Payment Is a Benefit and Why It Matters for Pediatric Trials

Abstract: Alan Wertheimer has argued persuasively that research ethics committees should be willing to count payment as a benefit when evaluating studies' risk-benefit ratios. In this paper, I begin by first recapitulating his argument and adding my own, complementary one. I then do two further things. First, I explain why the practical implications of these arguments for studies enrolling competent adults are less than fully clear. Second, I explain why the practical implication for trials enrolling children are clear and significant. I argue that we should be comfortable paying children to compensate them for undergoing research risks. I propose we do so by putting money into accounts that the child gains access to upon attaining majority.

Keywords: research ethics; risk/benefit analyses; children and families

1. Introduction

In a 2013 *Bioethics* paper, Wertheimer argued that payments to participants ought to be counted as a benefit during the course of risk-benefit analyses as carried out by research ethics committees (RECs); that is, adding payment to a proposed trial should be able to "cancel out" an equivalent quantity of its risks.[1] Those arguments are powerful, yet have been ignored. This is surprising, given that the view that payment should *not* be counted as a benefit is the standard view in the field; it is widely accepted and enshrined in current regulatory policy.[2] Given the apparent consensus the standard view commands, one might have expected it to receive prompt, vigorous defense.

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[1] Wertheimer, A. (2013). Is payment a benefit? *Bioethics* 27(2): 105-118.

[2] This claim is included in the classic synthesis presented in Emanuel, E. J., Wendler, D., & Grady, C. (2000). What makes clinical research ethical? *JAMA* 283(20): 2701-11. It is also the current guidance of the United States' Office of Human Research Protection. HHS. (2013). *OHRP revises its response to the question "when does compensating."* Retrieved from: https://www.hhs.gov/ohrp/news/announcements-and-news-releases/2013/ohrp-revises-its-response-to-the-question-when-does-compensating-subjects-undermine-informed-consent-or-parental-permission/index.html

It may be that Wertheimer's article has met with limited uptake because insofar as one focuses on trials enrolling competent adults, it's not clear that counting payment as a benefit has significant practical consequences. Perhaps partisans of the standard view have not felt the need to respond because they believe that regardless of the theoretical issues, the standard view is fully adequate to meeting RECs' practical needs in evaluating protocols.

But it is a mistake to focus only on studies enrolling competent adults. Consider instead pediatric research. It is common across jurisdictions to limit the degree to which the risks that participation in research imposes on children exceed the benefits they stand to gain—the "net risks"—to an extremely low level.[3] But if payment could be counted as cancelling risks, more could be done while remaining within that limit. Counting payment could thus enable socially valuable research, while still ensuring that children expect to appropriately benefit from their participation. This requires a mechanism for paying children; I propose putting money into accounts which become available to them upon attaining majority.[4]

My proposal may face difficulties in some jurisdictions, such as the United States, where there are additional requirements on pediatric research that are unrelated to its net risks. To the extent that such restrictions are incompatible with enrolling children in research with benefits which, in expectation, outweigh its risks, they should be modified. Properly taking account of

[3] In the US regulations, see 45 CFR 46 §404-407 and 21 CFR 50 §51-54. See also guidelines 4.8.13 and 4.8.14 of Dixon, J. (1998). The international conference on harmonization good clinical practice guideline. *Quality Assurance (San Diego, Calif.)* 6(2):65-74; as well as CIOMS' guideline 9. Council for International Organizations of Medical Science. (2002). *International Ethical Guidelines for Biomedical Research Involving Human Subjects.* Retrieved from: https://cioms.ch/shop/product/international-ethical-guidelines-for-biomedical-research-involving-human-subjects-2/. Because it is parallel to 45 CFR 46 in all relevant respects, I simplify discussion by omitting any further references to 21 CFR 50. For further discussion of the paths to approval available under 45 CFR 46 §404-407, see footnote 26.

[4] This choice of compensation mechanism explains why I focus on children and do not address other non-competent patient populations. I am open to the possibility of generalizing this account to adult patients who are temporarily incompetent, or never-competent patients who nonetheless benefit somehow from payments. But these possibilities, and especially the second, require specialized discussion that I will not undertake in this paper.

children's interests involves furnishing them with opportunities which are net beneficial in expectation, not denying opportunities which are net beneficial in expectation.[5]

2. Risk-Benefit Analyses and the Standard View

It is widely accepted that the risks research imposes on human subjects must be justified for the research to be ethical. RECs enforce this requirement. For instance, in the United States, Institutional Review Boards (IRBs) play this role, and are legally mandated with approving studies only when "[the r]isks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result."[6] But different national regulations, commonly cited documents, and prominent ethicists interpret the idea of an acceptable risk-benefit profile differently, and there are serious disagreements among them. Nonetheless, there are also points of broad agreement. Here I follow Rid and Wendler in their sensible synthesis, and I focus my summary on what is required for studies to have an overall acceptable risk-benefit profile.[7]

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[5] One anonymous reviewer objected that even if children benefit, it is possible to benefit while being problematically exploited. I respond: I accept Wertheimer's analysis of exploitation, and hence acknowledge that mutually beneficial exploitation is possible. Specifically, this occurs when two parties are both benefited by a transaction, but one captures an unfairly large portion of the gains. Arguably, participants in medical research are frequently exploited, insofar as they gain, but do not gain nearly as much as the companies which use the research to develop lucrative medical products. If this division is unfair, the research is exploitative. But even so, it would not follow that it is all-things-considered morally wrongful, and it especially would not follow that the appropriate remedy would be forbidding the research. It would be much better to instead continue conducting research while more fairly sharing the gains, e.g. by either paying participants *much more* than they currently are or by reducing the profits associated with drug development. Wertheimer, A. (1999). *Exploitation.* Princeton: Princeton University Press.

