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AGAINST HARMFUL RESEARCH ON NON-AGREEING CHILDREN

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ABSTRACT

The Code of Federal Regulations permits harmful research on children who have not agreed to participate, but I will argue that it should be no more permissive of harmful research on such children than of harmful research on adults who have not agreed to participate. Of course, the Code permits harmful research on adults. Such research is not morally problematic, however, because adults must agree to participate. And, of course, the Code also permits beneficial research on children without needing their explicit agreement. This sort of research is also not problematic, this time because paternalism towards children may be justifiable. The moral problem at the center of this paper arises from the combination of two potential properties of pediatric research, first that it might be harmful and second that its subjects might not agree to participate.

In Section 2 of this article I explain how the Code permits harmful research on non-agreeing children. Section 3 contains my argument that we should no more permit harmful research on non-agreeing children than on non-agreeing adults. In Section 4, I argue that my thesis does not presuppose that pediatric assent has the same moral force that adult consent does. In Section 5, I argue that the distinction between non-voluntary and involuntary research is irrelevant to my thesis. In Section 6, I rebut an objection based on the power of parental permission. In Section 7 I suggest how the Code of Federal Regulations might be changed.

1. INTRODUCTION

In this article, I will argue for two related theses. First, the Code of Federal Regulations Title 45 (Public Welfare), Part 46 (Protection of Human Subjects), hereafter referred to as *CFR 45.46*, permits harmful research on children who have not agreed to participate.[1] Second, CFR 45.46 should be no more permissive of harmful research on such children than of harmful research on adults who have not agreed to participate.

[1] Code of Federal Regulations. Title 45, Public Welfare, Department of Health and Human Services, National Institutes of Health, Office for Human Research Protections, Part 46 *Protection of Human Subjects*. Bethesda, MD. 2009. Available at: http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html [Accessed 30 Jun 2014]. Future citations to this document will merely give the relevant section of CFR 45.46.

Of course, CFR 45.46 permits harmful research on adults. Such research is not as morally problematic as the sort of research that is my focus, however, because adults must agree to participate. And, of course, CFR 45.46 also permits beneficial research on children without needing their explicit agreement. This sort of research is also not problematic, this time because paternalism towards children may be justifiable. In other words, the moral problem at the center of this article arises from the combination of two potential properties of pediatric research, first that it might be harmful and second that its subjects might not agree to participate. Take away either of those two properties, and the resulting research might still have a reasonable chance to be morally justifiable, but not if both properties remain. Or so I will argue, anyway.

In Section 2 of this article I explain how CFR 45.46 permits harmful research on non-agreeing children.

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Section 3 contains my argument that we should no more permit harmful research on non-agreeing children than on non-agreeing adults. In Section 4, I argue that my thesis does not presuppose that pediatric assent has the same moral force that adult consent does. In Section 5, I argue that the distinction between non-voluntary and involuntary research is irrelevant to my question. In Section 6, I rebut an objection based on the power of parental permission. Section 7 is the conclusion, where I suggest how CFR 45.46 might be changed.

2. CFR 45.46

My use of 'non-agreeing' can be explained by discussing the distinction between consent and assent. CFR 45.46 uses 'consent' to refer to an adult's agreement to participate in research, but, following earlier precedent in the bioethics literature, it uses 'assent' to describe a child's agreement to participate in research.[2] The difference in terminology is supposed to signal that an adult's consent typically has more moral force than a child's assent does, presumably because adults are more capable of autonomous decisions than children are. Of course, just as both children and adults can agree to participate in research, so also might they both (1) merely not agree, (2) positively disagree, or (3) be incapable of agreement, for example because they are comatose. I will use the word '*non-agreeing*' to cover all three of these cases where agreement is lacking, and I will use the word for both adults and children.

I first show that CFR 45.46 allows harmful research on non-agreeing children. The relevant clause of CFR 45.46 occurs in §408a:

> If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of research, the assent of the children is not a necessary condition for proceeding with the research.

This passage provides for two avenues by which a researcher might justify harmful research on children without their agreement. The first avenue is insufficient capacity for consultation. Presumably this covers newborn infants, the severely mentally disabled, and the comatose, among others. CFR 45.46 straightforwardly removes the assent requirement for harmful research on this group of children.

