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# Which Benefits of Research Participation Count as 'Direct'?

**Alexander Friedman**, **Emily Robbins**, and **David Wendler**

## Abstract

It is widely held that individuals who are unable to provide informed consent should be enrolled in clinical research only when the risks are low, or the research offers them the prospect of direct benefit. There is now a rich literature on when the risks of clinical research are low enough to enroll individuals who cannot consent. Much less attention has focused on which benefits of research participation count as 'direct', and the few existing accounts disagree over how this crucial concept should be defined. This disagreement raises concern over whether those who cannot consent, including children and adults with severe dementia, are being adequately protected. The present paper attempts to address this concern by considering first what additional protections are needed for these vulnerable individuals. This analysis suggests that the extant definitions of direct benefits either provide insufficient protection for research subjects or pose excessive obstacles to appropriate research. This analysis also points to a modified definition of direct benefits with the potential to avoid these two extremes, protecting individuals who cannot consent without blocking appropriate research.

### Keywords

direct benefits; fallacy of the package deal; informed consent; vulnerable subjects

Guidelines for clinical research stipulate that individuals who cannot provide informed consent should be enrolled only when the risks are low or the research offers a compensating potential for 'direct' benefit. According to guidelines from CIOMS, clinical trials which pose more than a slight increase over 'minimal' risk (defined as the risks of routine examinations) should enroll individuals who cannot consent only when the research offers them the prospect of 'direct benefit'.1 The International Conference on Harmonization guidelines allow individuals who cannot consent to be enrolled in clinical research when the risks are low or the research offers them the potential for 'direct clinical benefit'.2 Similar risk-benefit guidelines are included in many national guidelines for clinical research, including the US federal regulations which allow institutional review boards to approve pediatric research that poses more than a minor increase over 'minimal' risk (defined as the risks of daily life or routine examinations) only when it offers the 'prospect of direct benefit to the individual subjects'.3

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The opinions expressed are the authors' own. They do not represent any position or policy of the National Institutes of Health, Public Health Service, or Department of Health and Human Services

[1]Council for International Organizations of Medical Sciences. 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*: Geneva, Switzerland, guideline 9.
[2]International Conference on Harmonization. 1996. *Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance*. Guidelines 4.8.13 and 4.8.14.
[3]Department of Health and Human Services. Code of Federal Regulations. Title 45, Part 46, *Protection of Human Subjects*, subpart D; Food and Drug Administration. Code of Federal Regulations. Title 21, Part 50. *Protection of Human Subjects*, subpart D.

Accurate implementation of these risk-benefit guidelines is crucial to protecting research subjects who cannot provide informed consent. Unfortunately, the literature offers conflicting views on which benefits count as 'direct', undermining confidence that those who cannot consent are being adequately protected. The present paper attempts to address this concern by considering first what additional protections are needed for individuals who cannot provide informed consent. Specifically: what protections, beyond those that apply to research with competent adults, are needed to enroll individuals who cannot consent in riskier research, defined as research that poses greater than minimal risk or, perhaps, greater than a minor increase over minimal risk?

The present analysis suggests that existing definitions of direct benefits are inadequate. Some of these definitions offer insufficient protection for research subjects who cannot consent, while other definitions block some appropriate research. The present analysis also points to a modified understanding of 'direct' benefits, one that has the potential to protect individuals who cannot provide informed consent without blocking appropriate research that is needed to develop improved methods to treat the medical conditions that affect them. This modified account defines direct benefits as those benefits that research subjects realize from the procedures which are scientifically necessary to evaluate the intervention under study. This account suggests, contrary to the view of many commentators, that the potential benefits of experimental interventions can justify the risks of other procedures that must be included in the study to test the experimental intervention. Amending current practice in this way would allow approval of important and appropriate clinical trials that are precluded under the existing definitions of direct benefits.