[6] 45 CFR 46 §111(a)(2)

[7] Rid, A. & Wendler, D. (2011). A framework for risk-benefit evaluations in biomedical research. *Kennedy Institute of Ethics Journal* 21(2): 141-79. Note that, in addition to requiring an *overall* acceptable risk-benefit profile, it is standard to also require that each individual intervention, or packages of related interventions, included in a study also satisfy appropriate constraints on their risks and benefits. I raise and then respond to an objection based on this feature of standard approaches at the end of section 6.

First, an REC must determine whether the benefits of participation outweigh the risks for participants. The most influential approach to making this determination involves comparing the direct benefits associated with receiving the intervention under study against the full risks of participation.[8] In singling out so-called "direct benefits," this process ignores any indirect or "inclusion benefits," benefits which are associated with participation but independent of the study intervention itself—such as free, high-quality ancillary care, the psychological benefits of altruism, and/or any payments received.

If the expected direct benefits of participation outweigh the total risks, then the protocol is *net benefit*. By contrast, if the risks outweigh the benefits, the protocol is *net risk.* If those net risks exceed an absolute upper threshold, which is unspecified for competent adults and specified and low for minors, then the study is not approvable regardless of other considerations. Otherwise, the REC should proceed to compare the sum of net risks to participants against the social value of the study. If the social value outweighs the risks, then the study has an acceptable overall risk-benefit profile. If the social value does not outweigh the risks, it doesn't, and cannot be approved.

The decision not to count inclusion benefits—and *a fortiori*, payments—as benefits capable of cancelling risks means that some studies that would be approvable instead are not. This is true even if researchers would like to offer them, and participants would like to enroll. What justifies the regulations in restricting researchers' and participants' ability to enter into such mutually agreeable arrangements?

[8] King, N. & Churchill L. (2008). Assessing and comparing potential benefits and risks of harm. In Emanuel E. J., Grady C., Crouch, R. A., Lie, R. K., Miller, F. G., and Wendler, D. *The Oxford handbook of clinical research ethics.* Oxford NY: Oxford University Press.

3. Risk-Benefit Analyses and Participant Interests

First, ask why should RECs be in the business of regulating research's risks and benefits *at all?* Wertheimer's answer is that regulating studies' risk-benefit profiles is an instance of justified paternalism.[9] He prefers a *soft* paternalist justification: medical research is technically complex, and subjects are likely to suffer misunderstandings. As a result, even the apparently voluntary consent may fail to appropriately reflect the participant's values.[10] Still, despite preferring a soft paternalist justification, he also recognizes the availability of *hard* paternalist rationales: perhaps some choices are simply too imprudent to allow.

Regardless, Wertheimer holds that *both* justifications involve RECs taking it upon themselves to promote subjects' good in one way or another—either by ensuring their choices are truly autonomous, or just by outright forbidding imprudent, harmful choices. But neither of these justifications can explain why RECs should ignore payment when assessing research benefits. Seeking payment can be an obvious justification for a fully autonomous choice, and payment can also be prudent to seek and beneficial to receive.

Take a study which would fail a standard risk-benefit assessment, but where counting payment as a benefit would leave it as net beneficial for participants. If an REC refuses to approve such a study, it denies potential participants the chance to realize what is by description

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[9] His discussion is focused on the United States and thus he asks about "IRBs." I use "REC" as a more general term for the same entity.

[10] For a fuller development of a soft paternalist understanding of the justification of research regulations, see Miller, F.G & Wertheimer, A. (2007). Facing Up to Paternalism in Research Ethics. *Hastings Center Report* 35(3): 24-34. See also my own argument for and application of a soft paternalistic understanding of risk limits in Steel, R. (2020). Reconceptualizing Risk-Benefit Analyses: The Case of HIV Cure Research. *Journal of Medical Ethics* 46(3): 212-219.

a beneficial opportunity. But *no* form of paternalism supports denying people access to beneficial opportunities.[11]

Importantly, the thought that payment is a benefit and should be counted as such is still compatible with maintaining that RECs must minimize the potential for undue inducement. Doing so with respect to study payments requires assessing whether specific monetary awards are so significant that they're likely to dazzle potential participants in ways that lead to distortions in their reasoning, for instance by causing them to focus exclusively on the prospect of payment and fail to notice important information about risks and burdens. This mandate to prevent undue inducement is simply orthogonal to whether payment is a benefit. After all, people can also be unduly induced by the prospect of *medical* benefit, e.g., by the hope for otherwise unobtainable improvement in their conditions. So there is no *special* issue here to justify the standard view's distinction between payment and other forms of benefit.[12]

4. The Objectivity of Assessment: Health vs. Money

Why would anyone think RECs *shouldn't* count inclusion benefits? King and Churchill have influentially argued that although inclusion benefits are indeed relevant to individuals' personal deliberations, REC review is both "logically" and "temporally" prior to enrollment

[11] Wertheimer explicitly says as much, though he also muddies the waters by relying on soft paternalism in his response to the "objective interests" objection. Wertheimer *op. cit.* note 1, p. 112.