The second avenue – prospect of direct benefit – requires more discussion. Now, one might think that research justified via this second avenue is not really harmful. The problem, though, is that the prospect of direct benefit is not the same as net benefit.[3] Research is net beneficial when all of its harms and benefits taken together are beneficial overall, in the same sense that losing \$3 and gaining \$7 is still a net monetary gain. Clearly, what we should care about in research is whether it is net beneficial or net harmful, not whether it has isolated elements that are beneficial or harmful.

A prospect of direct benefit, however, is merely the chance of some (direct) benefit, ignoring rather than accounting for potential harms. Analogously, losing \$3 for the uncertain prospect of gaining \$7 is not necessarily a net gain. And returning to research, a study with a small chance of a small direct benefit, while incurring a large and certain harm, would satisfy the 'prospect of direct benefit' criterion as articulated in §408a.

Now, one might respond that we often do not know whether the proposed study will be, on net, beneficial or harmful until we carry it out; after all, finding out whether the experimental therapy is beneficial is often the point of the study. The problem with this response, though, is that we can and should estimate the *expected value* of engaging in the proposed study, where the expected value of an act is the sum of the value of each of its possible outcomes, as weighted by that outcome's chance of occurrence. My proposal, more explicitly, is that CFR 45.46 permits studies on non-agreeing children where the *net expected value* of participation is lower than that of non-participation.

Still, what I have just said is compatible with it being in a child's (or an adult's, for that matter) overall interest to participate in a study with a prospect of direct benefit, even if the said participation is certain to incur significant harms. For example, suppose a study tests the efficacy of a new drug for an otherwise incurable cancer, where there is some chance that the new drug might cure the cancer, although only after several months of grueling pain, nausea, and vomiting while being treated. If the only way to get access to this drug is by participating in the study, such participation might be rational even if the drug is known to cause much more harm via its side effects than the current standard of care does. If so, however, such cases would not count as harmful in the sense relevant to this article, of *net expected* harm. In net expected harmful research, the total expected harm outweighs the total expected benefit. While the harms in the hypothetical study are certain to occur, the expected benefit of a complete cure might still outweigh those

[2] CFR 45.46 §402b. For the precedent, see Committee on Bioethics. Informed Consent, Parental Permission, and Assent in Pediatric Practice. *Pediatrics* 1995; 95: 314–317.

[3] There is another problem, which I will not explore: indirect benefits (such as payment) should be counted too. See A. Wertheimer. Is Payment a Benefit? *Bioethics* 2013; 27: 105–116.

harms, even when weighted by a low probability of achieving that cure.

Of course, a child may not be able to reason correctly about such complex matters, and so a child may disagree to participating in the study, even though participating is in her best interest. The important point, though, is that such a case cannot be described as a child refusing to participate in *net expected harmful* research. Rather, it is a case where a child does not want what she unjustifiably thinks is going to be harmful, when in fact the study is on net expected to benefit. Forcing the child to participate in such cases may be justifiable on paternalistic grounds, but if so then such cases are for this very reason not my topic.

There is a further objection to the second avenue by which I claim that CFR 45.46 licenses harmful research on non-agreeing children. This objection reminds us that CFR 45.46 already partitions each permissible pediatric study into exactly one of four categories, which I paraphrase slightly:

(1) research not involving greater than minimal risk (§404)
(2) research involving greater than minimal risk but with prospect of direct benefit (§405)
(3) research involving greater than minimal risk, no prospect of direct benefit, but likely to yield knowledge about the subject's disorder or condition (§406), and
(4) research that is not otherwise approvable via (1) through (3) (§407).

The objection then points out that the second avenue for licensing harmful research on non-agreeing children requires the prospect of direct benefit, and any research with the prospect of direct benefit must fall into categories (1) or (2) above. For category (1), the prospect of direct benefit is coupled with at most minimal risk, so it is arguably net beneficial, or at any rate close enough. In category (2), CFR 45.46 states two further restrictions: that the risk must be justified by the anticipated benefits, and that the relation between risk and anticipated benefit must be at least as favorable to the subjects as that presented by alternative approaches.[4] These two further restrictions also ensure that the resulting research will be beneficial to its subjects, and indeed they ensure that the research cannot be any less beneficial than the next best alternative (clinical care, typically) would be.

