seems that any attempt to choose a particular group of children as the referent is relativistic. It identifies one group of children’s daily lives as morally relevant and requires non-therapeutic research risks to be assessed relative to this group of children’s daily experiences. To put it another way, the relative judgment is that the risks of a study’s non-therapeutic procedures may be measured against the daily experiences of some—but not all—children. It follows that a uniform interpretation does not seem to exclude all relativistic judgments.

Another example further illustrates this point. One might endorse an interpretation in which the referent for minimal risk is an average child. This interpretation is uniform; it measures minimal risk according to the daily experiences of average children. But it

also permits differences between what counts as minimal risk for different children. Average infants have different daily experiences than average 8 year olds. As a result, what counts as minimal risk for an average infant will differ from what counts as a minimal risk for the older child. There is a difference in the way we understand minimal risk for children of different ages, but it is a justified difference within a uniform standard.

Further, a relative interpretation does not preclude a uniform one. On a relative interpretation of minimal risk, the degree of risk that can be considered minimal varies according to the levels of risk experienced in the daily lives of different children. But a variable standard does not preclude a uniform determination. Relativity and uniformity are not mutually exclusive concepts. For example, the phenomenon of sunset can be understood as both relative and uniform. The timing of sunset may vary according to an observer's position on the earth. But the timing of sunset can also be understood as uniform; the sun sets when the sun disappears below the western horizon. Thus, sunset can be understood as having both properties. Similarly, the relative interpretation can be understood as involving a uniform determination. It involves a consistent, non-fluctuating standard: the minimal risk standard. Minimal risk is the unchanging rule that limits the degree of permissible risk. That is, a relative interpretation of minimal risk could be understood as involving a uniform application of the minimal risk standard (in addition to a variable determination about the degrees of risk that should count as minimal).

There is an important difference in the way each of these interpretations treats children in research. But the distinction between uniformity and relativity does not capture the morally relevant difference between these competitors. Describing the debate over minimal risk as a disagreement between a uniform and relative interpretation suggests that the morally relevant difference between the two is a difference about which standard (i.e. uniform or relative) is morally appropriate. But both interpretations involve relativistic and uniform aspects. Thus, this description impedes progress on the debate over minimal risk by obscuring the main point of contention between the competing interpretations. What seems to be important is not whether or not a relativistic or uniform judgment is made (it is made in both cases) but instead, whether or not the meaning of minimal risk should be permitted to vary on the basis of a child's health status. Focusing

on uniform and relative standards obscures the central point of disagreement, which is about whether health is the morally relevant property justifying differential treatment between children in research. Thus, focusing on the uniform and relative interpretations obscure the fundamental difference between proposals for who should be the referent for minimal risk.

(2) The first objection identifies a problem with the distinction drawn between the two competing interpretations of minimal risk. A second objection concerns the uniform interpretation specifically. The uniform interpretation fails to identify one clear and consistent group of children as the referent for minimal risk. In the traditional formulation of the debate, commentators identify the uniform and relative interpretation as the two central competing interpretations of minimal risk. They then ask: “which kind of standard is morally appropriate?” These discussions aim to determine which, if either, of the two interpretations is consistent with the moral requirements of justice in research with children. This is an important question. However, it is different from the central question generated by the minimal risk standard. Minimal risk is defined according to daily life, but it is not clear whose daily life is morally relevant. Accordingly, we must determine “who should be the referent for minimal risk?”

The uniform interpretation does not focus uniquely on identifying the referent for minimal risk; it is also unclear about which group of children should be the referent. The uniform interpretation is attributed to a variety of commentators (Kopelman, 2004b; Fisher, Kornetsky, & Prentice, 2007; Wendler, 2010; Davidson & O’Brien, 2009; Diekema, 2006; Flotte et al., 2006; Glantz, 1998; Tauer, 2002) as well as committees commissioned to explore the ethics of research with children (National Commission, 1977; IOM, 2004; NBAC, 2001; NHRPAC, 2001). However, a close examination of the language in these documents reveals that there is less consensus than is often recognized. The position called the uniform interpretation can be divided into four positions that identify unique groups as the referent for minimal risk. These descriptions give rise to different and, at times, conflicting standards for minimal risk. Thus, proponents of the uniform interpretation do not all seem to support the same interpretation of minimal risk.

What is, at times, taken to be one position (the uniform interpretation), is more accurately described as four positions. The first identifies the referent for minimal risk as

“healthy children” (National Commission, 1977). The second identifies the referent for minimal risk as “normal, healthy, average children” (IOM, 2004; NHRPAC, 2001; AAP, 2003). The third identifies the referent for minimal risk as “normal, average, healthy children living in a stable society” (SACHRP, 2005) and the fourth identifies the referent for minimal risk as “the general population” (NBAC, 2001).

Four descriptions of the uniform interpretation

1. Healthy children
<p><u>National Commission (1977):</u> “minimal risk’ is the probability and magnitude of physical or psychological harm that is normally encountered in the daily lives, or in the routine medical or psychological examination of healthy children”.</p>
2. Average, healthy, normal children
<p><u>Institute of Medicine (2004):</u> “In evaluating the potential harms of discomfort posed by a research protocol that includes children, investigators, and reviewers of research protocols should interpret “minimal risk” in relation to the normal experiences of average, healthy, normal children”</p> <p><u>American Academy of Pediatrics (2003):</u> “The AAP interprets the definition of “minimal risk” to be that level of risk associated with the daily activities of a normal, healthy, average child”.</p> <p><u>National Human Research Protections Advisory Committee (NHRPAC, 2002):</u> “We interpret the definition of minimal risk to be that level of risk associated with the daily activities of a normal, healthy, average child”</p>
3. Normal, average, healthy children living in safe environments
<p><u>Secretary’s Advisory Committee on Human Research Protections (SACHRP, 2005):</u> “The definition of ‘minimal risk’ at 45 CFR 46.102(i) when applied to Subpart D should be interpreted as those risks encountered during daily life by normal, average, healthy children living in safe environments or during the performance of routine physical or psychological examinations or tests”</p>
4. The general population
<p><u>National Bioethics Advisory Commission (2001):</u> “Research, then, involves no more than “minimal risk” when it is judged that the level of risk is no greater than that encountered in the daily lives of those in the general population. The general population standard is less restrictive than the healthy individuals standard; however, the general population standard more accurately captures the risks that are familiar to most persons”.</p>

There are important differences between these four descriptions. They give rise to unique and, at times, conflicting standards for minimal risk. Each identifies a distinct referent for minimal risk. (1) The first interpretation identifies “healthy children” as the referent for minimal risk. On this interpretation, procedures can be determined to involve no more than minimal risk because either the procedure is in fact encountered in a healthy child’s daily life or it is sufficiently similar to those routinely encountered, such as the procedures in a healthy child’s routine examination. The risks healthy children face in daily life include risks such as riding in a car, crossing the street, riding a bicycle, and playing in a playground. The components of a routine well-child examination are reasonably well characterized (IOM, 2004, p.124). These visits include procedures such as routine age appropriate physical and psychological examinations or tests, guidance and education (IOM, 2004, p.124) as well as routine immunization, modest changes in diet or schedule, obtaining blood or urine specimens, developmental assessments, questionnaires, and observational techniques (National Commission, 1977). Thus, we have some sense of the risks a healthy child may face in daily life or during a routine examination.

(2) The second description identifies normal, healthy, average children as the referent for minimal risk. This description involves different criteria than the first. The terms “normal” and “average” are added to the term “healthy” and impose different constraints on the group of children who should be identified as the referent for minimal risk. Any given community includes both children who are healthy and those who suffer from common diseases, disorders or conditions. Some children suffering from common diseases, disorders or conditions are likely “normal” or “average” though not necessarily healthy. Thus, if the second interpretation recognizes normal, healthy or average children as the referent for minimal risk, then this description seems to refer to a broader group of children as the referent for minimal risk.

Is this description meant to measure minimal risk according to healthy children, normal children, average children or all three? Commentators endorsing this interpretation clearly intend to restrict their interpretation to “healthy children” rather than a broader group also including normal and average children. For example, Kopelman— a member of the IOM committee that endorses this interpretation—

explicitly rejects the notion that sick children should be the referents for minimal risk.

She argues:

Children facing death or disability may have painful experiences far removed from those normally encountered by most people in their daily lives. Their difficult daily experiences should not be used to “justify” higher risks as minimal for them, or the door is open to treating some groups in a discriminatory way and exploiting them. (Kopelman, 2000b, p.754)

Thus, the second description is perhaps best understood as equivalent to the first.

(3) The third description identifies normal, healthy, average children living in a stable environment as the referent for minimal risk. Adding a “stable environment” clause restricts membership in this group. On this definition, minimal risk is measured according to the daily lives of healthy children but excludes healthy children living in unsafe environments. Kopelman argues that this description reflects a particular moral judgment about the societies in which it is appropriate to conduct research. She writes: “since everyday risks are not necessarily trivial or minimal, a moral judgment must be made about which group (refugees, firefighters, or librarians) in what community (peaceful or at war) should be used in making comparisons between everyday risks and minimal research risks” (Kopelman, 2000a, p.3-6). Furthermore, she cites the South African guidelines concerning research with children as an example of guidance providing additional protections for children as the result of their inclusion of the “stable society” clause. This description is narrower than the first two. It refers to the subset of healthy children who live in stable environments.

(4) Although some commentators (Tauer, 2002; Wendler, 2004) have understood it as an equivalent formulation of the uniform interpretation, the fourth interpretation, which identifies “the general population” as the referent for minimal risk, gives rise to a broader interpretation of minimal risk than the healthy child (or subset of healthy children) description of the uniform interpretation. It includes people who are sick. Children in the general population include children suffering from common diseases, disorders, and conditions. NBAC endorsed this interpretation, not as an equivalent formulation of the “healthy child” interpretation of minimal risk, but as a more

permissive interpretation (NBAC, 2001). They argue that it is appropriate because it accurately captures the risks that are familiar to most persons.

NBAC's examples of minimal risk procedures—including driving to work, crossing the street, getting a blood test, or answering questions over the telephone (NBAC, 2001, p.83)—resemble the examples of minimal risk provided by the National Commission's more restrictive interpretation. However, certain procedures that count as minimal on a general population interpretation would pose more than minimal risk if the referent for minimal risk is a healthy child. For example, a child with diabetes would be included in this category but excluded from the "healthy child" interpretation of minimal risk. Diabetes is one of the most common chronic conditions in children (Clinical Practice Guidelines, 2008, p.S150-S162). The general population includes children suffering from diabetes. The daily life of a diabetic child will include an insulin therapy regimen, involving multiple daily injections or subcutaneous insulin infusion (insulin pump therapy). In addition, children with diabetes are at higher risk for hypoglycemia, DKA, and autoimmune thyroid disease than healthy children (Clinical Practice Guidelines, 2008). Thus, the daily experiences of a diabetic child may involve higher degrees of risk than those encountered in the daily life or routine examination of a healthy child. Consequently, it is important to differentiate between the "healthy child" description and the "general population" description of the uniform interpretation. They permit different degrees of risk to count as minimal.

Thus, the uniform interpretation does not identify a clear, consistent, and useful referent for minimal risk. The terms "uniform" and "relative" shift the focus of the debate away from the identification of the referent for minimal risk. They also obscure the central ambiguity in the definition of minimal risk. Some descriptions of the uniform interpretation identify the referent as healthy children, others identify the referent as normal, average, healthy children in stable societies, and others identify the referent as the general population. Thus, discussing a uniform interpretation does not necessarily result in a clear answer about which group of children is morally relevant. Instead, focusing on the uniform and relative interpretations seems to leave us with the same questions with which we began: who should be the referent? How should we interpret the definition of minimal risk? Finally, describing the competing interpretations over

minimal risk as a uniform or relative interpretation impedes progress on the clarification of the ambiguities in the concept of minimal risk.

3.4 A new formulation of the debate

Progress on the debate over minimal risk can be made by reengaging with the central—and unanswered—question: is health the morally relevant property justifying different treatment between children in research? In other words, should healthy children or the subjects of the research—including both sick and healthy children—be the referent for minimal risk? To answer this question clearly, commentators should separate arguments about which standard (uniform or relative) meets the requirements of justice from arguments identifying specific groups of children as candidates for the referent for minimal risk.

Analyzing whether healthy children or the subjects of the research should be the referent will help focus attention on the main moral concerns that arise when choosing a referent for minimal risk. For example, what, if anything, is morally relevant about health? Is it permissible for sick children—an already burdened group of children—to be exposed to higher levels of research risk than healthy children? Do healthy children who face high risks as the result of their socio-economic status, geographic location or experiences at school require additional protections in research? Separating the two questions will also help to identify a group of children whose daily lives might provide appropriate guidance for permissible risks in research that doesn't aim to offer the prospect of direct benefit. Finally, protecting the interests of children without delaying or preventing valuable research requires that we reconsider the debate over minimal risk; we must focus directly on the identification of a specific group of children who should be the referent for minimal risk.

Chapter 4

Who should be the referent for minimal risk?

I've argued that the ethical justification for the inclusion of children in research depends on the concept of minimal risk. But the definition of minimal risk is ambiguous; it is often defined by appealing to the risks of 'daily life', but it is not clear whose daily life should serve as the baseline measure. Thus, the question arises: who should be the referent for minimal risk? Arguments in research ethics often identify the referent for minimal risk as either healthy children or the subjects of the research, which includes both healthy and sick children. I argue that neither healthy children nor the subjects of the research are the morally appropriate referent for minimal risk. Both interpretations fail to find a morally appropriate balance between the ethical requirement to protect children in research and the requirement to permit valuable research to proceed.

In this chapter, I propose a novel interpretation of the referent for minimal risk, informed by an insight from theories of distributive justice: justice does not require uniform treatment for all children in research. But it does require uniform treatment of like cases and a justification for unequal treatment. If that is true, only a morally relevant property can justify departures from equal treatment. I propose that the morally relevant property justifying different treatment between children in research is *undue burden*. I argue that children are not unduly burdened if their lives are going well and propose a set of conditions that must obtain for a child to fare well. I conclude that the referent for minimal risk should be interpreted as children who are not unduly burdened by their daily lives, and that children who are not unduly burdened by their daily lives are those who fare well.

My argument proceeds in the following steps: I argue that healthy children should not be the referent for minimal risk, that the subjects of the research should not be the referent for minimal risk, and that proposals for hybrid interpretations are especially problematic. I then propose a novel interpretation according to which the referent for minimal risk should be understood as children who are not unduly burdened by their

daily lives, which I take to refer to children who fare well. I then unpack the concept of children's welfare.

4.1 Background

In the previous chapter, I argued that the uniform interpretation and the relative interpretation complicate efforts to identify a justified referent for minimal risk. These interpretations misconstrue the main moral question by focusing on what kind of standard—rather than which group of children—is morally relevant. I conclude that progress on the identification of a justified referent for minimal risk requires that we re-engage with the central, and unanswered, question: which group of children's daily lives are morally relevant? In what follows, I tackle this question; I examine whether healthy children or the subjects of the research should be the referent and then defend a novel interpretation.

4.2 The healthy child interpretation

Commentators often claim that healthy children or a subgroup of healthy children should be the referent for minimal risk (Kopelman, 1981; Kopelman, 2002a; Kopelman, 2004b; Wendler, 2009; Wendler, 2005; Shah et al., 2004; IOM, 2004; Resnik, 2011; Shah, 2011; NHRPAC, 2002; SACHRP, 2005; Presidential Commission, 2013). Little is said about why this group is appropriate. The idea seems to be that restricting the risks of non-therapeutic procedures to a *low* and *non-variable* degree—that is, the degree faced daily by healthy children—will help to prevent the exploitation in research of unlucky children who face high daily risks. These arguments can be divided into two claims: (1) Children must be protected from variable treatment in research, which may result in exploitation and (2) the degree of non-therapeutic research risk to which it is permissible to expose children should be low.

The first claim suggests that variable treatment is unjust. For example, Kopelman argues that justice requires one uniform standard for all children. She writes: “Having one standard for everyone seems to meet justice requirements to treat people equally and

share burdens and benefits of research fairly” (Kopelman, 2004b, p.361). Wendler agrees. He writes:

This interpretation [that is, any interpretation permitting variability] would allow researchers to expose children who face greater risks in daily life to greater risks in research...Children who live in violent neighborhoods or who face greater than average environmental health hazards could thereby be exposed to greater research risks simply because they face greater risks in their daily lives. This result seems unjust, a kind of societally induced double jeopardy. To avoid taking advantage of some children’s unfortunate circumstances in this way, most commentators endorse this objective interpretation of the minimal risk standard. (Wendler, 2005, p.827)

The IOM concurs. They write:

The threshold of minimal risk should thus be the same for healthy and ill children. Furthermore, the interpretation should not change for groups of healthy children whose daily experiences involve risks greater than those that most other children experience as part of daily life. Thus, children who live in dangerous environments (e.g., with abusive parents or in unsafe housing) would not be exposed to more research risk than children who live in safer environments. (IOM, 2004, p.122)

The claim seems to be that identifying the referent as healthy children will prevent variable treatment, which is thought to violate the ethical principle of justice that burdens and benefits of research be distributed equitably.

The second claim is that the permissible degree of risk should be low. The idea seems to be that healthy children face low degrees of daily risks and accordingly, if they are identified as the referent for minimal risk, then the risks of non-therapeutic procedures will be restricted to a low degree, that is, the same low degree these children face daily. If children are exposed only to a low degree of risk without corresponding medical benefit then they are unlikely to be exposed to unjustifiably high degrees of risk. Thus, identifying the referent as healthy children helps to meet the objective of the minimal risk threshold by ensuring that children will not face overly high degrees of research risk without corresponding medical benefit.