[12] This is not to say that counting payment as a benefit won't alter any of the ways that RECs deliberate about undue inducement; for instance, as an anonymous referee helpfully pointed out, it would mean that they could no longer rely on Largent and Lynch's defense of payment, given that that defense takes as a crucial premise that payment is *not* counted as a benefit by RECs. The claim I make in the main text is not that RECs wouldn't need to change how they think, but that they have the ability to think in those new ways should they choose to. Largent, E. & Lynch, H.F. (2017). Paying Research Participants: The Outsized Influence of "Undue Influence." *IRB* 39(4): 1–9.

decisions. [13] REC review is conducted before enrollment opens, so they do not have access to individualized information about potential enrollees. Instead, they must understand the risks and benefits of the study in a way that will be objectively valid across the whole population that meets eligibility criteria. But inclusion benefits are idiosyncratic. For instance, some people experience the extra attention that comes with frequent study visits as a benefit, yet others may experience it as a burden. Although they allow that *some* inclusion benefits may indeed be universally valued, they claim their value-sensitivity generally marks them out from medical risks and benefits.

Whatever plausibility this argument has for marginal or particularly value-sensitive inclusion benefits, such as extra attention from study staff, it is significantly less plausible when applied to payment. Payment is generally valued. Granted, it is too simple to assume that payment is *only ever* desirable, as participants may sometimes prefer to act out of more pure intrinsic motivations. For instance, one study shows a small monetary incentive significantly suppressing blood donations.[14] But the evidence on the crowding out effects of payment mixed, even just in the case of blood donation.[15] With respect to research itself, participants do report payment as a motivation—particularly for healthy volunteers.[16]

Still, it might be argued that even if money is widely valued, the precise *amount* that any given individual values money is still too variable for RECs to meaningfully estimate. For his part, Wertheimer allows that trying to balance medical risks against financial benefits is difficult

[13] They in fact offer three arguments. I leave the other two—that counting incidental benefits could allow researchers to balance out gratuitous risks, or that it might induce bad differences between clinical care and research—as already adequately addressed by Wertheimer. Wertheimer, *op. cit.* note 1, King & Churchill, *op. cit.* note 8.
[14] Lacetera, N., & Macis, M. (2010). Do all material incentives for prosocial activities backfire? The response to cash and non-cash incentives for blood donations. *Journal of Economic Psychology* 31(4): 738-48.
[15] Chell, K., Davidson, T. E., Masser, B., & Jensen, K. (2018). A systematic review of incentives in blood donation. *Transfusion* 58(1): 242-54.
[16] Grady, C. (2005). Payment of clinical research subjects. *The Journal of Clinical Investigation* 115(7): 1681-87.

because they are different kinds of thing. But he responds that it is no harder than other tasks RECs must undertake anyway.[17]

In my view, that response is too concessive. It begins by conceding that medical-financial comparisons face a special difficulty that medical-medical comparisons don't. But it is worth asking: what is it even supposed to *mean* to compare two health risks? Is comparing the severity of two different health risks like comparing the length of two rods, or the weight of two blocks? Weights and distances are real, and their relative amounts are given by the world. But even if there is some underlying objective reality ranking the healthiness of different conditions of people *qua* human organisms, it's dubious that such a ranking is what we care about with respect to our health. For instance, dyslexia is the same objective condition regardless of whether one lives in a literate or illiterate society, yet the degree to which dyslexia matters to us as a problem worthy of attention is clearly not the same in either case.[18]

Rather, *the way that health matters to us* is most rigorously and systematically captured by summary measures of health-related quality of life. These measures map diverse health states onto a common scale, thereby enabling comparative assessments of "how bad" different conditions are (for instance, by scoring conditions according to "QALYs," or quality-adjusted life years).

But how does anyone decide exactly what quality level to assign a given condition? Current summary measures use surveys deploying preference elicitation tools, asking, for instance, what chance of death a respondent would be willing to assume in exchange for being

[17] i.e. comparing personal risks and benefits against social value, which are also comparisons of different kinds of thing, Wertheimer *op. cit.* note 1, pp. 112-113.
[18] Compare with Hausman's reconstruction of an argument due to Broome. Hausman, D. (2015). *Valuing heath: well-being, freedom, and suffering.* New York: Oxford University Press, 66-68.

cured of something. Under some further assumptions about people's values, direct queries of a tractable number of health states yield an implicit valuation of hundreds of thousands more.[19]

This methodology renders health risks commensurable with monetary ones in both an obvious way and a subtle way. The obvious way is that such measures are used in cost-effectiveness analysis to literally put a price on health: the point of quantifying health gains is to rationalize payments for health services. But the more subtle way is this: although the survey questions which inform summary health measures ask respondents *about* health states, what they actually *measure* is those respondents' preferences across those states. They could just as well ask about their preferences across other kinds of state. If they did, then they would in principle return equally valid results.