The problem is that not all research with the prospect of direct benefit must fall into categories 1 or 2. In particular, research that involves greater than minimal risk, with a prospect of direct benefit, but where that risk is *not* justified by the anticipated benefit, would instead fall into category 4, the grab-bag of all research that is not otherwise approvable. In other words, CFR 45.46 can allow an IRB to approve a study with the following profile:

- Its subjects are children.
- It has the prospect of direct benefit.
- It is net harmful.
- The children are capable of assenting, but the children do not assent.

Of course, a conscientious IRB should deny permission to conduct such a study, but the point is that CFR 45.46 does not explicitly say that IRBs *must* do so, as I will argue that it should. Similarly, we cannot appeal to the nebulous clause §407b2ii ('the research will be conducted in accordance with sound ethical principles') as presupposing or entailing that category 4 research with an unfavorable risk-benefit ratio must be deemed off limits.

I have just argued that CFR 45.46 permits harmful research on non-agreeing children. You might think that this is the result of unanticipated loopholes in CFR 45.46's language. I doubt it, though. After all, the structure of CFR 45.46 allows for pediatric research without assent in each of the four categories I mentioned above. If CFR 45.46 really had intended to restrict research on non-agreeing children to research with trivial harms (category 1) and research that is net beneficial (category 2), they could easily have moved the language granting an exception to the demand for assent to those two sections, eliminating the possibility of exceptions in the last two, more controversial categories. Instead, the clause granting an exception to the assent requirement (§408a) is explicitly written into the regulations four times, once for each of the four categories of research I listed above.[5]

3. THE ARGUMENT

Before I present my argument, I discuss two caveats. First, harmful research on non-agreeing children is sometimes justifiable. Societal benefits can outweigh the wrong of forcing children to participate in harmful research, especially in cases where the benefits are extremely large and the harms extremely small, and it is important to emphasize that harmful research on non-agreeing children is sometimes morally appropriate. However, this concession is also true of adult subjects, and my thesis is essentially comparative. I will argue that we should be no *more* willing to allow harmful research on non-agreeing children than we are willing to allow research that is equally harmful to non-agreeing adults. Thus, for example, we should be no more willing to conduct harmful research on children who lack the capability to agree, perhaps because they are mentally disabled or temporarily unconscious, than we are to do the same to

[4] CFR 45.46 §405a and §405b, respectively.

[5] CFR 45.46 §404 for category 1, §405c for category 2, §406f for category 3, and §407b2iii for category 4.

adults in the same conditions. And the mere prospect of direct benefit, when uncoupled from a favorable risk-benefit ratio, is just as irrelevant for the ethics of research on non-agreeing children as it is for the ethics of research on non-agreeing adults.

It is also worth pointing out that even the absolutist proposal that we may *never* conduct harmful research on non-agreeing children will not result in nearly as significant a loss of research as, say, the ban on harmful research on *all* children, agreeing or otherwise. Similarly, it would of course be a devastating blow to research if we were to ban all harmful research on adults, but we might think that the loss to research that results from restricting harmful research only to *consenting* adults is an acceptable price to pay in order to obey the dictates of morality. We might likewise think that the loss to research that results from restricting harmful pediatric research only to assenting children is an acceptable price to pay in order to benefit the dictates of morality.

The second caveat is that I want to focus on children who are at least a few years old, say three. I do this to avoid two irrelevant controversies. First, perhaps children who are very young cannot even assent. This is controversial because maybe a toddler's cry when she is picked up by a stranger, as contrasted with her smile when she is picked up by her mother, is evidence that she agrees to her mother picking her up but not to the stranger doing the same thing. I do not want to engage in this controversy, so I will focus on children who are at least old enough to verbalize their desires. The second controversy I want to avoid is the morality of infanticide. Some philosophers argue, albeit controversially, that a newborn has fewer and less significant interests than an older child does, to the point where infanticide can sometimes be permissible.[6] I want to avoid this controversy as well, so I will confine my discussion to children who, unlike newborns, clearly have strong interests, including interests stemming from self-awareness.

My argument is straightforward. Abstracting away from research for a moment, it is in general no more acceptable to harm non-agreeing children in order to benefit others than to harm non-agreeing adults for the same benefit. If anything, children should be protected from forced harm even if adults must be subject to it, though my argument will not depend on this stronger claim. Thus, for example, suppose that in a certain risky situation child soldiers would be as effective as adult soldiers, perhaps because they can be trained just as easily to follow orders and shoot their guns. To ensure that everything else is equal, let us also assume that child soldiers are no more effective than adult soldiers in this situation. Now, we might have good moral reasons to conscript adults to fight in this situation, because their forced sacrifice is for the greater good, but we have no additional moral reasons in favor of conscripting children in this situation. In fact, if anything, we have independent moral reasons against conscripting children – perhaps because children have not yet lived as full lives as adults have – even though we would be requiring children to make the same sacrifice for the same greater good.