These arguments are vulnerable to at least four objections. First, commentators' objections to variability are surprising. The quotes above suggest that treating children variably in research is unjust. But at other times, the same commentators endorse some kinds of variability. For example, the IOM write that interpretations of risk may "take into account children's developmental status or age because the physical or psychological risk of a research procedure can vary for younger and older children. That is, what is minimal risk for an 8-year-old may be high risk for an infant" (IOM, 2004, p.122). Similarly, Wendler argues that minimal risk should be assessed differently for very young children and older children who can understand and agree to participate (Wendler, 2009, p.115). Further, Kopelman points out that some differences between children—such as the differences incurred as the result of some diseases or disorders—sometimes justify different degrees of permissible risk between children in research (Kopelman, 2004c, p.752). Commentators' claims that risk determinations should take into account—and vary according to—some differences seem to be on solid ground. Assessing risks properly depends on recognizing some differences, like physiological differences, between infants and adolescents. But this suggests that some variable treatment between children in research is permissible and desirable. It follows that arguments endorsing the healthy child interpretation because it meets the requirements of justice by prohibiting variable treatment are not persuasive.

Second, there is no clear and uncontroversial definition of health, which means that identifying healthy children as the referent for minimal risk does not identify one clear and consistent group of children whose daily experiences should be measured against non-therapeutic research procedures. Different interpretations identify varying groups of people as healthy (Nordenfelt, 2006). Boorse thinks that health is defined as the absence of disease (Boorse, 1975). On his account, health can be assessed by examining the biological functions of the body (Boorse, 1975). But others believe that health is a broader concept that also depends on a person's quality of life (Nordenfelt, 2006). For example, the WHO defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO, 1948). Still other commentators define health with reference to personal goals (Richman, 2003) or as the phenomenological experience of being at home in one's lived body (Carel, 2007; Carol,

2008). Depending on which definition one appeals to, a healthy child is disease free, is able to pursue his goals or is comfortable in his body. A child who is disease free may also be comfortable in his body, but these two requirements are not necessarily linked in any obvious way. Commentators endorsing the healthy child interpretation offer no guidance about how to navigate through these intricacies. Little is said about how to understand health or why it should be understood in a particular way. Consequently, this interpretation does not identify one clear and consistent group as the referent for minimal risk.

Third, identifying the referent as healthy children may not successfully restrict non-therapeutic research procedures to a low degree of risk. A child's health is not the exclusive—and perhaps not even the primary—determinant of her daily risks. Children living in poor neighborhoods, war zones or in geographically dangerous areas face degrees of daily risk that seem impermissibly high. But on some, if not all, of the definitions of health described above, these children might be considered healthy. And if they are healthy, there is nothing to prevent the high degrees of risk they face daily from counting as minimal in research. Thus, identifying healthy children as the referent may not prevent the inclusion of children who face particularly and unjustifiably high degrees of daily risk in research involving comparable risk levels.

To address this problem, some commentators suggest that health is not the only relevant criterion to consider. They add a set of features that constrain the healthy child interpretation. For example, NHRPAC and others (IOM 2004; SACHRP 2005) identify the referent as a subgroup of healthy children: those who are also 'normal,' 'average,' and live in a safe or stable environment. This strategy aims to capture only fortunate groups of children, who experience uniquely low daily risks. But this list still neglects some children who face high risks. Some normal, average, healthy children living in a safe environment are exposed to experiences at school that threaten their self-image, such as relentless teasing by peers. These daily experiences can be pernicious to a child's self-image (Thompson, 1990) and should not be used to justify her exposure to similar experiences in research (Ross, 2003). In short, it is hard to identify a subgroup of healthy children that faces only low daily risks.

Fourth, and most importantly, identifying the referent as a fortunate group of

children who usually face low risks is based on the goal of avoiding exploitation by restricting risks as much as possible. But this strategy neglects the fact that a justifiable risk threshold must fulfill multiple functions. It must protect children but it must also permit valuable and ethically permissible research to proceed without unnecessary delay. A research-friendly and morally justified threshold requires more than risk restriction. It requires a convincing reason why some group of children's daily lives involve a morally relevant degree of risk. The mere fact that 'normal, average, healthy children in safe environments' face low degrees of daily risk is not a persuasive reason to use their lives as the basis for minimal risk. Low risks are not necessarily low enough or (perhaps more likely) may be so low that they impede the progress of useful and justifiable research. Given that there is clear reason to think that the degree of daily risk faced by these children is morally appropriate, there is no obvious reason to restrict the risks of non-therapeutic procedures to the same level. It follows that current arguments aiming to establish that healthy children or a subgroup of healthy children should be the referent for minimal risk are not persuasive.

4.3 The subjects of the research interpretation

The second argument frequently found in research ethics proposes to identify the referent as the subjects of the research. According to this interpretation, minimal risk should be measured according to the daily lives of healthy children as well as sick children who are eligible for participation in a given study. Non-therapeutic research procedures can be deemed permissible when they pose no more risk than the eligible study population already experiences in her daily life. The main difference between identifying the referent as healthy children and identifying the referent as the subjects of the research is that the latter permits variable treatment between children in research. Some children—including some sick children—face higher daily risks. And, according to the subjects of the research interpretation, these children may face comparably high degrees of non-therapeutic research risks. Thus, some children whose diseases, disorders or conditions expose them to higher risks in daily life may be exposed to higher non-therapeutic research risks than children who face lower daily risks.

Why might we want to permit sick children to be exposed to non-therapeutic

research procedures involving higher degrees of risk? Some sick children face higher daily risks than healthier children. Permitting a variable risk standard that allows these children to face risks of non-therapeutic research procedures that are comparable to their daily risks may help to promote the development of valuable knowledge of disease states affecting certain children and for which they are the only appropriate research subjects (National Commission, 1976, p.154).

The pursuit of valuable scientific knowledge that can improve the care of current and future children is a good reason to subject some sick children to higher risks than healthier children. But is this variable treatment ethically permissible? Some commentators argue that because children's daily lives differ (according to health, living circumstances or other factors), it may be permissible to expose them to different degrees of research risks (Freedman, Fuks, & Weijer 1993; National Commission, 1976, p.9; Morris, 2012, p.667). The common thread in these arguments is that children's different experiences may contribute to differences in the way children experience various procedures. Also, differences in the way children experience procedures may justify their exposure to different—and sometimes higher risk—procedures in research. The main idea is that children's familiarity with different experiences leaves them and their parents in a good position from which to make informed decisions about whether they wish to undertake comparable risks purely in the interests of a research study.

For example, as the result of her illness, a diabetic child is likely to receive multiple daily pinprick blood tests, whereas on an average day a child without diabetes will receive none. When it comes time to receive a pinprick blood test during the course of standard care or as part of a research protocol, one can reasonably expect the child without diabetes to be apprehensive about the procedure. This reaction is understandable given that the procedure is unfamiliar and expected to involve some degree of pain or discomfort. But a diabetic child familiar with the procedure is likely to have a different reaction. She may be fearful of the discomfort she knows accompanies each pinprick blood test or she may experience no apprehension at all, given that she is familiar with, and untroubled by, the relatively minor degree of discomfort that accompanies a pinprick blood test.

The difference between the diabetic and healthy child is that the diabetic child has

different experiences than children without diabetes. Her familiarity with the procedure as well as its associated discomforts, leaves her (and her parents) well-positioned to make an informed prediction about how she will react to an additional procedure of this sort, administered purely in the interests of a research protocol. It follows that the different experiences that some sick children experience place these children and their parents in a good position to decide whether undertaking comparable risks in research that doesn't aim to offer the prospect of direct benefit is a significant hardship.

One might object to this argument for failing to protect sick children in research. For instance, Ross argues that this interpretation cannot accommodate sick children who have adverse reactions to various procedures and may consequently be even more fearful of undergoing that procedure than a healthy "procedure-naïve" child (Ross, 2003, p.109). According to Ross, understanding the referent as the subjects of the research entails the belief "that it is more acceptable to enroll a child who has been treated for cancer in a study that requires multiple blood draws over a short period than a healthy child because the cancer survivor has experience with multiple blood draws" (Ross, 2003, p.109).

This objection is not successful. The claim is not that familiarity with higher risk experiences automatically justifies the exposure of sick children who experience higher daily risks to comparably high-risk procedures in research. Instead, it may be that familiarity with a procedure provides good reason to determine whether a similar procedure should be undertaken even if it offers no corresponding benefit. As commentators write:

[T]he requirement for commensurability [that is, for permitting different degrees of risk to count as minimal for different children] reflects the National Commission's judgment that children who have had a procedure performed upon them might be more capable than are those who are not so experienced to base their assent on some familiarity with the procedures and its attendant discomforts... (Levine, 1976, p.82)

Similarly, Miller & Weijer argue:

Parents and their ill children are familiar with higher than average levels of risk in everyday life, and are thus in the best position to decide whether to assume comparable risks for the purposes of research that may benefit others in a like

position. (Miller & Weijer, 2000. p.9)

That is, the claim is that children's familiarity with various higher risk procedures leaves them and their parents *in a better position to make informed decisions* about whether or not to undertake the same kinds of risks in the context of non-therapeutic research procedures. And this claim is more plausible. Familiarity with a procedure provides good reasons to predict how a child might react to the same or similar procedures in research.

The most powerful objection to the subjects of the research interpretation is that it does not provide adequate protections for sick children in research. Commissioner Turtle first articulated this objection in his statement dissenting to the National Commission's fifth recommendation, which permits sick children to be exposed to a higher degree of risk than healthy children in research that does not aim to offer direct benefit. He writes:

Children, who through no fault or choice of their own, are subjected to greater risks incident to their condition or necessary treatment, cannot ethically be assumed to qualify for additional increments of risk. To do so, is to add to the potential burdens that result, directly or indirectly from the child's illness.

(National Commission, 1976, p.148).

That is, some children's illnesses subject them to high daily burdens incident to their condition or medical treatment. Even though these risks are familiar to some children, it is unfair to think that commensurate risks in research that does not aim to offer the prospect of direct benefit to the child subject are permissible. Such research would unfairly add to the burdens of an already burdened class of children. Nicholson agrees. He argues that "some children are already exposed to such a high degree of risk that it would be unacceptable to increase that degree of risk by adding to it the risks of being a research subject" (Nicholson, 1986, p.103).

Ross elaborates on this argument. She argues that any interpretation of minimal risk that permits those who are medically burdened by their sickness, disorder or condition to be exposed to higher risk non-therapeutic research procedures is unjust; it adds to the burdens of already burdened persons (Ross, 2003, p.110). She bases her argument on an appeal to the requirements of justice as described in the Belmont Report. In the Belmont Report, the National Commission argue that fairness in the assessment of subject selection requires that already burdened groups should not be further burdened in

research. They write:

[S]ocial justice requires that a distinction be drawn between classes of subjects that ought, and ought not, to participate in any particular kind of research, based on the ability of members of that class to bear burdens and on the appropriateness of placing further burdens on already burdened persons.
(Belmont Report, 1979, p.18)

The idea is that identifying the referent as the subjects of the research fails to protect a burdened population in need of special protection from incurring the additional burdens of research participation.

Ackerman also expresses this concern (Ackerman, 1981). Following Frankena, Ackerman argues that justice requires a fair allocation of the burdens of social living. And a fair allocation of the burdens of social living should aim to equalize the opportunity of each person for achieving a good life. Since some children's opportunity for a good life is more seriously compromised—like children undergoing chemotherapy to treat their cancer—justice requires that we take additional measures to try and equalize their opportunity to achieve a good life. That is, we should try and minimize their exposure to physical and emotional suffering (Ackerman, 1981). With respect to participation in research that does not aim to offer the prospect of direct medical benefit, a fair distribution of research burdens requires that the risk of harm be reduced for people whose opportunity for a good life would be more seriously compromised by their research involvement (Ackerman, 1981). Equalizing the burdens of sick children in research requires that the risks to which they are exposed are reduced in proportion to the severity of their medical burdens. Insofar as identifying the referent as the subjects of the research does not offer any mechanism according to which to restrict or reduce the burdens of the medically burdened, it does not offer adequate protections for children in research.

This objection is persuasive. Some children experience significant medical or psychological burdens as the result of their disease, disorder or condition. When a child is significantly burdened by her disease and medical treatment—as a child is who is undergoing chemotherapy to treat her cancer—the child's familiarity with the procedures and her predictable reaction to similar procedures administered in the context of research

are beside the point. The daily risks this child faces are already so high that it seems unfair to add to her burdens by subjecting her to additional research risks that do not offer the prospect of direct medical benefit. Children significantly burdened by their sickness and treatment do not seem to be appropriate subjects for research involving higher degrees of non-therapeutic research risks. But identifying the referent as the subjects of the research does not say when, if ever, these children must be protected from additional degrees of non-therapeutic research risks. Thus, identifying the referent as the subjects of the research does not offer adequate protections to sick children in research. It follows that none of the subjects of the research, healthy children or a subgroup of healthy children should be the referent for minimal risk.

4.4 Hybrid proposals

Some commentators recognize that neither of the above interpretations of the referent for minimal risk is successful. Peerzada and Wendler (2006) as well as Snyder and colleagues (2011) argue that neither interpretation provides adequate protections for children in research while permitting important and ethically permissible trials to proceed. To resolve this problem, both sets of commentators suggest a hybrid solution, according to which the referent is usually identified as normal, average, healthy children but, under certain exceptional circumstances, the referent can be identified as the subjects of the research.

Peerzada and Wendler argue that institutional review boards should generally identify the referent as healthy, average children but that exceptions can be made to permit valuable research when three conditions obtain: (1) The research risks are no greater than the risks the child faces daily; (2) the daily risks faced by the child are considered acceptable by society; and (3) the research risks replace the risks in the child's daily life (Peerzada & Wendler, 2006, p.1618).

Peerzada and Wendler's criteria are problematic. The second condition restricts the invocation of the subjects of the research interpretation according to social mores. But this condition does not explain how or why societal acceptance should replace the identification of a justified referent for minimal risk. Further, social endorsement alone does not offer children adequate protections in research. For example, a child undergoing

chemotherapy to treat his cancer faces high daily risks as the result of his disease and medical treatment. The risks this child encounters during the course of his medical treatment may well be considered acceptable by society; they aim to treat his disease. But these risks seem impermissibly high in the context of non-therapeutic research procedures. It is unclear, at best, why and how the criterion of social acceptability (in addition to the risk replacement and daily life criteria) can replace the identification of a certain group of children whose daily lives involve morally relevant degrees of risk.

Snyder and colleagues' proposal to permit principled exceptions to the average, healthy child interpretation does not fare much better. Building on a proposal from Wendler (2004), Snyder and colleagues argue that identifying the referent as the subjects of the research can be permissible, but only when the research (1) is relevant to the needs of the host community, (2) meets the standard of scientific necessity, and (3) offers the host community indirect benefit (Wendler, 2004). To this proposal they add a fourth criterion, (4) requiring that research meet the requirement of clinical equipoise (Snyder et al., 2011). Snyder and colleagues argue that invoking these additional protections helps to protect children from exploitation under a subjects of the research interpretation of minimal risk.

However, Snyder and colleagues' criteria for invoking this interpretation do not restrict the scope of research in the way that they intend. Meeting their four conditions will not isolate a particular—and more restrictive—subset of approvable research protocols. Their criteria apply to the conduct of all research involving human subjects. These criteria appear in important guidelines governing the ethical conduct of all research with humans (CIOMS, 2002) and are commonly endorsed as necessary criteria for the ethical permissibility of all clinical research (Emanuel et al., 2000). I agree with Snyder and colleagues, as well as Wendler, that these conditions are essential to the ethical justification of a trial. But they do not limit the application of the subjects of the research interpretation of minimal risk to exceptional cases. Thus, Snyder and colleagues' position amounts to a widespread endorsement of the identification of the referent for minimal risk as the subjects of the research (Binik, Weijer, & Sheehan, 2011). But then this proposed solution is subject to the same problems as the original proposal to identify the referent as the subjects of the research: it cannot justify the additional burdens research

participation places on already burdened populations, such as children with cancer.

Moreover, both sets of commentators aim to resolve tensions that arise when identifying the referent for minimal risk as healthy children or the subjects of the research by endorsing hybrid solutions that permit principled exceptions to the healthy child interpretation. But this strategy is problematic. If the original rule is justified, then merely allowing exceptions to it is ethically impermissible. And if the original rule is unjustified, then it should not be invoked in the first place. Thus, the proposed criteria for exceptions fail doubly: they do not offer adequate protections to children while permitting valuable research to proceed and they fail to explain why exceptions to an ethical rule identifying the referent for minimal risk should be permissible under any circumstances.

4.5 A new proposal

I propose a new approach for identifying the referent for minimal risk, informed by an analysis of the requirements of justice in research with children. I argue that justice does not require equal treatment between all children in research. But it does require that only a morally relevant property can justify departures from equal treatment. I propose that the morally relevant property justifying differential treatment between children in research is *undue burden*. I then argue that children are not unduly burdened if their lives are going well and propose a set of conditions according to which one can measure whether a child fares well. I conclude that the referent for minimal risk should be understood as children who are not unduly burdened by their daily lives, and that children who are not unduly burdened by their daily lives are those who fare well, that is, children who possess sufficiently high degrees of the substantive goods of childhood.

4.6 The principle of justice

How does the moral principle of justice apply to research with human subjects? In the Belmont Report, the National Commission describes two ways of understanding the principle of justice in research with human subjects. First, they claim that justice requires a fair distribution of the burdens and benefits of research (Belmont Report, 1979). That is, justice can be understood as the ethical obligation to treat people fairly, which requires

that people receive access to benefits to which they are entitled and that they are not saddled with undue burdens. To meet the requirement of justice, researchers should not choose only favoured patients to be subjects in potentially beneficial research and they must also not choose “undesirable” people as subjects in high-risk research (Belmont Report, 1979). Further, they must not exploit vulnerable populations, select research subjects from groups who are unlikely to benefit from beneficial results of the research or use vulnerable subjects who constitute a population of convenience when it is feasible to use healthier, less vulnerable subjects (Belmont Report, 1979). Thus, the Belmont Report’s first conception of justice gives rise to a set of guidelines about how to select subjects for research fairly.