Concretely: a person's answer to questions like *what chance of death would you be willing to accept to cure a limp in one leg that moderately limits your mobility and causes minor chronic pain?* tells you something about how bad they think that condition is, relative to not having that condition. But, by the same token, so too does person's answer to questions like *what chance of death would you be willing to accept if doing so came with a million dollar check?* tells you something about how bad they think not having a million dollars is, relative to having a million dollars.

Granted, there are complications; the point of this section is not to defend the QALY framework generally, let alone in all its specific applications. Indeed, one can reject almost everything about the QALY framework as actually applied while still accepting the in-principle point being made here: that it makes conceptual sense to attempt to determine the value of health states by determining their value to the people who experience them. But an immediate

[19] The Health Utilities Index 3, for instance, generates values for 972,000 discrete health states, (ibid: Ch. 5).

consequence of this *aim* being sensible is that there is a straightforward way to compare health and money. Health and money can be compared against each other by comparing how much we value each.

Suppose, for the sake of argument, that I am correct on a theoretical level. But then what explains the widespread, contrary sense that making medical-medical comparisons is intrinsically easier than making medical-financial comparisons? I suspect that this is at least partially an artifact of standardly used examples. So, for instance, I do agree that trying to decide the *exact dollar amount* that a lumbar puncture is "worth" seems very difficult. But I claim that this is just because *any* highly exact value comparison is difficult, and the very same thing could be said of suitably parallel medical-medical comparisons. For example, consider a person who is considering enrolling in a phase 1 clinical trial of an experimental treatment for their terminal condition. The study drug involves minimal potential toxicities, and administration is easy. Nonetheless, they will have to undergo some lumbar punctures for research purposes, in order to measure whether the drug is entering their cerebrospinal fluid (as it is intended to do). At present there is some promising early data and some corresponding prospect of medical benefit, though that chance is both uncertain and low. Now ask: if we had to put a number on it, what *exact* chance of extending a patient's life by, say, a month or more would make the burdens associated with this treatment "worth it?" If King and Churchill's defense of the standard view were correct, then one would expect it to be hard to answer exactly how much money would successfully counterbalance a series of lumbar punctures, but easy to say exactly what percentage chance of increased survival would counterbalance them. But, to the contrary, a "correct" *exact percentage of increased survival* seems extremely difficult to come up with in just the same way that it is difficult to come up with a "correct" *exact dollar amount*.

Fortunately, RECs don't need a complete theory of how to trade off the various harms and benefits involved in research; consequently, they don't need to be able to state quantitatively exact thresholds wherein purely hypothetical sets of benefits and burdens would balance out. Instead, they only need to make the specific comparisons in front of them. Those comparisons need not be precise, and sometimes may be quite easy. So, for instance, when it comes to comparing health to health, it seems clear that a broken finger is, *ceteris paribus*, less bad than a broken arm is bad. That's an easy comparison. But, similarly, when it comes to comparing health to money, it seems clear that the discomfort of a blood draw is, *ceteris paribus*, less bad than $100 is good. That's also an easy comparison. So there's no reason an REC would need to struggle with *either* judgment. Of course, in either case, there might be some individuals in odd life situations for whom these assessments fail: the rich may have no need for $100; a hand model may care more about their finger than their arm. But RECs can reason ahead of time about how researchers should plan to take into account such possible edge cases, which, again, arise for *both* types of comparison.

The fact that RECs only need to be confident in the specific comparison in front of them deserves emphasis. Suppose I was wrong in my earlier arguments, and that medical-financial comparisons really are systematically harder than medical-medical comparisons. Even so, so long as an REC can confidently make *at least some* medical-financial comparisons, that's all they need to approve a study containing only those specific elements. And the idea that an REC could never be confident in *any* medical-financial comparisons is incredible. When it can do so confidently, it should be willing to.

5. Consequences for Adults

Suppose RECs were to consider money as a benefit in at least those cases where they are adequately confident in their judgments. What would the practical consequences be? In studies which enroll competent adults, that change *might* allow riskier research to be conducted. But it also might not. It depends on one's background views.

To illustrate, start by considering a study which would *fail* a standard risk-benefit assessment due to its unacceptably high risks.[20] First: how high is unacceptably high? For illustrative purposes, take Miller & Joffe's proposal that nontherapeutic, solid organ removal represents a level of individual net risk which is too high to permit in research. On that view, no matter the social value doing so might produce, it is never permissible to remove a kidney purely for research purposes.[21]

The qualification "purely for research purposes" is crucial. If, in addition to providing an opportunity to learn something important, removing the kidney also produced some clinical benefit, then that benefit would also need to be weighed against the risks. A large benefit might outweigh the risks entirely. In that case, it would be perverse to forbid the procedure as "too risky." It the *net* risks *after* benefits are subtracted that are relevant to determining when risks are too high.

But once we count payment as a benefit, then payment can function the same way. As a result, one might think that if payment is counted as a benefit then it follows that *any* level of

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[20] Recall that having unacceptably high net risks was *one* way a study could fail a risk-benefit assessment (sect. 2). It is not the only one, however, and payment might be relevant also in other cases. For instance, it might be thought that payment could justify the risks involved in studies with no social value. Payment also might be thought to be able to justify the risks of studies which involve some net risk, though not so much that it would have been too high in absolute terms, and also some social value, but where the amount of social value remained insufficient to justify the net risks. However, studies without social value are independently ethically controversial, and studies of the latter type are difficult to identify in practice. Hence the decision to focus in the main on unacceptably high net risks.