Likewise, consider the classic trolley problem in which a runaway trolley is hurtling down a track, where it will surely kill five people, unless a bystander flips a lever that switches the trolley down an alternate track, where it would strike and kill a single different person. Even if it is permissible to flip the lever so that only one person is killed, and even if flipping the switch is permissible when the lone person on the alternate track is a child, all else equal there is no additional moral reason in favor of flipping the switch if the lone person on the alternate track is a child rather than an adult. If anything, there are additional reasons against flipping if the sacrificial victim is still a child, as opposed to an adult, again perhaps because children have not lived as full lives as adults have.[7]

Now, I have suggested that, in general, it is no more acceptable to harm a non-agreeing child than an non-agreeing adult, even if that harm benefits others. That general claim is still true even if the harms and benefits in question are caused by research. For example, suppose that the military might conscript 100 child soldiers to fight in a battle to save a town of 100,000 people. The children will face a mortality risk of magnitude M, and their conscription increases the chance that the town will be saved by amount C. Presumably, such conscription is immoral for a wide range of $<M, C>$ pairs, though admittedly not for all such pairs. Now consider a research study forcibly conducted on 100 children, in order to help save 100,000 lives. Perhaps the children have leukemia, and the research might help cure that disease for a subset of patients. The children will face the same mortality risk M, and their participation in research increases the chance that the 100,000 lives will be saved by the same amount C. All else is equal, for any $<M, C>$ pair, a research protocol with that risk-benefit profile is no more justifiable than military conscription with the same profile.

[6] See, for example, P. Singer. *Practical Ethics*, 3rd edition. New York, NY: Cambridge University Press; 2011. ch 7; and M. Tooley. Abortion and Infanticide. *Philos Public Aff* 1972; 2: 37–65.

[7] According to some ethical theories, the death of a young child is not as bad as the death of a young adult. See, for example, J. McMahan. *The Ethics of Killing: Problems at the Margins of Life*. New York, NY: Oxford University Press; 2002. chapter 2, section 6. If so, then it is all else equal better to conscript child soldiers than adult ones, and better to turn trolleys onto children than onto adults. This view is controversial. See, for example, B. Bradley. *Well-Being and Death*. New York, NY: Oxford University Press; 2009. chapter 4. In any case, McMahan's view is inconsistent with CFR 45.46's general stance that children constitute a vulnerable population that deserves *more* protection than usual, rather than an easily exploitable one that deserves *less* protection than usual.

Table 1. Twelve Cases of Research

Case	*Subject*	*Study*	*Response*	*Moral Requirement to Respect Response?*
1	HEALTHY	BENEFICIAL	agree	yes
2	HEALTHY	BENEFICIAL	disagree	yes
3	HEALTHY	HARMFUL	agree	yes
4	HEALTHY	HARMFUL	disagree	yes
5	INCOMPETENT	BENEFICIAL	agree	no
6	INCOMPETENT	BENEFICIAL	disagree	no
7	INCOMPETENT	HARMFUL	agree	no
8	INCOMPETENT	HARMFUL	disagree	yes
9	CHILD	BENEFICIAL	agree	no
10	CHILD	BENEFICIAL	disagree	no
11	CHILD	HARMFUL	agree	no
12	CHILD	HARMFUL	disagree	yes

In other words, research is not special. As with any other intervention we might conduct on children, research comes with associated harms, and it comes with potential benefits. That these harms and benefits derive from research as opposed to some other enterprise has no moral significance. This is true even if the benefits to others are accrued by other children, and even if they are accrued by other children with the same disease as the harmed pediatric subject.[8] Of course, both children and adults might be more willing to agree to participate in harmful research if its beneficiaries are in the same social group as they are.[9] But that fact is merely contingent; some people might be more willing to agree to sacrifice for beneficiaries from different social groups, and the key issue is what to do when the particular subject in question does *not* agree to participate. Retreating to the fact that most other people would agree to participate if the benefit went to members of the same social group is a rationalization if the particular subject does not agree.