The National Commission also describes the principle of justice as the idea that equals ought to be treated equally and unequals treated unequally (Belmont Report, 1979). This insight—known as the principle of formal equality—can be traced back to Aristotle and is central to many egalitarian theories of distributive justice (Frankena, 1962; Aristotle; Sidgwick, 1907; Beauchamp, 1976; Rawls, 1971). It is also endorsed in commentary on research with children (Kopelman, 2004c; Lantos, 2004). The principle of formal equality points out that justice does not require uniform treatment for all subjects in research. Some distinctions—including those based on experience, age, competence, deprivation, merit and position—can sometimes justify differential treatment (Beauchamp, 1979; Belmont Report, 1979). But justice does require uniform treatment of like cases and a justification for unequal treatment. Unfortunately, the principle of formal equality has little to say about who is equal and which cases are alike. It is a basic, minimal or guiding principle (Beauchamp & Childress, 2001; Beauchamp, 1979), which provides no substantive information about the properties that are relevant when comparing people or groups of people (Beauchamp & Childress, 2001). Thus, one main task of theories of justice—and of ethics more generally—is to explain the morally relevant criterion that justifies departures from equal treatment. This morally relevant property is called the material principle of justice. Recognizing the need for a material principle of justice in theories of distributive justice helps to explain why one and the same standard for the permissible treatment of all children in research does not uphold the requirements of justice; it explains why it is sometimes permissible and necessary to

treat children differently in research. In addition, it emphasizes that the material principle of justice must be chosen with care. Preventing the exploitation of children with a variable standard requires that a morally relevant property be chosen as the material principle of justice.

4.6.1 The material principle of justice

What is the material principle of justice in research with children? Health should not be the material principle of justice. Justifying variable treatment according to an axis of health fails to protect some groups of healthy children—including those who are bullied at school or those who are members of low income families—whose daily lives involve significant burden from facing comparably, and inappropriately, high risks in non-therapeutic research procedures.

Further, identifying health as the morally relevant property justifying differential treatment between children in research restricts, without adequate reason, some sick children's access to research participation. Objections to the subjects of the research interpretation of minimal risk focus on sick children who are heavily burdened by their illness. For example, Ackerman restricts his analysis to children with cancer, who are likely to experience significant medical burdens as the result of their disease and treatment (e.g. chemotherapy) (Ackerman, 1981). I agree with Ackerman that children suffering from cancer are significantly burdened and that adding research burdens to their daily experiences is unfair. But this kind of reasoning does not apply to all children with diseases, disorders or conditions. It leaves open the possibility that there exists another class of sick children who are not heavily burdened by their sickness. And there is no obvious reason to require additional protections for children who are sick—but not heavily burdened by their sickness and treatment—when participating in research. For example, children with mild cases of asthma have an illness. This illness may contribute to differences between their daily experiences and those of children without asthma. But some children with mild asthma experience no significant burdens as the result of their sickness. And if they are not burdened by their disease and treatment then there is no obvious reason to protect them from comparable experiences in research. Thus, sickness is not a sufficient condition motivating differential treatment.

Providing unnecessary protection for sick children in research also risks violating the requirements of justice. Justice requires not only the protection of particularly vulnerable groups from research participation but also adequate access to research participation (Kahn, Mastroianni, & Sugarman, 1998, p.1-3). That is, justice also requires that we do not restrict or exclude, without legitimate reason, certain groups from participating in research. Given that some sick children are not heavily burdened by their sickness and treatment, justice requires that some sick children receive adequate access to research participation. It follows that their participation should not necessarily (or automatically) be restricted based on their health status. Thus, health should not be the morally relevant property justifying differential treatment between children in research.

Instead of health, I propose that the material property of justice justifying differential treatment between children in research is *undue burden*. Undue burden does not refer to burdens that are undeserved. Children do not experience burdens that are ‘due’ to them, in the sense of deserved. As a result, there is no reason to distinguish between deserved and undeserved burdens for children. Instead, undue burdens refer to burdens that are excessive or disproportionate. That is, the term ‘undue’ is meant to differentiate mild burdens, such as the inconvenience imposed by having to travel a long distance to get to school daily or perhaps mild burdens imposed by certain sicknesses and their medical treatment from heavy burdens, such as burdens incurred by living in a war zone or suffering from a serious illness. Identifying undue burden as the morally relevant property justifying different treatment between children in research helps to ensure that when children experience overly high daily risks, these risks cannot be used to legitimize similarly high risks in non-therapeutic research procedures.

Identifying the material property of justice as undue burden is derived from the idea that children who face high degrees of daily risk as the result of their illnesses, geographic locations or socio-economic status are different from more fortunate children. The daily lives of the former children involve significant hardships that are beyond their control. And this difference—the difference between high daily risk levels and low daily risk levels incurred as the result of the natural lottery (or chance)—is a morally relevant difference. The fact that some children face high daily risks as the result of chance should not be used to justify their exposure to additional research risks. This difference should

be used only to invoke additional protections for an already burdened group of children.

This claim is not entirely unique; it is the foundation for multiple arguments aiming to restrict the degree of non-therapeutic risks to those faced by healthy children. It shares with these arguments the common goal of protecting children from participation in high-risk research that is justified on the basis of difficult circumstances beyond a child's control. But identifying the morally relevant property of justice as undue burden reflects a new judgment about whose daily life is morally relevant. It reflects the idea that while multiple factors—such as health, wealth, and geographic location—may contribute to unfair differences between children's lives, the material principle of justice should be able to account for injustices incurred by any of these factors. It must be a broader principle that examines whether children are thriving.

4.7 Who should be the referent?

Identifying the material principle of justice as undue burden informs a new interpretation for the referent for minimal risk. The referent should be children who are not unduly burdened by their daily lives. Children are not unduly burdened if their lives are going well. But what does it mean for a child to fare well? Theories of welfare are theories of what is prudentially valuable; that is, a theory of welfare explains how well a life is going for the person living that life (Griffin, 1986, p.31-32; Crisp, 2008). In other words, theories of welfare tell us what make someone's life go better or worse, that is, what is non-instrumentally good for a person (Skelton, forthcoming).

Examinations of what makes a person's life prudentially good can be addressed from a number of different standpoints, including the point of view of a particular person trying to decide how to live, the point of view of a benevolent third party like a friend or parent who wants to improve a person's life or from the point of view of a conscientious administrator who is charged with acting in the interest of a particular group of people (Scanlon, 1993, p.185). Scanlon points out that it is worth keeping in mind the point of view from which an examination is undertaken since it is likely to influence the plausibility of a given answer (Scanlon, 1993, p.185). Following Scanlon's advice, I will identify my main question as "what makes a life a good one for a child?" and consider this question from the point of view of a research ethics board seeking to establish

whether it would be fair to compare the degree of risk posed by a non-therapeutic research procedure to that experienced by a child in her daily life.

To answer my question, I consider some of the main theories of well-being. Parfit divides these into three categories: hedonistic theories, desire-fulfillment theories, and objective-list theories (Parfit, 1984, p.493). I will argue that for the purposes of identifying a justifiable referent for minimal risk, the objective-list theory, understood as an account of substantive goods of a child's well-being, is best equipped to answer what it means for a child to fare well.

Hedonistic theories of welfare claim that welfare consists in happiness and that happiness consists in the greatest balance of pleasure over pain (Bentham, 1789). According to hedonism, the more pleasure one has, the better one's life is going and the more pain one has, the worse one's life is going. While some hedonists disagree over the nature of pleasure, most agree that it is a kind of mental state or feeling (Skelton, forthcoming).

One influential challenge to hedonism is that experiences are not the only things that matter to us. Nozick makes this case by appeal to the example of an "experience machine", which simulates pleasurable experiences—such as winning a Nobel prize or swimming in the ocean on a hot day. By plugging into the experience machine, a person can spend the rest of her life undergoing only pleasurable experiences of her choice (without knowing that she is plugged into the machine). Nozick argues that even though one's life would consist in a great deal of surplus pleasure—and so be the epitome of well-being on the hedonist account—people have good reasons not to plug into the machine. Choosing life in the experience machine causes us to lose contact with reality, which is undesirable; it is in our interests to actually do certain things and be certain ways and not simply to think we have done so (Nozick, 1974, p.43). Plugging into the experience machine seems to prohibit us from achieving the values of accomplishment, personhood, and authentic understanding (Crisp, 2006). Thus, some conclude that hedonism is unsuccessful.

Anthony Skelton argues that there is more to faring well for a child than surplus pleasure. His argument draws on our intuitive response to the following example: consider two ways in which your child will spend the afternoon that involve equal

amounts of pleasure. In the first option, the child's surplus pleasure is derived from playing outdoors with his friends while in the second option, the pleasure is taken in passive television watching. There is no reason to think that there is more long-term pleasure in one case than in the other. Skelton argues that we are not indifferent to which of these pleasures is preferable; most parents prefer the first option. But this suggests that there is more to faring well for a child than surplus pleasure (Skelton, forthcoming). Given that hedonism offers no basis from which to distinguish between these options, it does not provide an adequate account of children's welfare.

A second kind of welfare theory, the desire-fulfillment theory, explains that what is best for a person is what, throughout her life, best fulfills her desires. On these theories, occurrences in the outside world that fulfill a person's preferences contribute to her well-being (Scanlon, 1993, p.186). To fare well on a desire-fulfillment account, one must actually win the prize or be loved by friends and family, and not simply experience these things. By emphasizing the connection of actual occurrences in the world to well-being rather than relying exclusively on experiences, desire-fulfillment theorists are able to explain the reluctance of many to plug into Nozick's experience machine.

But desire-fulfillment theories are subject to different criticisms. We have desires that seem, on reflection, not to be prudentially good. That is, some of our desires seem to be bad for us. Wendler points out that "a fairly common and unfortunate feature of the human condition is that we are often wrong about what is in our interests" (Wendler, 2010, p. 113). For example, we might desire more than anything else to achieve fame, but upon achieving this fame, learn that it is not in our interest; it complicates privacy, which turns out to be more valuable.

A desire-fulfillment theorist might respond to this objection by arguing that welfare consists in the satisfaction of a person's informed or rational preferences (and not simply her revealed or expressed preferences). That is, what is important is not the satisfaction of a person's desires but the satisfaction of desires a person might have if she were informed and free of logical errors (Skelton, forthcoming). For example, on Griffin's informed-desire theory, a person is made better off by the "fulfillment of desires that persons would have if they appreciated the true nature of their objects" (Griffin, 1986, p.11).

However, this understanding of desire-fulfillment theories also seems to miss

something important about children's welfare. As Kraut argues, children have desires and preferences, including the desire for attention and preferences about favourite toys. But a child's welfare should not be constituted by the fulfillment of these desires and preferences alone. He writes: "babies must, for their own good, be nurtured in a way that gives them certain competencies and brings them into certain human relationships; but the states of affairs that are good for them are not already present to them as the context of their desires" (Kraut, 2007, p.105). That is, babies and young children do not and cannot know what is good for them; this is one of the reasons parents try to guide the preferences of their children. More generally, children's well-being is not properly captured by desire-fulfillment theories.

Skelton also points out that desire-fulfillment theories are ill-equipped to capture a child's welfare. He argues that these views rely on the existence of authentic desires that reflect one's autonomous self and can be reached after processing information and freeing it from errors (Skelton, forthcoming). That is, a main goal of these theories is to uphold a person's authority to determine what is in her interests. But this presupposes the existence of a fairly well-developed value system. And for children, there is no such authority to be preserved (Skelton, forthcoming). The main idea is that desire-fulfillment theories' aim of determining which of the things you already value is really good for you from your own perspective relies on the existence of a value-system that most children do not yet possess (Skelton, forthcoming). Consequently, desire-fulfillment theories do not adequately describe children's welfare.

A third kind of welfare theory—the objective-list theory—aims to identify a list of items that constitute a person's well-being. Items on objective lists appeal directly to facts about values; items on the list can be good or bad for a person irrespective of whether or not she seeks the good things and avoids the bad ones (Parfit, 1984, p.499). On objective list theories, the best life contains the greatest surplus of goods on the list. Objective-list theories are also accompanied by philosophical baggage, some of which Scanlon attributes to the name of the theory itself. He writes:

The name "objective list" theory is doubly unfortunate. The term "list" suggests a kind of arbitrariness (just what its critics would charge), and "objective" suggests a kind of rigidity (as if the same things must be valuable for everyone), as well as

inviting a host of difficult questions about the various forms of objectivity and the possibility of values being objective in any of these senses. One might think the name had been coined by opponent of views of this kind. (Scanlon, 1993, p.188)

That is, the name of the theory gives rise to the belief that items on a list are fixed and based on whim. But conceptualizing these theories in a different way may increase their plausibility. Scanlon proposes that, rather than objective list theories, we call them “substantive good theories”. Substantive good theories are “based on substantive claims about what goods, conditions, and opportunities make life better” (Scanlon, 1993, p.189). Following Scanlon, I henceforth call these theories “substantive good theories”.

This new title does not protect the theory from objection. A critic might argue that substantive good theories are implausible because they claim that certain things are good for all, even though some people may not care about or desire those goods (Crisp, 2008). That is, a substantive good theory must explain why and how some particular thing should be understood as good for a person in spite of the fact that she may not desire it. This is a powerful objection to the substantive list theories of adult welfare, but it is not clear that it applies with equal force to children. Children do not have fully formed wills. It is for this reason that we consider it appropriate for parents and guardians to make decisions on behalf of children and do not trust children to make overriding determinations about what is in their own interests. It follows that it should seem more palatable to say that certain things are good or bad for a child irrespective of whether she desires these things (although we should not necessarily disregard a child’s likes and dislikes).

The critic might reply that this objection cannot be overcome so easily. It may seem reasonable to overrule a child’s objection, when she disagrees with her parent about the kinds of things that are in her interest. But adults’ views about what is in a child’s interest may still conflict and it is not clear why an adult, who does not want a certain good for her child, should be persuaded that this good is in her child’s welfare simply because it is part of a list of substantive goods of childhood. More generally, disagreement between adults about the things that constitute a child’s welfare complicate efforts to construct a persuasive list.

My response draws on Scanlon’s reminder that we must keep in mind the point of

view from which the question is being considered. My question, “when does a child fare well?” should be considered from the point of view of a research ethics board trying to determine whether a child’s daily life involves a degree of risk that is also reasonable in non-therapeutic research procedures. This is a more constrained analysis than one that aims to determine whether a child fares well overall or for the duration of her childhood. Certain controversial questions about a child’s welfare that pertain to research participation may be less contentious when considered from the point of view of a research ethics board. For example, parents may reasonably disagree over whether stability is a substantive good of childhood. Different parents’ positions on the importance of stability may contribute to different determinations about whether it is in the long-term interests of children to move cities every two years during early childhood. Some might think that the new experiences that accompany frequent moves are in the interests of children, others may emphasize the value of stability for relationship building, and still others may think the value of stability depends largely on how a particular child copes with change. There is no obvious reason why one parent’s position on stability should supersede another’s. Consequently, these kinds of disagreements complicate efforts to develop an account of the substantive goods of childhood.

However, this problem is less pressing for an account of the substantive goods of childhood that is constrained to a research ethics board’s determination about whether a group of children fares well enough to be the referent for minimal risk in a particular study. A research ethics board should consider whether a group of children fares well at a given point in their lives, that is, at the time of trial recruitment. In making their determination, they need not (and could not) cast judgment on whether a child is likely to fare well throughout the course of her life. A research ethics board, after all, makes their determination with regards to a reference group of children and without any particular child in mind. Assessing whether a group of children fares well at a particular point in time helps to mitigate disagreement. The question ceases to be whether it is in a child’s future interest to move frequently and becomes, for instance, whether a child who has recently moved cities is less likely to fare well. The latter question may be easier to answer (I’ll say more about how to make this determination in the next sections). In short, constraining assessments of welfare to a group of children’s current circumstances

helps to reduce disagreement about the substantive goods of childhood.

Further, accounts of the substantive goods of childhood need not be fixed; they may be open to revision as evidence emerges about factors relevant to a child's welfare. Insofar as the substantive good theories are able to recognize and account for differences between children and adults and are also flexible enough to grow and change in response to research about children, they are best equipped to account for the welfare of children.

I've argued that substantive goods theories are best equipped to capture children's welfare for the purposes of identifying a justifiable referent for minimal risk. My goal is to help determine which group of children fare well enough that their daily lives are morally relevant comparators for the risks of non-therapeutic research procedures. This is a practical proposal. It is beyond the scope of this chapter to offer a comprehensive analysis of children's welfare. Nonetheless, it is worth pointing out that endorsing a series of goods in which children's welfare consists is consistent not only with substantive good theories, but also with some hedonist theories of welfare. The most plausible versions of hedonism also endorse a series of goods in which welfare consists.