[21] Miller, F. G. & Joffe, S. (2009). Limits to research risks. *Journal of Medical Ethics* 35(7): 445-49.

risk, no matter how high, could theoretically be zeroed out by just adding more payment. In their seminal article synthesizing contemporary research ethics, Emanuel, Wendler, and Grady offer this potential consequence as the principal reason why payment should not be counted as a benefit—because, if it were, "simply increasing payment… could make the benefits outweigh even the riskiest research."[22] So permitting payment to count as a benefit may appear to open up a slippery slope, at the bottom of which lies various dystopian scenarios wherein desperate people agree to horrifying invasions of their body in exchange for the promise of large paydays.

How morally troubling is the possibility of paying people large amounts of money in exchange for undergoing very serious risks? As Wertheimer notes, treating this possibility as a *reductio* appears to beg the very question at issue:

> "One can't argue that X is wrong because it might lead to Y when it is not obvious that Y is wrong. And why shouldn't it be ethically permissible to ask people to assume greater risks by offering them what they reasonably regard as greater and sufficient benefits if they do so?"[23]

I am sympathetic to Wertheimer here. And work on a closely-connected topic—the ethics of organ sales—has convinced me that appropriate regulation can head off the dystopian consequences routinely brought up in this context: that the poor would come to be seen as disposable bodies, that unwilling people would be pressured into violating themselves, and so on. Rather, a carefully designed system could enable true win-win-win exchanges wherein some trade organs for money in sufficient quantities that they are made better off, others receive

[22] Emanuel, Wendler, & Grady, *op. cit*. note 2, p. 2705.
[23] Wertheimer, *op. cit.* note 1, p. 108.

organs and are made better off, and the health system saves enough on care that it too is made financially better off. [24] Given that the issues are essentially parallel, I am inclined to say these same things about large payments as compensation for participation in very risky research. So rather than finding the possibility of high-risk high-pay studies a *reductio* of the very idea of counting payment as a benefit, I find it to be an option worth exploring.

Nonetheless, this is a contentious topic with a large associated literature. It is beyond the scope of this paper to convince skeptical readers to accept the moral legitimacy of extremely high-pay high-risk research. Instead, I aim to use this section to give a more limited argument: I'll argue that it is at least possible for RECs to consistently acknowledge payment as a benefit *without* thereby being forced into authorizing the aforementioned extremely high-risk high-pay research.

To see why, return to the case of a research study that involves solid organ extraction, with no offsetting medical benefits. This is, under our earlier stipulation, too risky to approve. Now suppose that researchers hope to use payment to cancel some of its risks, thereby taking it from being unapprovable to being approvable.

The payment researchers offer could be large or small. If solid organ extraction is only barely above the threshold for maximum allowable individual risk, then perhaps only a small payment would be necessary to nudge it back under. But the precise location of the maximum allowable risk threshold is uncertain and I doubt that an REC would ever feel confident enough to make finely grained judgments in this regard. So, in practice it is implausible to imagine that

[24] I am convinced that having the state act as sole buyer of organs and having it set a high minimum price resolves most reasonable objections to organ sales. I suspect the same system could be adapted *mutatis mutandis* for the "purchase" of risky research participation. See Semrau, L. (2015). The best argument against kidney sales fails. *Journal of Medical Ethics* 41(6): 443-46; Semrau, L. (2017). Misplaced paternalism and other mistakes in the debate over kidney sales. *Bioethics* 31(3): 190-98; and Sterri, A.B. (2021). Why States Should Buy Kidneys. *Journal of Applied Philosophy.* Online, early view. https://doi/10.1111/japp.12523

small payments would make a crucial difference to an REC which was considering whether or not to approve a high-risk study.

By contrast, it is much more plausible to imagine a large payment making a crucial difference. But once we focus on large payments, there are two further difficulties we must confront. The first difficulty is that it is harder to make out when it is personally beneficial to trade off large sums against serious medical risks. It may be easy to say that $100 is more than enough to compensate for a blood draw, but difficult to say whether $50,000 is enough to compensate for a kidney. As before, the difficulty of making *some* medical-financial comparisons should not dissuade us from making *any*. But the issue here is that comparisons of large financial benefits against serious medical risks may systematically fall among those that RECs feel least confident in, and, worse yet, where the consequences of mistakes are most serious. RECs could acknowledge that payment is a benefit, yet still insist that they are not competent to validate *every* potential tradeoff between payments and medical risks. Specifically, they could reasonably judge themselves incompetent to validate large-payment large-risk tradeoffs.