Of course, other factors are morally significant in assessing whether a particular study is ethical. One such factor, which I have already discussed, is the relationship between harm to subjects and benefit to society. Another such factor is whether the results of the research might be obtained without harming non-agreeing children. If we desperately need the results of some study, and the only way to get those results is by conscripting children, then recruiting adults, whether agreeable or not, is pointless.

A useful analogy here is to quarantine. If some children have a severe and easily communicable illness, but no adults do, then it is surely morally appropriate to quarantine the sick children rather than any healthy adults. However, children are not special here; the analogous claim about research on adults is also true, just as quarantine should focus on adults instead of children if only the adults are sick. Also, CFR 45.46 could easily include this proviso in its regulations on pediatric research, but it does not. We know that CFR 45.46 could easily include this proviso because it does include the proviso elsewhere, for example in regulating research on neonates.[10]

4. CONTRASTS

My argument does not assume that the moral force of a child's assent is the same as or even similar to that of an adult's consent. My argument can avoid evaluating the moral force of assent because it instead relies on the claim that the *absence* of agreement, whether assent or consent, to a *harmful* intervention carries the same moral force regardless of whether the agent in question is an adult or a child. Both the italicized words are crucial to the claim. Let me contrast several examples to make this clear.

Consider three different possible subjects: HEALTHY is a healthy, autonomous adult; INCOMPETENT is an adult with severe mental deficits; and CHILD is a healthy but non-autonomous five year old. Consider also two studies: BENEFICIAL is net beneficial, and HARMFUL is net harmful. Each subject can take (exactly) one of two responses to a given study: she may agree to participate, or she may disagree to participate. Thus, there are twelve possible permutations, and we can consider the moral force of the subject's response in each case, as in Table 1.

The first four, HEALTHY cases in the table are the easiest: unless something else unusual is going on (e.g.

[8] See A. Iltis. Justice, Fairness, and Membership of a Class: Conceptual Confusions and Moral Puzzles in the Regulation of Human Subjects Research. *J Law Med Ethics* 2011; 39: 488–501; E. Chwang. Shared Vulnerabilities in Research. *Am J Bioeth*, forthcoming.

[9] This idea is suggested by some of Richard McCormick's writing in the 1970s on pediatric experimentation, in particular his idea that children would agree to participate because they ought to agree in cases where they share a social connection with the beneficiaries. See, for example, R. McCormick. Experimentation in Children: Sharing in Sociality. *Hastings Cent Rep* 1976; 6: 41–46.

[10] CFR 45.46 §46.205b1ii states a necessary condition for permissible research on neonates of uncertain viability: 'The purpose of the research is the development of important biomedical knowledge *which cannot be obtained by other means* . . .' (My emphasis.)

inadequate information), a healthy, autonomous adult's decision must be respected. Of course, what it means to respect agreement differs from what it means to respect disagreement: respecting disagreement means that researchers must not enroll the subject, but respecting agreement (i.e. consent) means that researchers *may* enroll the subject, not that they *must*.

The four INCOMPETENT cases are more interesting. A mentally incompetent adult's consent may be morally invalid, so it need not be respected. Thus, in case 5 (an incompetent adult's consent to beneficial research), there could be beneficial studies where researchers are not morally permitted to enroll an incompetent adult, even if he consented. Maybe the risk of harm is too great or too poorly understood, for example, even if the study is expected to be on net beneficial.[11] Similar remarks apply with even greater force to case 7, an incompetent adult's consent to harmful research. It is worth pausing to consider case 6, an incompetent adult's refusal to participate in beneficial research. Here there may still be no moral requirement to respect the subject's refusal, because paternalism may be appropriate. In other words, even if an incompetent adult refuses to participate in beneficial research, we might decide on his behalf that he should participate anyway. Case 8 is interesting, but it should also be uncontroversial. If an incompetent adult refuses to participate in harmful research, we typically may not conduct it on him. He may be unable to comprehend the details of the study, but if the study is harmful then he will not benefit by being forced into it, in which case we cannot use paternalistic reasoning to justify his coerced enrollment. We might, of course, use consequentialist reasoning, saying that we desperately need the knowledge that could be gained from the research, so that societal benefit outweighs harm to the incompetent adult, but of course the same is true for case 4, where the dissent is that of a competent adult.