Above, I argued that hedonism is the view that welfare consists in one good, happiness, and that happiness consists in the greatest balance of pleasure over pain. But some versions of hedonism are more nuanced. Some argue that it is consistent with hedonism to desire more things than our own happiness and that we desire these things for themselves, that is, independently of the happiness they produce (Silverstein, 2000, p. 294). This idea is derived from what Sidgwick called the "paradox of hedonism" (Sidgwick, 2007). One version of the paradox of hedonism points out that if we aim only at happiness, then we cannot attain it. To achieve the highest degree of happiness, we must pursue it indirectly, through other goods (Silverstein, 2000). Further, over time, people move from valuing something as a means to happiness to valuing that thing in and of itself (Crisp, 2006). Thus, the best way to promote happiness is by coming to believe that a number of other things are intrinsically good. To put it another way, a plausible version of hedonism recognizes that a number of things are intrinsically good. It follows that the insight that our welfare consists in a list of substantive goods is common to both hedonism and substantive goods theories. This overlapping consensus between the two theories that children's welfare consists in a series of goods may add plausibility to my

proposal. It follows that my proposal may also be understood as a practical proposal that is the subject of an overlapping consensus between substantive goods theories and hedonistic theories, the two most plausible theories of children's welfare.⁸

4.8 The substantive goods of childhood

What goods contribute to a child's welfare? The substantive goods of welfare have traditionally been constructed with adults, and not children, in mind. And many of these accounts are ill-suited to represent children's interests (Skelton, forthcoming). For example, Brink proposes a theory of welfare "that counts reflective pursuit and realization of agents' reasonable projects and certain personal and social relationships as the primary components of valuable lives" (Brink, 1989, p.231). For Brink, the formation and pursuit of projects should be reflective and these projects should be integrated into a coherent life plan (Brink, 1989, p.231). This view seems plausible for adults, but not for children. It relies on capacities and traits that children do not possess or do not possess enough of (Skelton, forthcoming). Children are unable to form comprehensive and integrated life plans of the sort Brink has in mind. Consequently, Brink's theory does not offer a persuasive picture of what it means to fare well as a child.

However, there are two attempts to identify goods that are explicitly in children's interests that inform my account of the substantive goods of childhood. First, Kraut offers a view of children's welfare that appeals, at least in part, to an objective list of goods for children. He writes:

[I]t is good for us to receive loving attention as children, to acquire linguistic competence and the ability to communicate with others, to grow physically and make use of our sensory capacities, to mature sexually, to learn the complex skills of adulthood, to enrich and develop greater mastery over our emotions, to learn how to assess reasons and deliberate with an independent and open mind, and thus to interact with others as full members of the community. (Kraut, 2007, p.138)

⁸ The third main theory of welfare, the desire-fulfillment theory, does not share this insight, but I've argued above that it is less successful in accounting for children's welfare.

Some of the items on Kraut's list contribute to children's welfare. For example, it seems clear that children must be able to grow physically and receive loving attention to fare well. But Kraut's list is too heavily focused on rationality. His view emphasizes the development of various physical and psychological faculties, which seems too forward looking. For instance, it seems possible to fare well as a child without keen faculties of deliberation and without learning to master the complex skills of adulthood. But on Kraut's account, these are necessary goods for all children. Overall, some of the goods Kraut describes seem plausible, but the list needs modification.

A second account also helps to identify the substantive goods of childhood. Malek identifies a list of thirteen items that are in children's interests (Malek, 2009). Her goal is to defend the "best interests" standard that guides health-care decision making for children against charges of vagueness by providing specific and substantial guidance about what is in a child's interests. To this end, she considers the interests of children as described in the UN Convention on the rights of the child, Brazelton and Greenspan's *The Irreducible Needs of Children*, and Nussbaum's capabilities approach. Malek cross references the items in these sources and compiles a list of items relevant to children that appear in all three.

She explains the approach in the following way: "[A]uthors writing from political, medical, and philosophical perspectives with different goals in mind identified many of the same elements of well-being" and the high level of agreement between them "provides evidence that those elements are things that make children better-off. Further, because the accounts are drawn from the wisdom of three areas of study, there is at least some reason to believe that the list is fairly comprehensive" (Malek, 2009, p.5). Malek's list includes life, health and healthcare, basic needs, protection from neglect and abuse, emotional development, play and pleasure, education and cognitive development, expression and communication, interaction, parental relationships, identity, sense of self, and autonomy (Malek, 2009). She concludes that the overlapping consensus between the three accounts provides some evidence that these goods form a comprehensive list of children's interests (though the list is open to revision in light of new empirical data) (Malek, 2009).

Malek's list is plausible. It focuses on children, rather than adults, and recognizes a

wide range of goods, in addition to rational capacities, that constitute a child's welfare. But modifications to this list may help to identify children who fare well enough to be the referent for minimal risk. Malek's list involves thirteen goods, which is unwieldy. Given that my substantive good theory is part of a practical proposal that will require a research ethics board to assess whether a group of children possesses sufficiently high degrees of each of the goods of childhood, there is an advantage in constraining the list to the fewest number of substantive goods that accurately captures children's welfare. A shorter list may facilitate research ethics review.

Can Malek's list be constrained and still capture the substantive goods of children's welfare? As she recognizes, there is overlap in the goods on her list. For instance, the first four goods (life, health, basic needs, and protection from abuse and neglect) all refer to a child's physical well-being. But it is not clear that each of these must appear as a distinct good on the list. One might think that achieving a high enough degree of health to fare well presupposes the substantive good of life. That is, concern for someone's health requires that they be alive. Thus, one might be able to collapse life and health into one item on the list.

Further, both play and emotional development seem to be different parts of one same substantive good of childhood. On one plausible analysis, children's play is best understood as the way in which children develop emotionally. Schapiro describes play as a strategy in which children "try on" different characters for themselves. Children play in order to experiment with different personas and to learn what it will be like to inhabit the adult world in different ways (Schapiro, 1999, p.732). She writes that "play serves an essential function in children's lives which it does not serve in the lives of either animals or adults. Play is children's form of work, for their job is to become themselves" (Schapiro, 1999, p.732). That is, play helps children to develop their capacities and emotions. It follows that there may be good reason to understand play and emotional development as part of one substantive good of childhood.

The goods of interaction and parental relationships also overlap. Part of what it means to interact as a child is to have "intimate and consistent relationships with others" (Malek, 2009, p.6). But interaction undertaken as part of a continuing and meaningful relationship with a caretaker might be cast as a part of parental relationships, rather than

as an independent good. More generally, only might be able to account for the same substantive goods of childhood with a shorter list, which would be an advantage when assessing whether a group of children is an appropriate referent for minimal risk.

Building on Kraut and Malek's theories and also informed by other discussions of substantive goods, including Wendler (2010) and Nussbaum (1992;2000), I propose seven substantive goods of childhood that should be taken into account when identifying a referent for minimal risk. For a child to fare well enough to be the referent for minimal risk, the following conditions must obtain: (1) A child must be in good *health*. I take reasonably good health to refer to the absence of diseases, disorders or conditions that significantly impair (or whose medical treatment significantly impairs) normal functioning. (2) A child's *biological needs* must be met. Biological needs include sufficient food, water, sleep, and a safe home. (3) A child must be provided with *intellectually engaging activities*. Intellectually engaging activities involve activities that challenge a child's capacities. They may include playing with infants, reading to very young children, and formal education for older children. (4) A child must be involved in *meaningful relationships*. Meaningful relationships refers to loving attention from caregivers or guardians (i.e. parents or their equivalent). (5) A child must enjoy *unstructured, imaginative play*, which includes playing outdoors, laughing, and enjoying life. (6) A child must have *bodily integrity*, which refers to her ability to be safe from assault, including sexual assault and domestic violence. (7) A child must be *happy*. One plausible theory explains happiness as a sense of satisfaction, a positive attitude towards one's own life (Sumner, 1996, p.145). With respect to children, happiness consists in "what we commonly call a sense of well-being; finding your life enriching or rewarding, or feeling satisfied or fulfilled by it" (Sumner, 1996, p.146). Children fare well when they possess sufficiently high degrees of these seven substantive goods.

I've argued that the most plausible theories of welfare that are able to accommodate children's welfare involve a list of substantive goods in which children's welfare consists. I've also drawn on insights from plausible substantive good theories of welfare to compile a list of seven substantive goods that help to ensure that a child fares well enough to be the referent for minimal risk. My list avoids some of the problems encountered by other substantive good theories. It focuses on the goods of childhood in

particular, which helps to avoid the development of a plausible list of goods for adults, which don't capture children's welfare. In addition, it does not privilege rational capacities but recognizes a variety of goods that are in a child's interests. Further, it aims to limit overlap between the goods in each category to help facilitate determinations about whether children possess sufficient degrees of the substantive goods of childhood to be the referent for minimal risk. This list aims to offer a comprehensive account of the substantive goods of childhood that ensure that a child fares well enough to be the referent for minimal risk. In the next section, I consider how a research ethics board may assess whether children possess sufficiently high degrees of each of the substantive goods.

4.9 Guidance

I've argued that the referent for minimal risk should be children who are not unduly burdened by their daily lives, that children are not unduly burdened when they fare well, and that to fare well, children must have sufficiently high degrees of the seven substantive goods of childhood. But the success of this proposal depends on addressing additional questions: For instance, what is the relationship between these goods? What does it mean to possess a sufficiently high degree of each good? And how should an ethics committee determine if a child meets the required degree for each of the goods, that is, fares well enough to be the referent for minimal risk?

The substantive goods of childhood are not interchangeable; high degrees of one good should not be traded-off against deficits of another. That is, a child cannot fare well on balance by enjoying large amounts of one good but low amounts of another. For example, receiving a great deal of love cannot make up for an inadequate amount of food and water. Similarly, having a very high degree of education will not make a child fare well if she does not possess enough happiness.

What degree of each substantive good is sufficiently high? Nussbaum distinguishes between two distinct thresholds that help to explain the degree of goods that is sufficiently high to fare well. Nussbaum's first threshold identifies a level beneath which a life is so impoverished that it cannot be considered a human life at all (Nussbaum, 1992, p.221). Her second threshold is higher. She describes it as "a somewhat higher

threshold, beneath which those characteristic functions are available in such a reduced way that although we may judge the form of life a human one, we will not think it a *good* human life. The latter threshold is the one that will eventually concern us most when we turn to public policy..." (Nussbaum, 1992, p.221). Nussbaum's second threshold aims to show that receiving the bare minimum of the substantive goods is insufficient for faring well.

Nussbaum's claim that failing to possess any of the substantive goods of childhood will result in an impoverished life for a child is persuasive. It is unlikely that a child who does not have her biological needs met or has no meaningful relationships with caregivers can fare well. It follows that meeting the sufficiency requirement requires that a child must not lack any of the substantive goods of childhood. Nussbaum's claim that faring well requires more than having a bare minimal amount of each good is also persuasive. For instance, it seems reasonably uncontroversial to say that providing a child with just enough food to prevent starvation is inadequate; a child's success and satisfaction depend on having more than what is physiologically required to survive. Accordingly, faring sufficiently well requires more than a minimal amount of the substantive goods.

While it seems clear that faring well requires a child to have more than the basic minimum of each good, determining what degree of each good is 'sufficiently high' is less straightforward. One option is to understand a 'sufficiently high' degree of each good by comparison with the degree of substantive goods possessed by children determined by a research ethics board to be fairly well-off. Explaining the degree of a substantive good that is sufficiently high with reference to children determined by a research ethics board to be fairly well-off does not identify a rigid and fixed measure of the level of each good that is sufficiently high. It leaves research ethics boards with latitude in making their determinations. But it provides a research ethics board with a reference class of children to consult when trying to assess what is "enough" of each substantive good. To put it another way, this standard directs a research ethics board's attention to the main components of a child's welfare and asks them to measure these according to a high threshold. In the rest of this chapter and in the following chapter, I will elaborate on how a research ethics board should assess whether a group of children has roughly the same

degree of the substantive goods as children who are fairly well-off.

This standard is offered by way of contrast to the healthy child interpretation, which (at least on the WHO definition of health) recognizes only children who have a “*complete* level of physical, mental, and social well-being” as healthy (WHO, 1948). My standard does not necessarily require a child to be normal, average, healthy, and to live in a safe environment. Instead, it recognizes that some children with mild diseases or disorders or who live in sub-optimally safe environments may fare well, provided that their disease or disorder (and medical care) or living situation does not impose considerably more burdens on them than those experienced by a healthier child. More generally, this standard is based on the recognition that some children in less than optimal circumstances fare well, but their circumstances should not put them at a significant disadvantage compared to other children.

One advantage of this approach is that it directs research ethics boards’ attention to a relevant set of questions. For example, is an eligible study population likely to possess less of a substantive good of childhood than other groups of children? And if yes, then how much less of this good? It also provides a list of substantive goods that should be taken into account when assessing a child’s welfare. Accordingly, it helps to focus attention on the morally relevant components of a child’s welfare that may impact how she is treated in research. Further, assessing the degree of each good that is ‘sufficient’ by reference to the degree possessed by children who are reasonably advantaged helps protect children from being selected as the referent because their higher daily burdens would permit their exposure to comparably high risks in non-therapeutic research procedures. In other words, this standard helps to protect children from exploitation. But it also allows research ethics boards to use their discretion in determining which children are not unduly burdened, which may help to allow valuable research to proceed.

How should a research ethics board determine whether the eligible study population has roughly the same amount of each substantive good as a child who is fairly well-off? Procedurally, a research ethics board’s determination about whether a child has enough of each substantive good should be informed by several kinds of evidence. They should consider whether there is any intuitive connection between the goals of the study and a group that is likely to be disadvantaged. For instance, a study proposing to examine

attachment problems in children who grew up in orphanages targets a group of children that are hypothesized to be at risk of lacking meaningful attachments. Consequently, the eligible study population may be more likely to lack meaningful relationships and require additional scrutiny during ethics review.

In addition, a research ethics board should conduct a literature review of scientific research concerning the eligible study population. When empirical research exists, they should draw on it to inform their assessment of whether an eligible study population possesses sufficiently high degrees of the substantive goods.⁹ Of the seven substantive goods of childhood, perhaps the most research exists on how to measure health and happiness. There exist a growing number of policy measures, most of which consist in English language questionnaires, that can help assessing a child's health-related quality of life (HR-QOL) and may be of use in their determinations (Ravens-Sieberer et al., 2006).

For example, the Child Health Questionnaire, developed in the U.S. for use in children ages 10-18, evaluates HR-QOL by asking children to answer questions about their physical health (including their physical ability to function, bodily pain, and general health perception) as well as their psychosocial health (including their self-esteem). The measurement results of this tool can be aggregated into physiological and psychosocial sum values (Ravens-Sieberer et al., 2006). A second measurement tool, the Child Health and Illness Profile (CHIP), focuses on measuring the functional aspects of children's HR-QOL and a third, the How Are You Questionnaire (HAY), asks children to relay info about disease-related symptoms and self-management via smiley faces or pictograms (Ravens-Sieberer et al., 2006). A second group of instruments provides information about the QOL of children with particular diseases, such as epilepsy, cancer, asthma, juvenile rheumatoid arthritis, cystic fibrosis, gastrointestinal disorder, diabetes, eating disorders, AIDS, spina bifida, and other conditions (Ravens-Sieberer et al., 2006).

Similarly, empirical research aims to develop ways of measuring roughly how happy a person or group of people are. And a subset of this research offers tools for measuring happiness in children. For example, one self-reporting tool measures

⁹ An absence of empirical data about a substantive good of childhood may reflect a need for additional research about children's welfare.

happiness by presenting children with a horizontal sequence of drawings of faces that are identical except for the mouths, which vary from big smiles to deep frowns. Children (aged 8-12) are asked choose the drawing of the face that best corresponds to how they currently feel or feel at a particular moment (Holder, 2012, p.20). Other measures include a multi-item scale, which measures subjective happiness by asking a child four questions about how she considers herself with respect to most of her peers, a questionnaire involving multiple yes/no questions or an experience sampling method, which uses some form of a pager to signal participants at random times throughout the study and asks them to rate their current happiness level (Holder, 2012, p.20-25).

When these kinds of studies pertain to the relevant study population, a research ethics board should draw on them to inform their determination about whether a group of children has sufficiently high degrees of the substantive goods of childhood, that is, whether they are likely to have comparable amounts to children who are fairly well-off. In addition to reflective judgment and literature surveys, an ethics committee should, when necessary, consult with experts to obtain more knowledge about a particular group of children. Armed with relevant evidence from these sources, a research ethics board should pass judgment on whether the eligible study population has enough of the substantive goods of childhood to be identified as reasonably well off. If the research ethics board determines that the eligible study population possess sufficiently high degrees of the substantive goods to be the referent, then it is permissible for children enrolled as research subjects to face non-therapeutic procedures involving risks that are comparable to those they face in their daily lives.

These suggestions fall short of providing comprehensive guidance about the assessment of children's welfare. But they offer preliminary suggestions about how this proposal could be implemented. In the final chapter, I will elaborate on the implementation of this proposal by using the above criteria to assess whether a particular subject population fares well enough to be the referent for minimal risk.

4.10 Further reflections

Identifying the morally relevant criterion justifying unequal treatment between children in research as undue burden and the referent as children who fare well has several

advantages. Permitting some flexibility in the treatment of children in research lines up with our intuitions that (a) some differences merit differential treatment but also (b) that variable treatment must be constrained; no interpretation should permit particularly disadvantaged children's circumstances to legitimize their exploitation in research. My interpretation guards against this kind of unfair variation by requiring that a child fare well, which takes into account her socioeconomic status and geographic location as well as her health when assessing whether she should be the referent for minimal risk. More generally, it specifies how we can meet the requirement of justice that we should treat like cases alike and unlike cases differently.

Further, identifying the referent as children who fare well offers a research friendly means by which to protect children in research. It helps to explain why any children (healthy or not) who face risks that interfere with their well-being should not face comparable risks in research procedures that do not aim to offer them the prospect of direct benefit. But it explains it in a way that allows children who are not overly burdened by difficult circumstances, like some mild illnesses, to face comparable non-therapeutic risks in research.