The second difficulty is that large payments are more likely to have third-party effects. Recall that the basic argument we earlier borrowed from Wertheimer holds that insofar as limits on research risks are grounded in any kind of paternalism, they ought to be oriented toward the benefit of the subject, and insofar as they are oriented toward the benefit of the subject, they ought to count payment. But this is only applicable insofar as risk limits really are about protecting the subject. That may be true in most but not all cases. With large payments, it may be that other purposes become more salient, such as maintaining social trust in the research endeavor. Regardless of the underlying ethics, large payments for serious risk-taking may be

inherently prone to producing public scandals; the aftermath of the Jesse Gelsinger case shows how damaging scandals can be.[25] And we can also file the earlier gestured-at worries about how the availability of high-pay, high-risk research might change society under the category of potential third-party effects: e.g. if permitting such studies really would erode social solidarity and lead to the poor to be viewed as disposable bodies, then that is another risk that the research poses to third parties (we would all be such third parties, as we would all stand to be harmed by a transition to a more dystopian form of social life).

To summarize: RECs could acknowledge payment as being a benefit while still leaning on worries about the inherently difficult in making large-money large-risk comparisons, as well as the potential for serious third-party effects, to justify refusing to approve extremely risky research. So even if we take it for granted that high-pay high-risk studies are morally problematic and ought not be authorized, there is no need not resort to the implausible doctrine that payment is not a benefit to secure that result.

But isn't this at best a pyrrhic defense of the claim that payment is a benefit? It seems to defend the claim only by depriving it of the consequences that might have made it interesting and important. This reasonable worry. It is in some ways correct: the upshot of accepting payment as a benefit is unclear when it comes to research enrolling competent adults. But, importantly, that is not the only kind of research there is.

6. Consequences for Children

[25] Rinde, M. (2019). '*The Death of Jesse Gelsinger, 20 Years Later.'* Retrieved from https://www.sciencehistory.org/distillations/the-death-of-jesse-gelsinger-20-years-later.

What are the consequences of counting payment as a benefit when it comes to studies enrolling children? One possibility is that researchers could find a way of making large payments to children, and, by counting these payments as benefits, they could thereby justify trials with very high net medical risks. With respect to this possibility, the remarks of the previous section continue to hold *mutatis mutandis*. As a matter of pure principle, it is not obvious to me that compensating a child with a large amount of money in exchange for being subjected to serious medical risks is wrong. Nonetheless, the harm-benefit comparisons involved would be very difficult and there would be (controversial) risks of adverse third-party effects both to the institution hosting research and to its broader society; if anything, these points apply even more forcefully with children than they do with adults. Consequently, even once payment is counted as a benefit, RECs would still retain adequate grounds for refusing to authorize high-pay, high-risk studies on children.

The important *difference* between adult and pediatric research is that in research enrolling competent adults, low and moderate levels of net risk are already permissible, provided that those risks are both necessary to the study and that the study is expected to produce a large-enough social benefit. So, once high net risk studies are bracketed, there's no obvious work left over for payment to do in enabling research with low and moderate net risks; that research is already permitted. By contrast, studies in children generally do not allow for even low or moderate levels of net risk, not even when those risks are both necessary to the study and the study is expected to produce large social benefits. So, in the pediatric case there is still work left over for payment to do even once very high net risk studies are bracketed: payment could enable research imposing low and moderate net risks that would otherwise be unapprovable to proceed

while still ensuring that the child participants' interests are not only protected but actively advanced. Or, so I'll argue.

To begin, start with a review of the ethical and regulatory standards governing pediatric research. Across jurisdictions, regulations largely agree that only very low levels of net risk can be justified in research enrolling children. In the United States, studies enrolling children can be approved through several different regulatory clauses, but for our purposes it makes sense to focus on 45 CFR §46.406. Out of the clauses which are susceptible to routine use, this is the one that allows the highest level of net risk. It governs research with no prospect of direct benefit to its child subjects, and, hence, research where any risks imposed are also net risks (since no direct benefits exist to compensate for them). Of those risks, it specifies that to be approvable they must represent at most a minor increase over minimal risk.[26]

The choice of a very low net risk ceiling effectively requires that only personal benefits, and not broader social value, can play any role in justifying the imposition of more than minor risks on a child. This requirement is reasonable. Children cannot give full and voluntary informed consent for themselves. Since children cannot authorize tradeoffs between their interests and others, researchers cannot impose such tradeoffs on them either. Instead, researchers must only offer trials which are either net beneficial to individual participants or which, at worst, impose very low net risks.

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[26] There are four clauses in 45 CFR 46 through which pediatric research can be approved, codified in §404 through §407. §404 allows the approval of minimal risk research. §405 allows the approval of riskier research *but* where the risks of each intervention are fully compensated for by its the direct benefits. On a natural reading, this is another way of stating a zero net risk limit. §406, the clause I focus on in the main, allows for research with no prospect of direct benefit to be approved provided that its risks are no more than a minor increase over minimal (and provided it meets several further criteria which are orthogonal to the questions of acceptable risk raised in the main). Finally, §407 theoretically allows for research with even very high levels of net risk to be approved. However, it also requires that the Secretary of Health and Human Services convene an expert panel to judge that, *inter alia*, the study in question is for some reason ethically appropriate despite imposing serious uncompensated risks on children. This is, for obvious reasons, rarely used and is not designed for routine use. Hence, the highest level of net risk which can ordinarily be approved consistent with the US federal regulations is a minor increase over minimal risk, via §406, and that is why that is the standard I focus on in characterizing the status quo.