Now, finally, consider the four CHILD cases. Notice first that the presence or absence of a moral requirement to respect their four possible responses follows exactly that for INCOMPETENT: 'no' to the first three, 'yes' to the last. This is just as we should expect, because CHILD and INCOMPETENT share the same morally relevant property, namely a deficit in competent decision-making. Thus, a child's assent is not worth very much at all, as cases 9 and 11 illustrate: a child's assent to participate in research does not automatically license researchers to enroll that child, even if the study is on net beneficial (case 9). Maybe the risk of harm is too great or too poorly understood, for example, even if the study is expected to be on net beneficial. Similar remarks apply with even greater force to case 11, a child's assent to harmful research. It is worth pausing to consider case 10, a child's refusal to participate in beneficial research. Here there may still be no moral requirement to respect the subject's refusal, because paternalism may be appropriate. In other words, even if a child refuses to participate in beneficial research, we might decide on his behalf that he should participate anyway.

Case 12 (harmful research on a child who refuses to participate) is, of course, the central focus of this article. In general, a child's agreement or disagreement does not carry a lot of moral weight, agreement because children are not autonomous (cases 9 and 11), disagreement because paternalism may be appropriate (case 10). However, when paternalism is inappropriate, i.e. for harmful research, disagreement should have moral force, even if that disagreement is not autonomous (case 12). The reason for this is the argument I have given in section 3, and it does not presuppose, controversially, that pediatric assent (cases 9 and 11) has any moral force.[12] Note that, as with case 8 and case 4, the child's dissent may be outweighed by concerns of societal benefit; if we desperately need the knowledge to be gained from the harmful study, then it might be justifiable to conduct it in spite of the dissent of its subject. But, again, this is no more true for children than it is for adults, whether competent or incompetent.

5. NON-VOLUNTARY VERSUS INVOLUNTARY

Borrowing some terms from the euthanasia literature, I will say that research on a child who lacks the capacity to agree (for example because she is comatose or severely mentally disabled) is *non-voluntary*, whereas research on a child who has the capacity to agree but either disagrees or is never asked is *involuntary*. I have so far not distinguished between these two ways of failing to obtain

[11] In fact, the vast majority of potential new drugs never get to market, suggesting that many studies end up being harmful even if they intend to be beneficial. Further, even if subject benefit from a study is foreseen, it is rarely intended: studies are designed to gain knowledge, not to substitute for patient care. Thus, real world studies in the BENEFICIAL category may be rare: what we hoped would be a BENEFICIAL case will usually be a HARMFUL one instead.

[12] As evidence that my view about case 12 should be uncontroversial, compare my view with that of the Committee on Bioethics, *op. cit.* note 2, p. 316: 'There are clinical situations in which a persistent refusal to assent (ie, dissent) may be ethically binding. This seems most obvious in the context of research (particularly that which has no potential to directly benefit the patient).' Compare also with S. Leikin. Minor's Assent, Consent, or Dissent to Medical Research. *IRB* 1993; 15: 1–7, p. 6: 'Dissent [of a minor] from participation . . . is always to be honored unless the protocol affords access to a therapeutic intervention that is not otherwise available.' Note how my view is in fact more moderate than those expressed in the above quotes. I admit that dissented-to harmful pediatric research may sometimes be justifiable on grounds of societal benefit, though I insist that this is as true for adults as it is for children.

assent, and the distinction may matter. For example, non-voluntary research on a comatose child may seem less morally problematic than involuntary research on a conscious child who explicitly said she does not want to participate.

Indeed, CFR 45.46's differential treatment of its two avenues for allowing for harmful pediatric research, as articulated in §408a, reflects this view. Recall that the first avenue of justification is the lack of capacity to be consulted, and the second avenue of justification is the prospect of direct benefit. Given the terminology introduced in this sub-section, another way of stating these two avenues of justification is that *involuntary* pediatric research must meet an additional ethical criterion (namely, the prospect of direct benefit) that *non-voluntary* pediatric research need not meet. The issue is complex, but even if there is often a moral difference between non-voluntary and involuntary research, there is *no* moral difference between non-voluntary and involuntary *harmful pediatric* research. Thus, there is no need to distinguish carefully between the two for the purposes of this article, and the same ethical criteria should apply to both kinds of harmful pediatric research.