My proposal also offers some procedural guidance for research ethics committees. On my account, determinations do not end when a child or group of children is deemed to be unhealthy, poor or live in a resource-scare setting. Instead, it draws attention to a more nuanced set of questions, including whether children are unduly burdened by their medical or social circumstances, and whether a particular group of children face daily risks that interfere with their ability to live good lives. Determinations based on these questions will provide justifiable answers about who should be the referent for minimal risk.

It is worth pointing out that I expect there to be considerable overlap between the group of children that fare well according to my argument and those who are normal, average, healthy and living in a safe environment. The main difference between the healthy child interpretation and the undue burden interpretation is the motivation and justification. My list of substantive goods of childhood does not aim to restrict risk as much as possible but to restrict risk to the degree required by the moral principle of justice. Specifically, it is based on the idea that it is unfair to add to the burdens of the

significantly burdened (medically or otherwise) but also that it is unfair to restrict, without adequate reason, the degree of risk certain children may face in research. Thus, it identifies a similar group of children whose daily lives are morally relevant but does so for a more convincing set of reasons.

I conclude that the referent for minimal risk should not be healthy children or the subjects of the research. Instead, it should be interpreted as children who are not unduly burdened by their daily lives, and children are not unduly burdened by their daily lives if they fare well, that is, if they possess sufficiently high degrees of the seven substantive goods of childhood.

Chapter 5

Case analysis

The previous four chapters focus primarily on the development of a theoretical justification for minimal risk. This is a necessary part of an interpretation of minimal risk. But it is not sufficient. More needs to be said about how this proposal works in practice and why it is persuasive. In this chapter, I take up these tasks. I provide a preliminary sketch of how my interpretation may be implemented in practice and argue that it gives rise to intuitively compelling results. To this end, I analyze a case study of a controversial trial including children. The main function of the case study is to assess whether my proposal offers clear guidance to inform a research ethics board's determination about the permissibility of a trial and further, to assess whether my proposal contributes to a determination that lines up well with common moral intuitions about the treatment of children in research. I draw on this study to show that my interpretation of minimal risk, within a broader system for the evaluation of harms and benefits, meets these criteria.

I begin by examining some implications of my proposed interpretation of minimal risk: I ask (1) what are the implications of a research ethics board determining that a group of children is unduly burdened, that is, that they do not fare well enough to be considered the referent for minimal risk? and (2) in what ways, if any, does my proposed interpretation inform the analysis of research protocols involving therapeutic procedures? Following these questions, I present a detailed analysis of the National Institute of Health's (NIH) study of human growth hormone (hGH) in children with idiopathic short stature. In the final section, I consider whether my analysis contributes to plausible results. I argue that my proposal for identifying the referent for minimal risk generates more persuasive results than the two most prominent competing interpretations.

5.1 Practical implications

In the previous chapter I ask, who should be the referent for minimal risk? I answer that the referent should be a group of children who are not unduly burdened by their daily lives. I argue that children who are not unduly burdened are those who fare well and

defend a substantive good theory of children's welfare. In this section, I examine a related question: what are the implications of a child failing to fare well enough to be the referent for minimal risk? To put it another way, what happens when a research ethics board determines that a group of children should not be the referent for minimal risk?

One possible implication of a research ethics board determining that a child fails to fare sufficiently well is that a child should not be included in research at all. That is, if a child should not be the referent for minimal risk then she should not be a research participant full stop. One might reach this conclusion by reasoning that when a child is unduly burdened by her daily life, imposing on her the additional burdens of research would be unjust. This conclusion is problematic. It suggests that many, if not most sick children, and all those suffering from diseases and disorders whose medical treatment involves significant burdens should be excluded from research. But excluding these children from research would complicate or prevent valuable research—including research on children's cancer, diabetes, cystic fibrosis, and meningitis—which would delay the improvement of medical treatment of current and future children. Further, if this conclusion were correct, then it would follow that a great deal of the current research with children (which focuses primarily on sick children) is morally impermissible.

However, it is not the case that children who fail to fare well should be excluded from research participation. Identifying the referent for minimal risk is part of the broader project of assessing whether a research protocol involves a reasonable balance between harms and benefits. The analysis of harms and benefit aims to establish the degree of risk that is permissible in various research procedures; it is a requirement of the broader ethical principle of beneficence, which aims to ensure that benefits to research subjects are maximized and harms are minimized (Belmont Report, 1979).

Analyses of the principle of beneficence are separable from considerations about the fair selection of research subjects, which falls under the broader ethical principle of justice (and concerns the fair distribution of the burdens and benefits of research) (Belmont Report, 1979). Both of the principles of beneficence and justice are important; fulfilling the requirement of each is necessary for the ethical justification of a proposed research protocol. But they are separable and have different purviews. Harm benefit assessments govern the appropriate risk limits for research procedures. And this analysis

is separable from and presupposes that a research ethics board will also consider and pass judgment on who should be the morally appropriate subject population for a trial.

The relationship between the principles is not always straightforward. Insofar as identifying the referent for minimal risk requires us to identify a group of children whose daily lives are morally relevant, it involves the selection of a group of children. But this group is morally relevant not because they are appropriate research subjects for a given protocol. Instead, the relevance of this group of children is that their daily lives involve morally defensible degrees of risk. And consequently, their daily experiences are a justifiable standard for permissible degrees of risk in non-therapeutic research procedures. Insofar as the identification of a referent for minimal risk is part of a harm-benefit assessment, it should not necessarily influence the selection of morally appropriate research subjects. That said, the moral justification of a protocol will always depend on also fulfilling the justice requirement to choose research subjects fairly.

This analysis suggests that when a child does not fare well enough to be the referent for minimal risk, she should not necessarily be excluded from research participation. A research ethics board may find that it is consistent with the requirements of justice to provide a child who does not fare well enough to be the referent for minimal risk with access to participation in a given trial. For example, a child undergoing chemotherapy for treatment of a serious cancer probably does not possess sufficient amounts of the substantive goods of childhood to fare well. But a research ethics board may still determine that she is an appropriate subject in a trial examining new methods for managing the side effects of chemotherapy. In this kind of case, the child's failure to fare well does not exclude her from research. But it does require that she receive additional protections in research. She must not be exposed to non-therapeutic research procedures involving risks comparable to those she experiences in her own daily life (given that it likely involves risks that are higher than the morally justifiable degrees of daily risks faced by children who fare sufficiently well). Instead, she must only be exposed to non-therapeutic procedures involving no more risk than that which is experienced in the daily lives of children who do fare sufficiently well.

It is worth considering whether this analysis differs with respect to the other prominent interpretations of the referent for minimal risk. Identifying the referent as the

subjects of the research has no mechanism by which to provide additional research protections for a child heavily burdened by her disease. It follows that when the eligible study population for a trial is children undergoing chemotherapy for a serious cancer, then the risks of non-therapeutic research procedures should be comparable to the risks that child faces in her daily life. Thus, if a child's (imprudent) parents or guardians agreed to enroll her in this trial, she might face risks comparable to those of chemotherapy (e.g. significant discomfort or death) in research procedures administered without the prospect of benefit. These kinds of non-therapeutic risks are too high, but not clearly prohibited by the subjects of the research interpretation. Both my interpretation and the subjects of the research interpretation permit the enrollment of sick children in research, but my interpretation offers better protections than the subject of the research interpretation for sick children in research.

However, identifying the referent as healthy children yields similar results as my proposal. That is, if a child is identified as sick—and accordingly, her daily experiences are deemed inappropriate as a comparator for the risks of non-therapeutic research procedures—she is not necessarily excluded from research participation. Instead, she might be included but only on the condition that the risks of non-therapeutic procedures are limited to those comparable to the risks healthy children face in daily life. Thus, the implications of a child failing to fare well enough to be the referent for minimal risk are that if she is included in a trial, she may only be exposed to non-therapeutic procedures involving risks that are comparable to the daily experiences of children who fare well (and not her own higher risk daily experiences). The main point is that the referent for minimal risk is a reference class of children whose daily lives serve as a justifiable measure for the risks of non-therapeutic research procedures; identifying a group of children as the referent does not necessarily influence whether these children are appropriate research subjects.

5.1.1 Implications for therapeutic research procedures

Another important question about the implications of my argument is: in what ways, if any, does my proposed interpretation inform the analysis of research protocols involving therapeutic procedures? In chapter 1, I situate my analysis of minimal risk within a

broader system of analyzing harms and benefits. This system—component analysis—is based on the idea that a great deal of clinical research involves both therapeutic and non-therapeutic procedures and develops an approach found within the work of the National Commission. Therapeutic procedures and non-therapeutic procedures should be demarcated and are governed by separate moral rules (Freedman, Fuks, & Weijer, 1991; Weijer, 2000).

Minimal risk is a moral threshold governing the permissibility of non-therapeutic procedures on vulnerable populations. Accordingly, it exerts influence only over procedures that are administered in the exclusive interests of the study and not an individual subject. In other words, my interpretation of minimal risk elaborates on the assessment of non-therapeutic procedures. It has no direct impact on the moral assessment of therapeutic procedures, but it does help to identify the conditions under which a trial including therapeutic procedures may be found permissible. I've argued that all trials including therapeutic procedures also include non-therapeutic research procedures. Further, to be ethically permissible, both the therapeutic and non-therapeutic procedures of a trial must be deemed permissible. Thus, my analysis of minimal risk helps to explain the conditions under which a trial involving non-therapeutic procedures or a mixture of therapeutic and non-therapeutic procedures can be found ethically permissible.

5.2 The growth hormone trial

In this section, I assess the ethical permissibility of a controversial trial with children. I focus on a trial funded by the National Institutes of Health (NIH) and conducted in the 1990s that examined the effects of biosynthetic growth hormone (hGH) on healthy but very short children. This study is a useful case example because it generates difficult questions about which intuitions collide. For example, are child research subjects who do not receive growth hormone therapy unfairly deprived of medical treatment? Should placebo arms be permissible in research involving children? Analyzing my interpretation of minimal risk according to this case will help to determine whether my proposal can inform the ethical assessment of research with children by providing compelling guidance in complicated cases. I argue that analyzing this trial according to my

interpretation of minimal risk (within a broader system of analyzing harms and benefits) contributes to plausible results; it provides clear guidance that can help inform a research ethics board's determinations in complicated cases. Further, it generates results that are more persuasive than those of the most prominent competing interpretations of minimal risk.

The use of hGH therapy for children has a long history in the United States, but until the past few decades, the use of hGH was limited to children with a confirmed growth hormone deficiency. Prior to the early 1980s, hGH could only be obtained from the pituitary glands of cadavers, a limited natural source, and the shortage of natural hGH resulted in it being accessible only to children with a confirmed growth hormone deficiency and usually within research protocols (Protocol Review, 1992; White, 1993; Tauer, 1994). In 1985, the FDA approval of a synthetic hGH developed through recombinant DNA technologies (genetic engineering) increased the availability of the drug and made it possible to expand its use to larger numbers of children (Tauer, 1994; White, 1993; Protocol Review, 1992).

The increase in availability contributed to an increase in prescription of hGH, not only for growth hormone deficient children, but also for children with idiopathic short stature, that is, healthy but very short children.¹⁰ The increase in the use of hGH treatment for children with idiopathic short stature was motivated, at least in part, by demand. Many families of children with short stature seek medical intervention (Leschek et al., 2004). Short stature is one of the most common complaints received by pediatric endocrinologists, and hGH treatment is often considered (Cuttler et al., 1996). A survey of pediatric endocrinologists in the United States revealed that 94% of respondents reported recommending hGH treatment for some children with idiopathic short stature (Cuttler et al., 1996).

However, the increase in growth hormone treatment occurred in spite of inadequate testing of its safety and efficacy in non-GH deficient children (Leschek et al.,

¹⁰ Idiopathic short stature is defined as a “condition in which the height of an individual is more than 2 SD (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, nutritional, or chromosomal abnormalities” (Cohen et al., 2008). It is a heterogeneous group of children with many different and currently unidentified causes of short stature (Cohen et al., 2008).

2004; Allen, 2011). Bercu reports that the results of hGH treatment in children with idiopathic short stature reported at scientific meetings in the 1990s (the time of the NIH trial) were inconclusive. Some studies found that the intervention increased the children's height while others concluded that it did not (Bercu, 1996). Further, little was known about the satisfaction of the patient-subjects and their families with the result of the intervention. And the hGH treatment is accompanied by risks, including allergy, impaired glucose tolerance, pseudotumor cerebri, hyperlipidemia, slipped capital femoral epiphysis, transient peripheral edema, exaggeration of scoliosis, and leukemia (Bercu, 1996). It follows that more and better information about the use of hGH is needed to help determine whether hGH therapy is safe and effective for children with idiopathic short stature.

The NIH study aimed to generate knowledge that might help to inform hGH prescribing practices for non-deficient children. The study—a randomized, double-blind placebo controlled trial—aimed to investigate the effects of growth hormone therapy on the adult height of non-growth hormone deficient children with idiopathic short stature. It included 80 subjects—girls between the ages of 9 and 14 and boys between the age of 10 and 15¹¹—who were healthy but at least a 2.25 standard deviation below the mean height (Protocol report, 1992).¹² Children in the trial were randomized either to the intervention group and received growth hormone or to the control group, which received placebo injections. The growth hormone or placebo injections were administered by three subcutaneous injections per week until the child's bone age reached maturity, that is, until bone growth has ended. The total number of shots for each child in the study ranged from 600 to 1,100 (Protocol report, 1992). And because the study was double-blind, the

¹¹ My definition of a child—people below the legal age of consent who lack autonomy and competence—may exclude some of the older subjects in this study. But for the purposes of this case analysis, which aims primarily to demonstrate how to put my proposed interpretation of minimal risk into practice and why this is useful, I will treat the group of research subjects as children.

¹² The protocol's inclusion criteria were amended to 2.5 SD below the mean in 1987, but then amended back to 2.25 SD below the mean in 1990 (Protocol review, 1992). For North American adults, a 2.5 standard deviation below the mean is 5'3 for men and 4'10.5 for women (Tauer, 1994).

children in the placebo group received the same procedures—including the three weekly injections as well as regular check ups—as those in the intervention group.

This study generated controversy. An institutional review board¹³ initially deemed the study ethically permissible and a special panel convened to review the protocol midway through agreed. But others, including the Physicians' Committee for Responsible Medicine and the Foundation on Economic Trends (who called for a halt to the study midway through which led to the second review) as well as some ethicists (see Tauer, 1994 and Kopelman, 2002¹⁴) were less convinced. Both sides appealed to common moral intuitions as well as guidance governing the ethics of research with children in the U.S. in reaching their conclusions. But no consensus was reached. In the following, I examine this study according to my proposed definition of minimal risk within a systematic framework for analyzing harms and benefits. I argue that my interpretation offers principled guidance about how to determine the permissibility of this study and generates determinations that are more persuasive than those reached by competing interpretations of minimal risk.

In chapter 1, I proposed that component analysis provides the most successful conceptual framework for analyzing harms and benefits. In the following, I analyze the NIH growth hormone trial according to the moral requirements of component analysis (which relies on a minimal risk threshold). To recall, one main insight of component analysis is that clinical research often involves interventions administered with different purposes—some aim to benefit the individual research subject while others are administered exclusively to answer the scientific question at hand (Miller & Weijer, 2005). Moreover, these different interventions should be assessed according to different moral rules. Accordingly, the first step of component analysis is to demarcate the study procedures. The NIH growth hormone trial involved a number of procedures. To help determine eligibility, prospective subjects would be admitted to the clinical center at NIH for a 3-day initial evaluation that includes:

¹³ In the U.S., the ethical review of trials is conducted by institutional review boards, which are similar to the research ethics boards that assess the permissibility of research protocols in Canada.

¹⁴ Kopelman reports that the protocol review committee did not reach a unanimous decision that the trial was ethically permissible.

- Provocative tests of hGH response
- Standard blood and urine tests
- Tests of growth and bone maturity including X ray and MRI scans
- Nude photographs against a height grid
- Regularly repeated blood samples to measure the levels of hGH and other hormones, and
- Behavioural and psychological assessments. (Tauer, 1994).

Children accepted into the study undergo a number of other procedures:

- Subcutaneous growth hormone injections or saline injections administered three times a week for the duration of the study
- Some children in the study are randomized to a no treatment control
- Every 6 months, a child will return for blood and urine tests, body measurements, assessment of possible immune response to the study drug, and bone age X-rays.
- At the end of the first 6 months, each child would be readmitted to the clinic for three days for additional overnight measurements similar to those in the initial evaluation.
- After this 3 day visit, regularly scheduled visit (6 months or annual) during which some of the above measurements were repeated (Tauer, 1994).

5.3 Demarcating the procedures

In this section, I will demarcate the therapeutic and non-therapeutic research procedures of the growth hormone trial. Which procedures are therapeutic? Therapeutic procedures are those administered on the basis of evidence that they may benefit individual research subjects. These include both procedures administered during the course of a trial that are also part of standard medical care (and would likely be performed irrespective of a person's research participation) as well as experimental interventions aiming to benefit a subject.

It follows that demarcating the therapeutic procedures of this trial depends on identifying the components of standard care for the eligible study population. What does

standard clinical care involve for a child with idiopathic short stature? The diagnosis of idiopathic short stature is made by excluding underlying medical causes of short stature. Thus, when a very short child (and her family) seek medical help, standard care usually involves a number of procedures, most of which aim to exclude the possibility that she has a disease causing her short stature.

The first step is for a doctor to perform an initial evaluation to exclude any non-endocrine systemic diseases that may be causing the growth failure (Moshang, 2005, p.159). This evaluation includes a detailed history (including family history) and a comprehensive physical examination involving phenotypic characteristics, body proportions, and pubertal staging (Cohen et al., 2008; Van den Brande & Rappaport, 1993, p.192). A critical part of these examination are accurate height and weight measures in addition to carefully plotted growth curves (Moshang, 2005, p.157). When the medical history and physical examination do not suggest a particular diagnosis, a variety of screening lab tests are recommended (Cohen et al., 2008). A bone age x-ray should be examined to help determine the child's growth potential and to narrow the differential diagnosis, a measurement of IGF-I (insulin-like growth factor test), and in some instances, a skeletal survey (Cohen et al., 2008).