What counts as a "minor increase over minimal risk?" Minimal risks are defined as those which are no greater than the risks of daily life or routine physical and psychological examinations; the size of an acceptably "minor" increase over that minimal risk is not defined.[27] Neither standard is completely clear, but the operational consensus is one of caution.

Consider allergy skin testing. The World Allergy Organization reports the rate of systemic reaction to allergy skin testing serious enough to require epinephrine as 20 per 100,000.[28] A survey of the American Academy of Allergy, Asthma and Immunology physicians was able to identify a single fatal reaction to allergy skin testing as having occurred in the years 1990-2001.[29] Still, a survey of chairpersons of pediatric IRBs found that 70% categorized allergy skin testing as more than minimal risk, and 27% categorized it as a more than minor increase over minimal risk.[30]

Suppose that researchers wanted to do a study that involved performing allergy skin tests on children, but which lacked any potential for direct benefit for the children being tested. Regardless of how socially valuable we stipulate this research might be, the 27% of pediatric IRB chairs who found skin testing to be a more than minor increase over minimal risk would find the study unapprovable.

It would be different if there were some clinical benefit associated with the test. Suppose there were enough clinical benefit that participation was actually net beneficial. Then the study

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[27] Specifically: "minimal risk means that 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(j). For the introduction of the (undefined) language of a "minor increase over minimal risk" see 45 CFR 46 §406(a).

[28] Kowlaski, M. L., Ansoegui, I, Aberer, W., Al-Ahmad, M., Adkis, M, Ballmer-Weber, B. K., Beyer, K. … Zuberbier, T. (2016). Risk and safety requirements for diagnostic and therapeutic procedures in allergology: World Allergy Organization statement." *The World Allergy Organization Journal* 9(1).

[29] Bernstein, D. I., Wanner, M. Borish, L., Liss, G. M., & the Immunotherapy Committee of the American Academy of Allergy, Asthma, and Immunology. (2004). Twelve-year survey of fatal reactions to allergen injections and skin testing: 1990-2001. *Journal of Allergy and Clinical Immunology* 113(6): 1129-36.

[30] Shah, S., Whittle, A., Wilfond, B., Gensler, G., & Wendler, D. (2004). How do institutional review boards apply the federal risk and benefit standards to pediatric research? *JAMA* 291(4): 467-82.

would be approvable—as it should be![31] Children cannot offer their own full and voluntary informed consent, and this may prevent them from legitimately being entered into arrangements that sacrifice their interests in favor of the interests of others. But it would be perverse to take their inability to defend their interests and use it as grounds to exclude them from enrolling in *studies that are in their interests*. Children cannot give their full, informed consent to be fed dinner, either, but that doesn't mean we should let them starve.

Why should this point be any different depending on whether we are discussing health or monetary benefits? Suppose the researchers aim to offer financial benefits in exchange for the children receiving a skin test. If those benefits were sufficiently large, the result would again be a study that was in a child's best interests to enter.

Of course, the fact that children lack the capacity to manage their own affairs complicates the act of providing them monetary compensation. If one pays a child's parents, then one faces the prospect of parents using their children as a fundraising resource. It is reasonable to be leery of paying parents directly and it makes sense to avoid even the appearance of buying off parents to get them to surrender their children.

Fortunately, there are alternatives. One is to offer in-kind gifts directly to the children themselves, e.g. toys, gift cards, and the like. But our topic is payment. And although in-kind gifts may reasonably compensate some risks, it is worth exploring the more significant magnitudes of benefit that can be provided specifically by payment.

The precise vehicle for payment would depend on the legal tools available in the jurisdiction of research. Generally, compensation could be put into an instrument which only becomes available on majority and/or only releases funds to specific "worthy" expenses, e.g.

[31] Although it would have to be under 45 CFR 46 §405 rather than 45 CFR 46 §406, on which see footnote 26.

education or healthcare. Trusts can be arranged in this style. Yet there are expenses involved in establishing and managing trusts. Whether that overhead is sensible as a share of overall budgets would depend on the research in question.

Some creativity may reveal more easily administrable options. Consider, for example, the fact that some US governmental organizations and nonprofits have begun to experiment with establishing college savings accounts for children; Maine has been offering them to every child since 2008.[32] These accounts typically start with some seed money and may include limited future matching. If researchers were able to arrange deposits, then they would be freed of the burdens associated with managing the money themselves. They would just need to conduct their research in a community where such accounts had been established.

Abstracting away from implementation: imagine that researchers who were interested in running the nontherapeutic allergy study described above decided to offset the risks of participation by putting $1,000 toward each participating child's higher education. Individual children's financial situations will, of course, be different (much as their health and social situations are different). Nonetheless, it is hard for me to imagine that it wouldn't be in the interests of a great many children to enroll in such a trial.

What does a $1,000 gift accomplish? Among full-time college students in the US, approximately half are employed and approximately a quarter work more than 20 hours a week; the numbers are substantially higher for part-time students.[33] Suppose a working student is fortunate enough to take home $20 an hour, after taxes. The single allergy skin test they received

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[32] Mercer, M. (2015). *Children's savings accounts help states create 'college-going culture.'* Retrieved from http://bit.ly/1NNawCM ; Pender, K. (2019). *Newsom wants to expand programs that open a savings account for every kid.* Retrieved from: https://www.sfchronicle.com/business/networth/article/Newsom-wants-to-expand-programs-that-open-a-13638549.php

[33] National Center for Education Statistics. (2019). *The condition of education 2019.* Retrieved from: https://nces.ed.gov/pubsearch/pubsinfo.asp?pubid=2019144

as a youth could offset 50 hours of work. It could allow them to replace 50 hours of work with 50 hours of study; it could allow them to rest, with 50 additional hours of leisure and self-care.