Let me again consider the adult case first, as the contrast to the pediatric case will be instructive. I grant that, when the research is expected to *benefit* its subject, non-voluntary research on adults can be more morally palatable than involuntary research on adults is. What often justifies non-voluntary research is a *best interest* standard: when the subject cannot make decisions on her own, we decide on her behalf, trying to satisfy her interests, as best we can. Of course, best interest standards are otiose when the potential subject can make her own decision; therefore, involuntary beneficial research is still not justified.

What if the research is expected to be harmful overall? In that case, there is a further situation where non-voluntary research on comatose adults is less morally objectionable than involuntary research on conscious adults is: if the subject would have wanted to participate, non-voluntary participation may still be justified. This time, the justification of non-voluntary research appeals to a *substituted judgment* standard: when the subject cannot make decisions on her own, we decide on her behalf, trying to decide as she would have decided, as best we can. Of course, substituted judgment standards are otiose when the potential subject can make her own decision; therefore, involuntary harmful research is still not justified.

How does all of this apply to children? In particular, can best interest and substituted judgment standards justify the moral superiority of non-voluntary harmful pediatric research over involuntary harmful pediatric research? No. First, best interest standards are irrelevant, because our focus is on harmful pediatric research. What about substituted judgment, then? The problem here is not that children have no judgments for which we can attempt to substitute; a young child might want very much to help others, even at significant cost to herself. The problem, rather, is that, for paternalistic reasons, the substituted judgment standard is inappropriate for children, as it is for mentally incompetent adults. Substituted judgment is inappropriate for children because they are not capable of making good decisions for themselves. Thus, even if a comatose child would have wanted to sacrifice her own welfare for the greater good, we should still refuse to enroll her in a study non-voluntarily. The reason we should refuse is that, even if she would have wanted to participate, her decision clearly does not further her own interests, and we cannot yet tell if her imprudent decision is a reflection of a budding altruistic personality or merely foolish.

It is also worth pointing out that, in asking whether harmful pediatric research is morally better for being non-voluntary instead of involuntary, we must hold all else fixed. In particular, we must consider studies that are equally harmful to the non-voluntary subject as to the involuntary subject. If a comatose subject cannot feel the pain of a lumbar puncture, for example, then a study whose only intervention is a single lumbar puncture will be less harmful to a comatose subject than to a conscious one. More generally, people who lack the capacity to agree typically have fewer and less significant interests than do healthy people, and we must eliminate these differences. Thus, consider a study whose sole harm is physical pain, and consider a non-voluntary pediatric participant who is severely mentally disabled, but who is as sensitive to pain as his involuntary counterpart is. Clearly, we do not improve our moral situation by conducting this study non-voluntarily on the mentally disabled child instead of involuntarily on the otherwise healthy one.

Let me elaborate on the perversity of the idea that non-voluntary harmful pediatric research is morally superior to involuntary harmful pediatric research. If that idea were correct, then researchers should be delighted if their potential subject population suddenly all lapsed into temporary comas so that they can no longer refuse to participate (their research must be conducted in the next day, and the comas will last two days); that event should ease their moral conscience about their research, because they would then able to conduct non-voluntary rather than involuntary research. Likewise, researchers who are pessimistic about the odds for obtaining assent for their research should seek out a population of comatose children to use as subjects instead. In contrast, consider the distinction between involuntary and *voluntary* research. If, suddenly, a potential subject changed her mind and decided that she agrees to participate, then researchers should be delighted; that event should ease their moral conscience about their

research, because they would then be able to conduct voluntary rather than involuntary research.

6. PARENTAL PERMISSION

There is, I think, one last card to play for the defender of harmful research on non-agreeing children: permission from parents (or legal guardians). This strategy may seem especially promising, because it offers a way to differentiate pediatric research from adult research. However, the main problem with using parental permission to justify harmful research on non-agreeing children is that parents are supposed to look out for their children's interests, just as a guardian is supposed to look out for her incompetent adult ward's interests. That is, after all, the main reason we give parents discretion over how to treat their children: parents have a fiduciary obligation to promote their children's welfare. Thus, in clinical care, parental permission often trumps the child's wishes, because the child often simply does not know what is or is not in her interests, and similar things can be said on behalf of beneficial research: parental permission can trump a child's decision when the child does not know what is in her interests. Unfortunately, this trump card does not apply to harmful research.