Once non-endocrine underlying diseases have been ruled out, a pediatric endocrinologist examines whether the child has a growth hormone deficiency. No single test or set of tests can accurately identify growth hormone deficiency. Consequently, this diagnosis requires clinical as well as biochemical evaluation (Cohen et al., 2008). If growth hormone deficiency is ruled out and a child is determined to have idiopathic short stature, no treatment is usually prescribed, but regular doctor's visits are recommended to evaluate growth patterns. And at times, if puberty is significantly delayed, a clinician may also consider giving a 3 to 6 month course of sex hormones (Van der Brande & Rappaport, 1993, p.192).

Information about the procedures undertaken in standard care helps to determine which of the study procedures are therapeutic. Any intervention that a child seeking medical intervention would undergo irrespective of trial participation should be considered a therapeutic procedure. Consequently, a number of the trial interventions are therapeutic. All the procedures involved in the three day initial evaluation—hGH

response tests, blood and urine tests, tests of growth and bone maturity, nude photos against a height grid, blood samples, as well as behavioural and psychological assessments—are part of (or very similar to) the process a child would undergo in standard care as a clinician makes a diagnosis of idiopathic short stature. Thus, these are therapeutic procedures. Some of the follow up visits at regular intervals (the annual visits) repeating measurements are also therapeutic, as they resemble the interventions a child would undertake in standard care.

The visit at six months that repeats the procedures performed during the initial evaluation is harder to demarcate. Repeating the procedures of the initial evaluation seems superfluous to a child's care, which suggests that these are non-therapeutic procedures. But there may be good medical reasons for repeating the procedures. It is difficult to accurately diagnose hGH deficiency; no single test or set of tests can make an accurate diagnosis (Cohen et al., 2008). Further, a particular series of tests may suggest a child to be non-deficient even if she actually lacks adequate growth hormone (Tauer, 1994). Given that different treatment is suggested for children who are GH deficient, it may be in the medical interests of a child to undergo further testing to help confirm the diagnosis of idiopathic short stature. Thus, repeating these interventions may help to rule out the possibility that a child's short stature is the result of an endocrine dysfunction requiring treatment and may be best understood as part of good or optimal clinical care. Accordingly, these procedures should also be considered therapeutic.

In addition, the study's main active interventions, the therapeutic growth hormone injections and the no treatment control are therapeutic procedures. These are therapeutic procedures not because they are part of standard care, but because they are research interventions administered based on evidence that they may be in the medical interests of the research subjects.

It seems reasonably straightforward that the study's main non-therapeutic interventions are the three weekly injections for children randomized to the placebo group. These interventions are administered in the interest of answering the study question and not to benefit particular research subjects. In addition, the three-day overnight visits to the NIH clinical centre (to determine study eligibility and then repeated after six months or study enrollment) and some of the follow-up visits involving

measurements are non-therapeutic procedures. These procedures are not part of standard care and are not administered in the therapeutic interests of the research subject.

5.4 Evaluating the therapeutic procedures

Once the study procedures are demarcated, component analysis proceeds by evaluating the therapeutic procedures and non-therapeutic procedures according to separate moral rules. Therapeutic procedures must meet the requirement of clinical equipoise, that is, they must be consistent with competent medical care (Weijer & Miller, 2004). As described above, some of the therapeutic procedures of the NIH growth hormone study—including the blood and urine tests, body measurements, tests of growth and bone maturity, and the behavioural and psychological assessments—are part of standard or optimal medical care for children with short stature. It follows that they are consistent with competent medical care, that is, they meet component analysis' requirements for therapeutic procedures.

Determining whether the main active interventions, the growth hormone injections and the no treatment control meet the requirement of clinical equipoise requires careful scrutiny. To determine whether these interventions meet the requirement of clinical equipoise, a research ethics board should ask two questions: (1) is the evidence supporting the experimental intervention sufficient that, were it widely known, expert practitioners would disagree about the preferred treatment? (2) Is the control group being unfairly deprived of the experimental or proven, effective treatment? A research ethics board must answer yes to the first question and no to the second for the therapeutic procedures of the trial to be permissible.

To answer the first question, a research ethics board should examine whether there is disagreement within the community of expert practitioners about the efficacy of hGH for healthy children. A survey of the medical literature reveals that experts disagree about the safety and efficacy of hGH in healthy children. Several studies provide evidence that children with idiopathic short stature may benefit from an increase in height as the result of hGH interventions (Genentech Collaborative Study Group, 1989; Gertner et al., 1984). For example, the Genentech Collaborative Study Group's trial of 121 children with idiopathic short stature found that treating children with idiopathic short

stature with growth hormone for one year significantly increased their mean growth rate. They report that roughly 75% of children in the treatment group had an incremental increase in growth rate of more than 2 cm, whereas children in the control group showed no increase in predicted height (Genentech Collaborative Study Group, 1989).

However, others disagree; Allen argues that height gain attributed to hGH may be overestimated because untreated children with idiopathic short stature often show a spontaneous increase in height with age (Allen, 2006). Others agree that while hGH may help to increase height in children with idiopathic short stature in the short term, it has no effect on their overall adult height (Hintz et al., 1999; Allen & Fost, 1990). Some have also raised concerns about the role of hGH in the development and progression of certain cancers (Stoll, 1992). Finally, recent studies summarizing the current state of knowledge about the effects of hGH on short but healthy children conclude that the risks and benefits remain uncertain (Allen, 2011; Cohen & Cosgrove, 2010; Allen, 2006). The disagreement among expert practitioners over hGH treatment for healthy but short children suggests that a state of clinical equipoise exists.

To meet the moral requirements of clinical equipoise, researchers and research ethics committee should also examine whether the control group is being unfairly deprived of the experimental treatment. Unfair deprivation of an experimental intervention occurs when a subject's participation in a trial prevents her from receiving a therapy that she would otherwise receive as part of standard care. Children in the control arm of this trial receive a no treatment control. Are they unduly deprived of hGH? Allen and Fost reason that evidence suggesting that healthy children may respond to hGH interventions combined with the fact that hGH therapy is the standard medical intervention for children who are hGH deficient provides a compelling reason to provide healthy children with hGH treatment. Further, they think that depriving healthy but very short children of hGH treatment would be unfair discrimination on the basis of growth hormone deficiency (Allen & Fost, 1990). And if healthy but very short children are entitled to hGH treatment, then it follows that subjects in the placebo arm of the NIH trial would be unduly deprived of standard care.

However, a closer analysis reveals that offering no treatment to very short but medically normal children is consistent with standard care. A placebo control is morally

appropriate in several circumstances, including when there is no standard therapy for the condition of interest, and when treatment exists but “no treatment” is nonetheless consistent with competent medical care (Freedman, 1990; Weijer & Miller, 2004). For example, treatments exist for some minor medical conditions, like mild hypertension, but a competent physician may nonetheless recommend no treatment. In these kinds of situations, the use of a placebo control for minor medical conditions is permissible (Weijer & Miller, 2004). For children who are very short but medically normal, there is no standard intervention. Some physicians offer hGH treatment but others—perhaps because of safety or efficacy concerns as well as concerns over the cost or availability of the drug—prescribe no treatment at all. As a result, it seems reasonable for a research ethics board to conclude that subjects in the control arm of the NIH study were not unduly deprived of standard care. Given that a research ethics board could reasonably find that all the study’s therapeutic procedures meet the requirements of clinical equipoise, the NIH growth hormone trial meets component analysis’s moral requirements for therapeutic procedures.

5.5 Evaluating the non-therapeutic procedures

The next step of component analysis is to assess the permissibility of the study’s non-therapeutic procedures. Given that non-therapeutic procedures are administered to generate scientific knowledge and not for the benefit of an individual research subject, they must meet different moral requirements. Non-therapeutic procedures must be (1) minimized consistent with sound research design, (2) reasonable in relation to the knowledge that may be gained from the study, and (3) when a study involves a vulnerable population, a threshold should be invoked to limit the degree of non-therapeutic risks to which vulnerable subjects may be exposed (Weijer & Miller, 2004).

A research ethics board can help to ensure that the risks of a study are minimized consistent with sound scientific design by protecting patient-subjects from undergoing any additional procedures above and beyond those required to meet the scientific ends of the study (Miller & Weijer, 2006). Procedurally, risks of non-therapeutic procedures can be minimized by substituting procedures which are already being performed on the subjects during the course of their regular treatment and diagnoses (Weijer & Miller,

2004). For example, extra blood could be drawn for research purposes during a clinically indicated blood draw, thereby reducing the number of venipunctures a patient-subject must undergo (Weijer & Miller, 2004). The risks of non-therapeutic procedures can also be minimized when such procedures are administered by qualified health professionals.

Are the non-therapeutic procedures of the NIH growth hormone trial minimized consistent with sound scientific design? This trial involves a sham intervention—the administration of three saline injections a week to subjects in the control group for the duration of the trial. For these to be morally permissible, it must be the case that sound trial design requires this kind of control group. That is, it must be the case that the study would be compromised without the placebo injections. The primary motivation for including placebo injections in a trial is to preserve anonymity, which requires that subjects in the placebo arm undergo similar procedures as those undertaken by subjects in the experimental arm (Weijer, 2002). Blinding aims to protect the outcome of a trial from being affected by the placebo effect.¹⁵ But is blinding an indispensable feature of this trial? The outcome measures of the growth hormone trial include measurements of a child's height and weight. These outcome measures seem less likely to be affected by a placebo effect than other kinds of outcome measures, such as one's psychological well-being. That is, it seems implausible that a psychologically induced response will affect a child's height. But if this is the case, then the rationale for including sham procedures is not compelling; the trial might have been conducted unblinded, which suggests that the risks were not minimized consistent with sound scientific design.

Still, there may be good reasons for this trial to include the sham procedures. In their examination of the trial, the NIH protocol review panel identified the necessity of the placebo arm as a central question for analysis. They examined trial designs with other kinds of control groups and found them wanting. With respect to an unblinded study, they write:

The disadvantage is the concern that the placebo group will gradually become less of a true control group as they differentially receive other ancillary therapies, and also as a significant number of them probably receive hGH outside the study. There

¹⁵ The placebo effect is when the administration of an intervention leads to a psychologically induced response (Protocol Report, 1992).

are multiple examples from other clinical trials demonstrating that this is a real concern, not just a theoretical concern. (Protocol Report, 1992, p.24)

In making their determination, the panel took into account the small number of subjects enrolled in the trial, which was thought to complicate obtaining precise and credible results as well as the possibility that a placebo effect could lead to misleading trial results (Protocol Review, 1992). The panel concluded that in general, the best scientific design for a clinical trial is the randomized, double-blind concurrent control design and with respect to the growth hormone trial, “[m]ost members of the committee agreed that the study should be continued with double-blind, placebo controls” (involving the sham procedures) (Protocol Report, 1992, p.25).

The committee’s determination is controversial; they do not provide adequate information about why an unblinded study would result in insuperable problems of compliance and the panel itself reports that they did not receive enough information to either support or dispute the likelihood of a placebo effect (Protocol Report, 1992, p.25). But for present purposes, it is sufficient to recognize that there may be sound scientific reasons to include the placebo arm, that is, the non-therapeutic procedures of the trial may be minimized consistent with sound scientific design.

Assuming that this requirement has been met, does the NIH trial meet component analysis’ other constraints for non-therapeutic research procedures? In order to meet the second constraint—that risks associated with non-therapeutic procedures must be reasonable in relation to the knowledge to be gained—a research ethics board must pass judgment on whether the social priorities of the research stand in reasonable relation to the risks involved in the proposed procedures. This judgment relies on the research ethics board members’ scientific expertise as well as the community members’ appraisal of the social value of the research being pursued (Miller & Weijer, 2006b; Weijer, 2000). They must find that study risks are not excessive and that the study question is sufficiently important.

The current study includes three saline injections a week, every week, for multiple years. These injections are accompanied by the risks of inconvenience, discomfort, and pain. Specifically, subcutaneous injections may result in bruising, swelling or redness. Given that the total number of injections involved in the study falls between 600-1100

shots over multiple years—each of which may be accompanied by some or all of these burdens—the non-therapeutic risks of this study are not trivial.

On the other hand, the knowledge likely to be gained from the study is valuable. Short stature may be socially stigmatizing and, in some cases, can contribute to psychological problems as well as economic disadvantages (Allen & Fost, 1990). Perhaps for these reasons or as the result of these sorts of concerns, parents are increasingly requesting growth hormone for their children (Tauer, 1994). Further, in spite of inadequate testing of its safety and efficacy in non-GH deficient children, many children with idiopathic short stature have or are currently receiving growth hormone treatment (Lescheck et al., 2004; Allen, 2011). At the time of the study, the NIH panel estimated that roughly 15,000 children in the U.S. were receiving growth hormone therapy, and many of them were not deficient (Protocol Report, 1992, p.7). Consequently, finding out whether this treatment is safe and effective is valuable. It can help to determine what treatment is in the best interest of children with idiopathic short stature. In this case, the risks of the study are non-trivial but the knowledge to be gained is of considerable social and scientific merit. Consequently, it seems reasonable for a research ethics board to judge that the risks are reasonable in relation to the knowledge to be gained.

Component analysis's third constraint on non-therapeutic procedures is that when the research involves a vulnerable population, non-therapeutic risks must be restricted. When the trial involves a vulnerable population, it is not sufficient that the risks be reasonable in relation to the knowledge to be gained, they must also be limited to a low degree. Following the U.S. DHHS regulations, component analysis restricts the upper level of risk involved in non-therapeutic procedures to a minor increase over minimal risk, that is, a minor increase over the risks ordinarily encountered in daily life (Weijer & Miller, 2004). In chapter 2, I argued that for non-therapeutic research procedures to be justifiable, they should pose no more than minimal risk (rather than a minor increase over minimal risk). Accordingly, in the following, I will use minimal risk as the threshold for permissible non-therapeutic procedures within component analysis' framework for assessing harms and benefits.

How should a research ethics board assess whether non-therapeutic risks surpass the minimal risk threshold? To determine whether a study's non-therapeutic risks exceed

minimal risk, a research ethics board should ask two questions: (1) Is the group of children eligible for study population unduly burdened? (2) Are the non-therapeutic risks of this trial the same as, or sufficiently similar to, the risks the eligible study population faces in daily life? For the non-therapeutic procedures of a trial to be permissible, a research ethics board must answer no to the first question and yes to the second.

To answer the first question, a research ethics board must examine whether the eligible subject population, in this case children with idiopathic short stature, fares well. That is, they must consider whether this group of children is likely to possess sufficiently high degree of the seven substantive goods of childhood (i.e. health; biological needs; intellectually engaging activity; meaningful relationships; unstructured, imaginative play; bodily integrity; and happiness). In the previous chapter, I proposed that sufficiently high degrees of the substantive goods should be determined by reference to children who are fairly well-off. Procedurally, a research ethics board should make this determination based on considerations about whether the eligible study population has similar degrees of the substantive goods of childhood as children who are reasonably advantaged. This determination should be informed by reflective judgment, a review of scientific literature addressing the relevant population group, and, when necessary, consultation with experts.

Does the eligible study population possess comparable degrees of meaningful relationships, intellectually engaging activity, biological needs, unstructured, imaginative play, bodily integrity, happiness, and health as children who are fairly well off? In making this determination, a research ethics board should consider the context of the study, including its location as well as any defining socio-economic particularities about the group of children it aims to recruit. The eligible study population in the NIH trial is American children who seek medical intervention for their short stature. These children are also likely to be from reasonably affluent families. Thus, a research ethics board should consider whether affluent, American children with idiopathic short stature meet sufficiently high degrees of the seven goods of childhood.

Some peer-reviewed studies offer reasons to think that these children are part of caring families and have good educational opportunities available to them. For instance, the fact that children with short stature and their families often seek the advice of pediatric endocrinologists (Protocol Review, 1992; Cohen et al., 2008; Tauer, 1994)

suggests that many children with idiopathic short stature are part of loving families who care about their child's physical and social well-being. Further, a number of studies examining the impact of idiopathic short stature on children's lives use school performance as one of their outcome measures; they measure children with idiopathic short stature's school performances against those of their normal height peers (Downie et al., 1997; Sandberg & Voss, 2002). This suggests that children with idiopathic short stature have access to similar intellectually engaging activities as their normal height peers. They attend the same schools and have access to comparable educational opportunities.

In addition, there is some evidence suggesting that this group of children has their biological needs met. As noted above, idiopathic short stature is defined as "a condition in which the height of an individual is more than 2 SD score (SDS) below the corresponding mean height for a given age, sex, and population group without evidence of systemic, endocrine, *nutritional*, or chromosomal abnormalities" (Cohen et al., 2008, emphasis added). That is, part of the definition for this condition is that a child's short stature is not caused by nutritional deficiencies. It follows that in reaching a diagnosis of idiopathic short stature, a clinician will establish that some of a child's biological needs (her nutritional needs) are being met. Further, the context of the study, including its geographic location, as well as the way the eligible study population is constructed is reassuring. Children recruited for trial participation are from a developed country and a population group that seems likely to possess fairly high degrees of the substantive goods of meaningful relationships, education, and biological needs. Based on these kinds of considerations, it seems reasonable for a research ethics board to determine that children with idiopathic short stature have sufficiently high degrees of these goods.