I use college funds an illustrative example, but similar remarks apply to children who never attend college—so long as they work for wages, payments will be fungible with some number of work hours. In college or out of it, it seems obvious to me that the benefits associated with a $1,000 payment outweigh the very minor harms associated with undergoing an allergy skin test, and, as a result, that a trial with this risk-benefit profile should be understood as net beneficial.[34]

Perhaps the thought of children submitting to medical research to ease the burdens of their education is chilling. But recall: we are talking about an allergy skin test. The "minor increase over minimal" risk ceiling used in pediatric research is *extremely low.* That is why it is easy to imagine studies which are above that threshold, when payment is excluded, but where once payment is counted they become obviously net benefit. And once it is conceded that it does indeed *benefit* the children, ruling it out cannot be justified in terms of any type of paternalism. As we saw in section three, paternalism is about promoting a person's good; one does not promote a child's good by denying that child beneficial opportunities.

This point also dispatches various further ethical and regulatory objections—for instance, ethically speaking, some object to notion that benefits from one intervention could legitimately

[34] An anonymous reviewer suggested that this judgment may be complicated by time discounting: perhaps the discomfort of an allergy skin test is less bad than $1,000 is good, but, still, once the $1,000 is appropriately discounted according to the fact that the child will only gain access to it in the future, when they attain majority, it no longer successfully outweighs the present discomfort. I respond: even if time discounting is appropriate, which is controversial itself, we nonetheless do routinely find it appropriate to impose present harms on children in order to significantly improve their future (e.g., making them do their homework, to help them grow into diligent, intelligent people). Furthermore, the unpleasantness of a single day's worth of homework seems often greater than an allergy skin test, and the benefit of a single day's worth of homework seems often less than $1,000. Consequently, it seems that legitimate time discounting rates could not possibly be so steep as to interfere with this study being appropriately described as net beneficial.

cancel risks from another, and it is standard to require not only that a study have an overall acceptable risk-benefit profile, but also that each component of the study, or group of related components, also has its own acceptable risk-benefit profile when considered individually.[35] And, as a matter of regulation, the US regulation appear to encode this approach insofar as they treat the risks of a pediatric intervention as only being potentially cancelled by the direct benefits of that very same intervention.[36] Given that being paid for participation is in some ways separable from receiving an allergy skin test, my suggestion that payment could cancel the risks of allergy skin tests may contradict that requirement. Now, it is not fully clear how to best understand the US regulations on this point.[37] Nonetheless, my response to the regulatory objection is simple: once it is conceded that a trial of this form would be genuinely beneficial for the enrolled children, if the regulations nonetheless cannot be reconciled with it, then it is the regulations, not the trial, that are the problem. And my response to the ethical version of this objection is similar. If there is some putative ethical principal that risks and benefits can under no circumstances be "bundled" across distinct study interventions, and this putative principle serves to effectively forbid research which is good for children as a class, good for the children who enroll, and good for the society overall, then it is the putative principle, not the trials it rules out, which should be rejected.[38]

7. Conclusion

[35] See e.g. Rid and Wendler's discussion of "the fallacy of the package deal," *op. cit.* note 7 p. 159-162.
[36] 45 CFR 46 §405 and 45 CFR 46 §406
[37] Friedman, A., Robbins, E., & Wendler, D. (2012). Which benefits of research participation count as 'direct'? *Bioethics* 26(2): 60-67.
[38] The payment model I propose is distinguishable in several respects from those "package deals" that many find intuitively objectionable and that correspondingly motivate adopting an anti-bundling principle. See Rid and Wendler *op. cit.* note 7 p.159-162. Hence, I suspect that it would not be difficult to formulate a somewhat more complex version of the anti-bundling principle which permitted the payment model I propose while still ruling out the supposed bad cases. Furnishing the best version of such a principle is beyond the scope of this discussion.

People benefit from getting more money and suffer from losing it. Anyone who seriously doubts that is invited to send a substantial cashier's check to the address of the corresponding author. So: payment is a benefit. But what happens when RECs start counting it as one?

It is unclear how much classifying payment as a benefit would alter standard practice in trials enrolling competent adults. This is because the function of counting payment as a benefit is to cancel risks, but the acceptable risk ceiling for adults is both high and vague; as argued, this introduces its own complications. By contrast, counting payment as a benefit would make an obvious difference to trials in children, where the risk ceiling is both lower and clearer. Here we have a highly credible case for potential "win-win" trials. Children could win, by having the chance to enroll in more-than-minor-increase over minimal risk trials which compensate them generously enough to be net beneficial. And society could win at the same time, as the cost of such generous compensation could still be "worth it" in comparison to the value of the knowledge gained. The ethical and regulatory apparatus should not stand in the way of win-win trials without an extremely good reason.