Of course, we sometimes give parents discretion over how to treat their children even in cases where those parents do things that positively harm the children. For example, parents are allowed to move the family across the country, even if doing so severs some of their child's relationships and so harms her. Perhaps more relevantly for our discussion, it might be reasonable for parents to force their children to do yard work for the neighbors, perhaps as a means of instilling moral character. Likewise, maybe parents should be allowed to force their children to participate in harmful research, perhaps as another means of instilling moral character.

However, there are a couple of problems with this 'parents have wide discretion' rejoinder. First, we should allow the guardian of an incompetent adult to move across the country, even if doing so harms the ward. And, to the extent that an incompetent adult can learn moral character, her guardian should be allowed to force her to do yard work for her neighbor. In other words, we still have not found a rationale for forced and harmful pediatric research that does not also apply to forced and harmful adult research. Of course, wide discretion would not apply to *competent* adults. For example, it is inappropriate for the parents of a competent adult to force that adult to move across the country, and it is inappropriate for the parents of a competent adult to force that adult to mow the neighbor's lawn. But the point of comparison between adults and children must hold all else fixed, including competence. My goal is to show that age is irrelevant to the moral question of harm without agreement, not that competence is irrelevant.

Second, and more importantly, the appeal to wide parental discretion – appeal, that is, to parental discretion even to harm their children – is inconsistent with the spirit of CFR 45.46 and so proves too much. Recall that CFR 45.46 allows two avenues by which harmful pediatric research can be approved without the assent of its subjects: (a) cases where the subject lacks the capacity to assent, and (b) cases where there is the prospect of direct benefit. The problem is that even if parents have wide parental discretion, surely such discretion is not limited to cases where the child in question lacks the capacity to assent or where the child in question stands to gain something (direct) from the harm. Indeed, CFR 45.46's restrictions are positively inimical to instilling moral character (a dubious motivation for enforced research participation, but never mind). After all, the comatose and the profoundly mentally disabled cannot learn from their research experience, and the prospect of direct benefit may blunt the force of the lesson that it is morally good to sacrifice for the sake of others, as when parents pay their children to engage in community service.

More plausible rationales for CFR 45.46's two avenues for licensing research on non-agreeing children are that, in favor of the first avenue, we should grant exceptions to the assent requirement when that requirement is impossible to fulfill, and, in favor of the second avenue, we should grant exceptions when there is a real chance for gain. My criticism – that we should not allow research on non-agreeing children if it is *harmful* – is consistent with these rationales, whereas the proposal that we should allow parents wide discretion to harm their children is not.

7. CONCLUSION

I have at several places tiptoed around the question of when exactly it is permissible to conduct harmful research without the agreement of its subjects, whether pediatric or adult. However, the bar currently set for children is surely too low, even if the bar currently set for adults is also too high. One reasonable start at raising the bar for children is to require that research on non-agreeing children has a favorable risk-benefit ratio.[13] One could ensure this by amending §408a as follows, where the italicized portion of the text is my suggested amendment:

[13] Although see A. Rajczi. Making Risk-Benefit Assessments of Medical Research Protocols. *J Law Med Ethics* 2004; 32: 338–348 for a skeptical argument to the contrary. Rajczi's alternative principle is counterfactual, asking whether competent and informed decision-makers would enroll rather than whether benefits outweigh risks. This proposal would be easy enough to write into CFR 45.46 as well.

> . . . If the IRB determines that the capability of some or all of the children is so limited that they cannot reasonably be consulted or that the intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of research, *and if the risk is justified by the anticipated benefit to the subjects*, the assent of the children is not a necessary condition for proceeding with the research . . .

An even simpler proposal in the same spirit would replace both of CFR 45.46's original two avenues of justification with a third one, favorable risk-benefit ratio:

> . . . If the IRB determines that *the risk is justified by the anticipated benefit to the subjects*, the assent of the children is not a necessary condition for proceeding with the research . . .

In effect, my proposal is to add the content of §405a directly into §408a. Now, this clause may in fact go too far in the other direction, as it would eliminate the possibility of conducting harmful research on non-agreeing children, no matter how great the countervailing benefits to others.[14] However, this amendment would bring CFR 45.46's regulations governing pediatric research closer in line with its regulations regarding adult research, and it is superior to §408a as currently written.

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[14] However, my proposal would be consistent with the conclusion urged by the Committee on Bioethics, *op. cit*. note 2 and Leikin, *op. cit*. note 12.