Determining whether children with idiopathic short stature have sufficient degrees of unstructured, imaginative play, and bodily integrity is more complicated. A literature search reveals no studies examining correlations between idiopathic short stature and these components of a child's welfare. More of these studies would help to determine whether children with idiopathic short stature have sufficiently high degrees of these substantive goods. But there is no plausible intuitive connection between play or bodily integrity and a child's height. Consequently, it seems reasonable for a research ethics

board to determine that children with idiopathic short stature also possess sufficiently high degrees of these substantive goods.

What about happiness and health? Meeting the requirement for happiness and health seems to pose the most formidable challenge for children with idiopathic short stature. One main reason that parents and their very short children seek medical help is because of the concern that a child's short stature will contribute to problems in her normal functioning, which may, in turn have a negative impact on her happiness. The concern for these children is that they will experience ridicule or bullying from their peers that will render them worse off than children of normal height.

This concern is reflected in some analyses of children with short stature and the efficacy of growth hormone intervention. For example, Law (1987) claims that "few paediatricians would deny that children with extreme short stature face a disability that may affect their physical, psychological, and social well-being" (Law, 1987, p.855) and concludes that these children face high incidences of behavioural disorder, the most prominent of which are social isolation and lack of appropriate aggressive drive. Similarly, Allen and Fost find that school problems occur more often in children of short stature, which contributes to these children's feeling of incompetence and low self-esteem (Allen & Fost, 1990). It follows that a research ethics board should examine whether children with idiopathic short stature have enough of these substantive goods carefully.

A literature review found no studies examining the happiness of children with short stature directly, but several HR-QOL studies offer insight that pertain to children with idiopathic short stature's happiness in addition to their health. That is, these studies often measure self-esteem, which relates to a person's life-satisfaction (i.e. happiness), in addition to other aspects of health or function. Thus, the HR-QOL studies offer valuable information that can help to inform a determination about whether children with idiopathic short stature possess comparable degrees of happiness and health to children who are fairly well off.

The most recent HR-QOL studies suggest that children with short stature's quality of life is similar to that of normal height children (Ferguson, 2011). For example, Ross and colleagues (2004) following a group of 68 children (including children with

idiopathic short stature and regular height controls between ages 9-16 years old) over four years found that short stature was not associated with problems in psychological adaptation or self-concept in children with idiopathic short stature. Parent's responses to a child behavioural checklist and children's responses to a self-perception profile and silhouette appreciation technique revealed no significant differences between children with idiopathic short stature and the control group (Ross et al., 2004). Other studies show similar results. Downie and colleagues (1997) found no significant difference between children with idiopathic short stature and normal height controls on measures of self-esteem, self-perception, parent's perception or behaviour (Downie et al., 1997). Sandberg and Voss conclude that short stature holds little value as a predictor of quality of life (Sandberg & Voss, 2002). And a consensus statement on the diagnosis and treatment of children with idiopathic short stature finds that "[o]verall, both clinical and population studies indicate that most short individuals are functioning within the broad range of normalcy" (Cohen et al., 2008, p.4212). Sandberg and Voss summarize the situation well. They write:

The association between short stature and psychological disadvantage 'has been found largely on older, poorly designed clinic-based studies and laboratory investigations of beliefs about the association between stature and individual characteristics. In contrast, data from more recent and better designed clinical and community-based studies show that, in terms of psychosocial functioning, individuals with short stature are largely indistinguishable from their peers. (Voss & Sandberg, 2004, abstract)

The most recent literature suggests that children with idiopathic short stature's quality of life, which measures components of the substantive goods of health and happiness, is roughly comparable to that of children without idiopathic short stature. They may be at higher risk for some psychosocial problems, such as low self-esteem and being bullied. But these risk factors may have more to do with other factors—including parental attitudes—than with a child's short stature (Cohen et al., 2008). The literature suggests that children's responses to idiopathic short stature vary considerably and it is difficult to make accurate generalizations about them as a group (Cohen et al., 2008), but that overall, their daily lives are roughly comparable to those of their taller peers. Based on

these kinds of evidence, it is reasonable for a research ethics board to conclude that children with idiopathic short stature, as a reference class, are likely to possess sufficiently high degrees of health and happiness to fare well. It follows that a research ethics board may plausibly find that children are not unduly burdened by idiopathic short stature, that is, they may plausibly answer ‘no’ to the first question. It follows that children with idiopathic short stature eligible for trial participation (in addition to other children who fare well) should be considered the referent for minimal risk in this study.

Nonetheless, it does not necessarily follow that the non-therapeutic procedures of the study are permissible. To recall, meeting the minimal risk threshold requires that a research ethics board also answer a second question: are the non-therapeutic risks of this trial the same as, or sufficiently similar, to the risks of daily life? This second question aims to ensure that procedures identified as minimal risk not only refer to a justifiable study population but also pose degrees of risk that are comparable, or sufficiently comparable, to the daily experiences of these children.

To answer the second question, a research ethics board should reason by analogy (Freedman, Fuks, & Weijer, 1993); they should consider whether the degree and kind of risk posed by the non-therapeutic procedures are sufficiently similar to the degree and kind of risk the referent is likely to face in daily life, for instance, the kinds of risks encountered during the performance of routine physical examinations or tests. What experiences are involved in the daily lives of children with idiopathic short stature? When a child and her family seek medical help for very short stature, they are likely to undergo a series of doctor visits and tests to help rule out diseases and establish a diagnosis of idiopathic short stature. Some of these procedures—such as tests of bone maturity—differ from procedures a healthy child would undergo in a routine examination. Further, once a diagnosis of idiopathic short stature is made, a child will have routine check-ups with a doctor that will involve height and weight measurements. These visits may be more frequent or involve more careful examinations than those faced by a taller child of the same age.

In addition, a child with idiopathic short stature’s daily life is likely to involve similar experiences as those of normal height children living in the United States, such as riding a bicycle, riding in a car, and attending school. Thus, the daily experiences of

children with idiopathic short stature are likely to involve more medical tests to establish that they are not growth hormone deficient and more frequent doctor visits than healthy normal height children but also average daily activities such as attending school and playing with friends. Their daily experiences are perhaps best understood as being different from those of healthy normal height American children, but not necessarily unduly burdensome.

Are the risks of the study's three day visits to the NIH clinical center (repeated twice) as well as 600-1100 saline injections administered for up to seven years comparable to what children with idiopathic short stature would experience daily? Children with idiopathic short stature may visit the doctor more frequently than some other children, but these visits do not involve overnight stays. Further, the standard care of children with idiopathic short stature does not usually involve growth hormone therapy. Consequently, they are unlikely to receive three weekly injections over a long period of time. This seems to suggest that the non-therapeutic risks of this study are not comparable to the daily risks of a child with idiopathic short stature.

However, the fact that these interventions are not part of the risks that a child literally faces on a daily basis does not necessarily suggest that the study's injection regimen poses more than minimal risk. A risk of daily life may be the risk involved in an activity undertaken by all or a majority of children on a daily basis. But it may also be an activity undertaken by all or most children less frequently as long as the risks posed are the kind of risks that are and should be accepted by society or by responsible parents on behalf of their children.¹⁶ Accordingly, a useful rule of thumb to help determine what counts as a risk of daily life is that these risks may be thought of as a background level of risk accepted by most reasonable members of society and by responsible parents on behalf of their children. In other words, the degree of risk that should count as minimal may be the literal risks of daily life or a background level of risk accepted by society and by responsible parents on behalf of their children to promote valuable ways of life.

¹⁶ I've argued (in chapter 2) that socially accepted risks are morally relevant because they are part of a reasonable trade-off between personal safety and the pursuit of the kinds of lives we find valuable.

Do the growth hormone trial's non-therapeutic procedures pose more than minimal risk understood in this way? It seems reasonably likely that responsible parents will agree that an extra doctor visit or two a year involving a detailed physical exam (above and beyond those encountered by children with idiopathic short stature face in practice) fall within the background range of risks that are permissible for a responsible parent to undertake on behalf of her child. It follows that while these are not part of the risks children with idiopathic short stature literally face on a daily basis, they might reasonably be found to involve no more than minimal risk.

The 3-day overnight visit to determine trial eligibility and repeated after six months of the trial is less straightforward. It would be reasonable for some parents to be concerned about the potential stress caused to a child by these overnight visits. The overnight visits take place in a carefully regulated clinical center with trained professionals, but overnight visits in unfamiliar clinical settings involving medical tests seem likely to cause stress for many children. Accordingly, there is some reason to think that these risks may be considered higher than children's daily risks of the background level of permissible risks a parent should undertake on behalf of her child or at least to think that reasonable parents may disagree about whether these risks should count as minimal.

Further, the study's non-therapeutic procedures involved subcutaneous injections administered three times a week for up to seven years. Do thrice weekly saline injections pose more than minimal risk? In their discussion of the degree of risk posed by these interventions, the protocol review committee reported "disagreement on how heavily to weigh the pain, discomfort, and inconvenience of the many shots each child would receive" (Protocol Review, 1992, p.16). Accordingly, it is perhaps unsurprising that the panel's discussion of the risks of this intervention is unclear. On the one hand, the report claims that only one member of the group identified the discomfort and inconvenience of the injections as more than a minor increase over minimal risk (Protocol Review, 1992, p.16). But this is hard to reconcile with the committee's claim that the "requirement for multiple injections represented, if not a substantial risk, nonetheless one significantly greater than minimal, especially with respect to potential benefits" (Protocol Review, 1992, p. 16; Tauer, 1994). While it is unclear whether the committee determined the

study to pose a minor increase over minimal risk or a higher degree, all committee members agreed that the risks of the injections posed more than minimal risk (Protocol Review, 1992). This determination by experts provides some reason to think that the risks of the injections pose more than minimal risk.

Further, Tauer points out that there is some information available about children's reactions to long-term administration of growth hormone that may be instructive in determining the risks of the trial injections (Tauer, 1994). She draws attention to Rotnem and colleagues' examination of the psychological responses of children receiving growth hormone injections. Rotnem and colleagues found that some children receiving growth hormone injections "saw themselves as victims of painful and useless injections, and persistently or intermittently resisted the shots and directed angry feelings toward their parents" (Rotnem et al., 1979, p.516). This study suggests that some children will experience three weekly injections as burdensome. But it does not provide conclusive evidence. It measured only 11 children, a small sample size that may not be representative of the experiences of a broader group of children with idiopathic short stature. And further, some of the children studied demonstrated mild symptoms of depression before the growth hormone treatment (Rotnem et al., 1979). Accordingly, this study is perhaps best understood as offering limited evidence that children may have adverse reactions to these injections.

More research about the way children with idiopathic short stature experience injections should be undertaken and will help to determine the degree of risk posed by placebo injections for children with idiopathic short stature. But even with the deficit of clear evidence about children's reactions to these injections, it seems reasonable to determine that these interventions pose more than minimal risk. Each saline injection poses some risk of discomfort, inconvenience, pain, swelling, redness or bruising. In addition, the large quantity of injections (600-1100) combined with the length of the study (up to roughly seven years) increases the likelihood of subjects experiencing adverse reactions to these injections. The additional procedures undertaken by a child with short stature in standard care are mostly measurements, which are less invasive than injections. Further, this number of injections seems to pose more than the usual daily risk that a responsible parent might permit for a child. It follows that a research ethics board

would be justified in determining that the risks of the non-therapeutic saline injections pose more than the risks of daily life.

Given that a trial may only be found permissible provided that the risks of a study's non-therapeutic procedures do not exceed a justifiable threshold and these risks exceed the minimal risk threshold, the NIH growth hormone trial does not meet the requirements for non-therapeutic procedures and consequently, should be found ethically impermissible. In the following section, I will consider how this determination differs from—and is more persuasive than—the prominent competing interpretations of minimal risk.

5.6 Further reflections

The above analysis of the NIH short stature trial demonstrates that my interpretation of minimal risk, applied within component analysis's framework for the evaluation of harms and benefits, offers practical guidance to research ethics boards assessing the permissibility of research protocols. If my arguments are successful, then one main advantage of my proposal is that it offers clear guidance based on sound reasoning. It helps to focus research ethics boards' attention on morally relevant questions, provides a standard according to which to make determinations, and suggests relevant sources of empirical information to consult that may inform a determination. This guidance may help to produce clear answers in difficult cases. But ultimately, the success of my proposal depends on more than its ability to yield clear answers. Another important measure of an ethical argument's success is whether it yields conclusions that are persuasive. In particular, my argument should contribute to determinations that are more persuasive than those of other prominent interpretations of minimal risk.

It is worth emphasizing that the reason the growth hormone trial may be found ethically impermissible is because the risks of the study's saline injections pose more than the daily risks of children with idiopathic short stature, which is impermissible. The problem with the trial is not that children with idiopathic short stature should not be the referent for minimal risk. I've argued that children with idiopathic short stature possess sufficiently high degrees of the substantive goods of childhood that it is permissible to expose them to non-therapeutic procedures involving risks that are comparable to their

usual daily risks. In the following, I will examine how my proposal compares with the most prominent competing interpretations about the referent for minimal risk in the NIH growth hormone for short stature trial. The overall determination about the trial's permissibility according to competing interpretations may vary depending on the framework within which the minimal risk constraint is employed (e.g. component analysis, the DHHS regulations, etc.). But given that each of these frameworks relies on a concept of minimal risk, and my goal is to provide a justified interpretation of minimal risk, I will focus on whether my proposal offers a more persuasive determination regarding the referent for minimal risk rather than on the final determination about the trial's permissibility.

Interpretations of minimal risk that identify the referent as healthy children or normal, average, healthy children living in a safe environment would reach a different conclusion about children with idiopathic short stature. As noted in chapter 3, different descriptions of this interpretation identify different referents for minimal risk. But the prevailing understanding of this interpretation identifies the referent as a subgroup of healthy children. Specifically, the National Commission first identified the referent as healthy children (National Commission, 1977), but most subsequent commissions and commentators identify the referent as a narrower group. For example, both NHRPAC (2002) and the IOM (2004) identify the referent as normal, healthy, average children. SACHRP (2005) identifies the referent as normal, healthy, average children living in safe environments and the most recent commission to consider the question, the Presidential Commission for the Study of Bioethical Issues (2013), identifies the referent as a healthy child living in a safe environment. More generally, the prevailing trend is to identify the referent as a subgroup of healthy children, perhaps normal, healthy children in a safe environment.

Does the eligible study population in the NIH short stature trial meet these constraints? On the WHO definition, health is “a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity” (WHO, 1948).¹⁷

¹⁷ As noted in chapter 3, commentators do not explain what they mean by health. Nonetheless, the trend in the literature, which aims to identify a subgroup of healthy children who are not only disease-free, but also possess additional characteristics (e.g.

Children with idiopathic short stature do not meet this definition. If they were completely healthy, then children with short stature and their families would not seek the help of pediatric endocrinologists. Further, while the most recent scientific literature supports the idea that children with idiopathic short stature function within the “broad range of normalcy” (Cohen et al., 2008, p.4212)¹⁸, they may still be at a somewhat higher risk for psychosocial problems than their normal height peers (Cohen et al., 2008). That is, they do not seem to be completely healthy. The point is even clearer if we understand this interpretation of minimal risk as identifying the referent as a subset of healthy children who are also normal, average, and live in a safe environment. The eligible study population in the NIH trial are children who were at least 2.25 SD below the average height. By definition, this group of children is not normal or average; they are considerably shorter than their peers. Consequently, they would not be identified as the referent for minimal risk.

What are the implications of this determination? It follows that according to the healthy child interpretation of minimal risk, children with idiopathic short stature are not part of a morally justifiable reference group for minimal risk. They may still be research subjects, but the non-therapeutic risks of the trial would have to be measured against the daily risks of a healthier group of children. The main point is that according to this determination, the daily lives of children with idiopathic short stature are found to involve a morally impermissible degree of risk. It follows that procedures a child with idiopathic short stature undertakes as part of standard care that are not part of a normal child’s experiences—such as additional doctor visits or height and weight measurements—are inappropriate when administered without the intention of offering a child direct medical benefit. These kinds of procedures would be understood as exploiting a child’s unfair circumstances.

normal, average, live in safe places) that are thought to contribute to daily experiences involving low risks, suggests that commentators have in mind a definition of health similar to the WHO’s definition (which also accounts for more than a child’s diseases or disorders).

¹⁸ Cohen et al note that children less than 2.5 SD have not yet been adequately studied. More research about subgroups of children with idiopathic short stature would be useful to help determine whether they have similar experiences as their slightly taller counterparts.

This determination is not compelling. The literature suggests that while idiopathic short stature may be a risk factor for some social problems, children with this condition are not at a significant disadvantage with respect to their peers. To put it another way, idiopathic short stature does not necessarily compromise the daily lives of these children. Their daily lives are likely different than those of taller children, but these differences are not obviously problematic. Consequently, there is no compelling reason to protect them from facing comparable experiences in research that does not aim to offer them the prospect of direct benefit.

One might argue that some children with idiopathic short stature derive anxiety from their condition or from the additional procedures they experience in medical care. Consequently, this additional protection is desirable; it protects these children from facing comparable anxiety in research. It is true that some children with idiopathic short stature will derive more anxiety than others from their condition and medical procedures. But this is not a persuasive reason to prevent all children with this condition from being the referent. Given that children with idiopathic short stature and their families are familiar with the experiences that commonly accompany this condition, they are best placed to decide whether to undertake comparable procedures uniquely in the interests of the research. To put it another way, this kind of reasoning may provide a persuasive reason for a parent to decide not to include her particular short child in a trial, but it is not a persuasive reason for a research ethics board to impose additional protections on all children with idiopathic short stature when, on the whole, this group is not unduly burdened by their daily lives.

My interpretation of the referent for minimal risk recognizes that some children with mild disorders or conditions are not heavily burdened by their circumstances and do not necessarily require additional protections in research. Consequently, it lines up with the common moral intuition that children who are not completely healthy or those who deviate from normal in a minor way do not necessarily suffer on account of these differences. This determination is more compelling than the healthy child interpretation's determination that any child who is not completely healthy or deviates from normal should be protected from non-therapeutic research procedures comparable to her daily experiences.

What does the subjects of the research interpretation conclude about children with idiopathic short stature? To recall, this interpretation measures minimal risk according to the daily lives of the eligible study population, including healthy children as well as children with diseases, conditions or disorders. Given that children with idiopathic short stature are the eligible study population for the NIH trial, these children are the referent for minimal risk. This interpretation reaches the same determination as mine—that children with idiopathic short stature should be the referent for minimal risk. But it does so without considering the welfare of this group of children. That is, the subjects of the research interpretation reaches the conclusion that the daily lives of children with idiopathic short stature involve morally permissible degrees of risk without examining the burdens involved in the daily lives of these children. If it were the case that most children with idiopathic short stature faced significant bullying that resulted in severe psychological problems, this interpretation would provide us with no obvious reason for restricting these children's exposure to comparably high risks in research procedures that do not aim to offer the prospect of direct benefit. And this conclusion is undesirable. By determining the referent based on an assessment of whether the eligible study population is unduly burdened, my interpretation avoids the potential injustices of the subjects of the research interpretation. It recognizes that some, but not all, children with diseases, disorders or conditions experience morally relevant degrees of risk in their daily lives. Thus, my interpretation of the referent for minimal risk also offers more compelling results about the referent for minimal risk in the NIH short stature protocol than the subjects of the research interpretation.

More generally, my proposal offers a more moderate approach than the healthy child interpretation or the subjects of the research interpretation of the referent for minimal risk. The healthy child interpretation protects sick children from facing heavy burdens as the result of their illness or medical treatment from facing comparably high risks in non-therapeutic research procedures. But it offers this protection at a cost. It is unable to recognize that some children who are not healthy, normal, and average, that is, some children who are different, are not significantly burdened by these differences. Some of these children fare well. And these children need not be protected from their daily experiences when participating in research. Thus, the healthy child interpretation is

overly strict. On the other hand, the subjects of the research interpretation is overly permissive. It permits the exposure of children whose daily experiences involve high risks to face comparably high risks in non-therapeutic research procedures. Thus, children with imprudent parents willing to provide proxy consent for their child's participation in research that involves procedures that are equally burdensome to those their children face daily may face impermissibly high risks in research.

My proposal that the referent for minimal risk should be children who are not unduly burdened by their daily lives, understood as children who fare well, strikes a middle ground between these two interpretations. It restricts the degree of permissible risk in non-therapeutic research procedures for children—healthy or not—who are unduly burdened by their daily lives. And it does so without imposing unnecessary restrictions on all children who aren't healthy, average, normal, and living in a safe environment. By focusing on undue burden and children's welfare, my interpretation provides a way in which to identify the relevant features—and only the relevant features—of a child's circumstances that should impact her ethical treatment in research. Thus, identifying the referent as children who are not unduly burdened by their daily lives offers intuitively plausible results.

Chapter 6

Conclusion

The work in this thesis aims to fill in a missing component of the ethical justification for research with children. The ethical justification for research with children depends, in part, on an assessment of a trial's harms and benefits. For a trial proposing to enroll children to have an appropriate balance between research harms and benefits, the upper limit for the risks of non-therapeutic research procedures must be restricted. Limiting the risks of non-therapeutic procedures helps to ensure that vulnerable populations are not exposed to unfairly high degrees of research risk that offer them no prospect of corresponding benefit. But what degree of risk is permissible in non-therapeutic research procedures? The morally appropriate limit for research risks that offer no prospect of corresponding benefit is often measured according to the concept of minimal risk, but the concept of minimal risk has not been adequately justified. In the previous chapters, I proposed a new justification for why minimal risk should be interpreted according to daily life and identified a novel referent for minimal risk.

In chapter 1, I raised the main problem concerning the ethical inclusion of children in research and surveyed the solutions to this problem in research ethics. I argue that in general, a research subject's participation in a trial is justified, in part, by informed consent, a moral principle that helps to uphold the principle of respect for persons and their autonomous decisions. But children's limited cognitive competencies and experiences restrict their capacity to provide informed consent for research participation. This gives rise to a problem: If informed consent is a necessary component of the ethical justification of research with human subjects and children are unable to provide informed consent, then research with children seems to be impermissible.

I identified four arguments in research ethics that offer partial solutions to this problem, each of which is a necessary component of the ethical justification for research with children. The first argument appeals to social utility. The inclusion of children in research is in the interests of children as a group; it is the source of a critical public health benefit: it can improve the medical care of current and future children. Thus, children

should participate in research. But alone, this insight is insufficient to justify the inclusion of children in research. It seems to legitimize high degrees of risk to particular children on the basis of the benefits it may confer to others. Further, it does not explain why it is permissible to expose any particular child, who cannot consent for himself, to research risks for the benefit of others. Thus, it cannot, on its own, offer a successful justification for research with children. A second argument fills part of this gap by explaining that one need not always act in the best interests of children; at times, it may be permissible to expose a particular child to risk purely in the interest of others. It may be permissible to expose children to risks when the risks to a particular child are counterbalanced by benefits to another family member (or to the family as a whole) as well as in some instances when a child's exposure to risks contributes to important social goals, such as the success of a social community. Together, these two arguments successfully explain that it is in the medical interests of children to participate in research and that it can be permissible to expose a particular child to some risks purely for the sake of others. But they do not explain whether and why research is permissible in the absence of informed consent or the degree of risk to which a child can be exposed in research.

A third argument helps to resolve this problem by pointing out that the ethical requirement to obtain informed consent applies only to people who can make autonomous choices. Given that children are not autonomous, respecting them as persons does not require that they consent for research participation. Parents or guardians can provide surrogate consent for children's participation in research. This insight helps to explain why a child may participate without the ability to provide informed consent. But it does not explain the conditions under which it is permissible to provide surrogate consent for a child's participation. A fourth argument addresses this problem by appealing to the conditions that help to legitimize the inclusion of adults in research. Adults can enroll when a research ethics board determines that a protocol is ethically permissible, a determination that relies on an assessment of whether a protocol offers a reasonable balance between the harms and benefits of research participation. When a protocol involves children, a reasonable balance between harms and benefits requires that the risks of non-therapeutic procedures be restricted. They must pose no more than a low degree of risk, which is often measured according to the concept of minimal risk. But the

concept of minimal risk is under-theorized. It is not clear why minimal risk is a morally relevant threshold or how it should be understood and applied. Thus, I focused on explicating and justifying the concept of minimal risk.

In Chapter 2, I examined what should be a morally relevant comparator for the risks of non-therapeutic research procedures with children, that is, I examine the interpretation and justification of minimal risk. I defend the idea that minimal risk should be understood as the risks of daily life. The daily life interpretation draws on the fact that, no matter how careful a person is, carrying out her usual daily activities involves exposure to some risk and this inevitable degree of risk should be understood as minimal risk. It seems reasonably uncontroversial that our daily activities expose us to some degree of risk. But what, if anything, is morally relevant about these risks?

I reject the idea that the risks of daily life are morally relevant because they replace (and do not add to) the risks a child faces in her usual activities. The risks of non-therapeutic procedures are not constrained to the period of time during which the procedure is administered. For example, the risks of an injection with an investigational drug may continue after that child leaves the hospital or clinic. It follows that a child may simultaneously experience the risks of daily life and of a non-therapeutic research intervention. Consequently, the risks of research may add to, rather than replace, the risks a child would otherwise face at any given time.

Instead, I propose that the risks of daily life are morally relevant because they are the kinds of risks that most reasonable people have good reason to recognize as 'safe enough'. That is, they are risks that are—and should be—deemed socially permissible. Most people undertake the risks of daily life without much thought or calculation and irrespective of whether they offer the prospect of direct benefit. To put this another way, they are an approximate lowest common denominator of acceptable risk; they reflect the risks that most people in a society deem socially acceptable.

Moreover, they are the kinds of risks that should be deemed socially permissible. Accepting the risks of daily activities is not the result of mistaken or ill-formed judgment about the degree of risk involved in our usual activities. Instead, our belief that the risks of daily life are safe enough should be understood as a reflection of our values. We accept the risks of daily life because they are part of a reasonable trade-off between

personal safety and being able to pursue meaningful lives. That is, we accept daily risks because they are a necessary and reasonable sacrifice to the goal of pursuing projects and activities that contribute to ways of life that we value. Thus, the risks of daily life are morally relevant because they represent the lowest degree of risk that most people are willing to accept in order to promote and reinforce the kinds of activities, projects, and ways of life that they cherish.

Identifying daily life as morally relevant has important implications for research with children. I argued that it is permissible to expose children to some minimal degree of risk that is not in their direct interests but that this degree of risk must be low. I also argued that daily risks are the lowest degree of risk commonly considered an acceptable sacrifice in the interests of pursuing valuable goals. Given that clinical research with children is a valuable social project that promotes improved care for current and future children, it seems reasonable that it should expose participants to some risk that is not administered in their interest. When research subjects, such as children, cannot provide informed consent for the risks incurred on behalf of others, the degree of non-therapeutic research risk to which they should be exposed should be constrained. It seems reasonable to constrain these risks according to the most basic level of risk that is deemed acceptable in the pursuit of other valuable social endeavours. That is, non-therapeutic research risks on children should be constrained according to the risks of daily life. Finally, this argument explains why the risks of daily life may be morally relevant, but the success of this analysis also depends on specifying whose daily life is morally relevant.

Chapters 3 and 4 focus on this task. In chapter 3, I examine arguments in research ethics aiming to identify a referent for minimal risk. I argue that commentary on this question is unclear. When examining who should be the referent, commentators also ask a second question: does a relative standard or a uniform standard governing research with children meet the moral requirements of justice? That is, should minimal risk apply to all children in the same way or are there morally relevant differences between children that justify differential treatment in research? This second question is important; it asks what kinds of moral rules are justifiable in research with children, but it is distinct from and obscures the identification of a group of children whose daily lives should serve as the morally relevant comparator for minimal risk. I conclude that progress on the

identification of a morally justifiable referent for minimal risk requires that we separate examinations about what kind of standard is morally appropriate from attempts to identify a group of children who should be the referent for minimal risk.

In chapter 4, I argue that neither healthy children nor the subjects of the research is the morally appropriate referent for minimal risk. Some healthy children, such as those who are heavily burdened by their family's poverty, and some sick children, including those suffering from terminal diseases, face daily risks that seem unjustifiably high in the context of research that doesn't offer the prospect of direct benefit. The daily lives of these two groups of children are not justifiable comparators for the risks of non-therapeutic research procedures with children and consequently, neither interpretation identifies a justifiable referent for minimal risk.

I then defend a novel interpretation of the referent for minimal risk, informed by an insight from theories of distributive justice: justice does not require uniform treatment for all children in research. But it does require uniform treatment of like cases and a justification for unequal treatment. That is, only a morally relevant property can justify departures from equal treatment. I propose that the morally relevant property justifying different treatment between children in research is undue burden. I argue that children are not unduly burdened if they fare well. I then propose a substantive good theory of children's welfare, according to which a child fares well when she possesses sufficiently high degrees of the seven substantive goods of childhood: health, biological needs, intellectually engaging activity, meaningful relationships, unstructured, imaginative play, bodily integrity, and happiness.

Identifying the morally relevant criterion justifying unequal treatment of children in research as undue burden helps to ensure that when a child's socioeconomic status, geographic location or disease prevent her from achieving a sufficiently high degree of well-being, these circumstances cannot be used to legitimize her exposure to higher degrees of non-therapeutic research risks than children who are more fortunate. It also helps to ensure that children who are not heavily burdened by mild illnesses—like some cases of asthma—do not receive unnecessary protections when participating in research. I conclude that the referent for minimal risk should be interpreted as children who are not unduly burdened by their daily lives, and that children who are not unduly burdened by

their daily lives are those who fare well, that is, children who possess sufficiently high degrees of the substantive goods of childhood. Finally, in chapter 5, I analyze a controversial trial involving children using my proposed interpretation, situated within component analysis, and argue that my conclusions are more persuasive than those of the competing interpretations of minimal risk.

6.1 The criteria of a successful account revisited

I have proposed that to be successful, an interpretation of minimal risk must meet four criteria. It must meet the requirements of practicality, generality, fidelity, and it must also limit risk to a defensible degree. Does my account meet these criteria?

My proposal provides guidance for research ethics boards about how to measure whether children possess sufficiently high degrees of the substantive goods of childhood. It directs their attention to the right kinds of questions to ask and the relevant goods to consider when assessing whether a child fares well enough to be the referent for minimal risk. Further, it is situated within component analysis' comprehensive framework for harm-benefit assessment. Consequently, it meets the requirement of practicality.

Further, measuring permissible risks according to the daily lives of children who fare well is a flexible threshold that varies according to the daily experiences of children of all ages. No matter what age a child is, her daily experiences are the morally relevant comparator for the risks of non-therapeutic procedures provided that she is not unduly burdened. Thus, my proposal meets the requirement of generality.

My proposal explains why minimal risk should be constrained to the risks of daily life; I argue that daily risks are morally justifiable because these kinds of risks are a reasonable trade-off between personal safety and the pursuit of a valuable life. They are the risks that reasonable people have good reasons to undertake. My proposal also explains whose daily life should be morally relevant. I argue that the referent for minimal risk should be children who are not unduly burdened by their daily lives, that is, children who fare well. These arguments provide the theoretical justification for a successful proposal. By explaining why daily experiences are relevant and whose daily experiences are relevant, this proposal meets the requirement that the degree of permissible risk must be limited to a defensible degree.

Finally, my proposal offers intuitively compelling results. It does not necessarily exclude children with mild diseases and disorders from facing comparable risks in non-therapeutic research procedures. But the flexible risk standard is subject to constraints. My proposal does not permit children to face non-therapeutic risks comparable to their daily experiences when their daily lives are unduly burdened. Thus, it helps protect children in unfortunate circumstances from being exploited in research. My argument offers a more moderate approach than identifying the referent as healthy children or a subgroup of children on the one hand or as the subjects of the research. On the other hand, it identifies a reference class of children who face morally relevant degrees of daily risk irrespective of whether they are healthy or not. And this lines up with the common moral intuition that some, but not all, children with diseases, disorders or conditions require additional protections in research. Consequently, it meets the requirement of fidelity. It follows that interpreting minimal risk according to the daily lives of children who are not unduly burdened meets the necessary criteria for a justifiable interpretation of minimal risk.

6.2 Further work

In chapters 4 and 5, I propose preliminary guidance about how my interpretation of minimal risk can be implemented in practice. The guidance suggests that faring well should be established by reference to children who are fairly well off. Further, it illustrates the kinds of literature an ethics committee should use to inform their determinations and identifies a relevant set of questions on which ethics review should focus. But it falls short of offering a set of comprehensive recommendations for research ethics review. Perhaps the most obvious extension of the work in this thesis is to connect these ideas with the kinds of empirical work that inform research ethics boards' deliberations. That is, a future project will undertake an empirical examination of how to measure whether a child fares well.

The goal of this project will be to develop comprehensive guidance about how to assess children's welfare. This kind of policy guidance will offer a clearer picture of the degree of the substantive goods of childhood possessed by a child who is fairly well off and more information about how research ethics boards should make their

determinations. Developing this guidance will help my proposal achieve its full potential of offering useful practical recommendations based on a sound ethical analysis. Further, it may help researchers and research ethics boards to arrive at determinations that will offer children justifiable protections when participating in research. Future work towards this goal will benefit from collaborations with epidemiologists, social scientists, policy writers, as well as research ethics board members.

Another future project will examine the success of competing systems for harm-benefit assessments in research with children. My analysis of minimal risk is situated within component analysis' framework for assessing harms and benefits. Component analysis originates in the work of the National Commission and is based on the idea that different kinds of research interventions should be subject to different moral rules. But this framework has strong competitors. Wendler's net risks test claims to offer a persuasive alternative (Wendler, 2006). The net risks test relies on the idea that research interventions that fail to offer participants a compensating potential for clinical benefit must not pose excessive risks (Wendler, 2006) and proposes to determine whether this threshold is met by comparing risk-benefit levels against available alternatives. Specifically, if the net risks are at least as favourable as the risk-benefit levels of available alternative, then a trial should be permissible (Wendler, 2006). The U.S. DHHS regulations propose still another approach to analyzing the permissibility of research with children. These guidelines are also based on the recommendations of the National Commission but arrive at somewhat different conclusion regarding children's participation in research than component analysis. Each of these frameworks relies on the concept of minimal risk, but they implement it in different ways and for different kinds of procedures.

I will evaluate the success of these systems for harm-benefit assessment for research involving children. To this end, I will examine the philosophical foundations of each framework and explore their determinations about trials involving children as subjects. This analysis will help to justify the framework within which my proposal for minimal risk should be situated. Further, it will contribute towards the development of a system for evaluating permissible degrees of risk in research with children that rests on a sound philosophical foundation and applies to research ethics review internationally.

To conclude, the work in this thesis contributes to the ethical justification for research with children. It recognizes that children's vulnerability gives rise to problems that complicate their participation as research subjects. Further, it recognizes that solutions to these problems rely on a number of different and complementary arguments—including arguments for social utility, proxy consent, the appropriate treatment of children in the family context, and the ethical assessment of harms and benefits. My aim has been to contribute to this literature by developing a justified interpretation of minimal risk, a central component of the ethical analysis of the harms and benefits of research. I have defended an account of why minimal risk should be interpreted in terms of daily life and proposed whose daily life should be morally relevant. My main goal has been to fill in a missing aspect of the philosophical justification for research with children but also to provide guidance that may help to refine and improve the system for ethical review of current and future research proposing to include children as research subjects.

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