## DIRECT BENEFITS AS LIKELY OR SIGNIFICANT BENEFITS

The distinction between direct and indirect benefits was introduced in 1979 by the US National Commission as part of its recommendations on research with individuals who cannot provide informed consent.4 The Commission argued that these vulnerable subjects should be enrolled in clinical research only when the risks are low or the research offers them sufficient potential for benefit. To implement the latter protection, the Commission introduced the concept of 'direct' benefits which it defined as 'fairly immediate' benefits for subjects as a result of their participation in clinical research.5 The point was to ensure that individuals who cannot consent are exposed to greater research risks only when they themselves had the chance to benefit. The Commission attempted to implement this requirement by focusing on benefits that are fairly immediate. The Commission was concerned that potential benefits which would be realized in the distant future are too speculative to justify enrolling vulnerable subjects, and exposing them to greater than minimal risks.

Other commentators use the concept of direct benefits to try to ensure that vulnerable subjects are enrolled in clinical research only when the potential benefits for them are of sufficient *magnitude*. For example, it has been argued that direct benefits are those benefits which represent significant 'improvement or a slowing of a degenerative process'.6 Similarly, a US Institute of Medicine report maintains that a direct benefit is a significant 'positive outcome (e.g. cure of disease, relief of pain, and increased mobility) that may be experienced by an individual'.7

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[4]The Commission held that the most problematic research with those who cannot consent is 'research that presents more than minimal risk without immediate prospect of direct benefit'. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. The Belmont Report.

[5]Report regarding the ethics of research involving people institutionalized as mentally infirm. *Federal Register* 1978: 11334.

[6]E. Keyserlingk, K. Glass, S. Kogan & S. Gauthier. Proposed guidelines for the participation of persons with dementia as research subjects. *Perspect Biol Med* 1995; 38: 319–361.

Attention to the likelihood, as well as the magnitude, of the potential benefits of clinical research is important to ensuring that individuals who cannot consent are enrolled in riskier research only when the research offers them an appropriate balance of risks and potential benefits. Yet, how likely and how significant the potential benefits must be to justify the enrollment of those who cannot consent depends on the level of risks they face in the research. This consideration, while vital to protecting vulnerable subjects, does not appear to be reflected in some guidelines on clinical research. The Declaration of Helsinki allows incompetent subjects to be enrolled in research that poses more than minimal risk simply when it offers the 'likelihood of benefit for them'.8 Similarly, the Canadian Tri-Council guidelines stipulate that individuals who are not competent may be enrolled in research that poses greater than minimal risk when the research has the 'potential for direct benefits to them'.9

To ensure adequate protection, research guidelines should stipulate that individuals who cannot consent may be enrolled in riskier research only when the potential benefits to them are sufficient, taking into account *both* probability and magnitude, to justify the risks they face.10 This requirement presses a further question: when determining whether riskier research offers sufficient potential benefit to subjects who cannot consent should ethics review committees take into account only some of the potential benefits that these subjects might realize? Put in the negative, are there some types of potential benefits that ethics review committees should not take into account when deciding whether the risk-benefit profile of a given clinical trial is appropriate for individuals who cannot consent?

## THE RISKS OF ADD-ON BENEFITS

The stipulation that individuals who cannot consent may be enrolled in riskier research (again: research that poses more than minimal risk, or more than a minor increase over minimal risk) whenever the potential benefits to them are sufficient would allow essentially any type of benefit to justify the risks these individuals face. With only this requirement in place, the risks of being enrolled in clinical research could be justified by the potential to earn wine or money, gain a new friend or an opportunity to contribute to an important cause. What we might think of as the principle that 'all benefits are created equal' would imply that this is the right approach. Assuming that enrollment is in the interests of individuals who cannot consent, why should it matter in what way they stand to benefit, or in what way their interests might be promoted? Why should it matter whether the potential benefits are 'direct' or 'indirect'?

In effect, the question here is whether the potential benefits need to be direct only in the sense of being ones that accrue to the subjects themselves. Or does protection of those who cannot consent require further distinction between types of potential benefits to subjects. One argument for requiring a finer distinction would be that some benefits simply are not appropriate in the context of clinical research. Most prominently, some commentators express concern regarding the appropriateness of offering research subjects money in exchange for facing research risks.11 This concern might be defended on the grounds that

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[7]Institute of Medicine. 2004. Ethical Conduct of Clinical Research Involving Children, 132.

[8]World Medical Association. 59th General Assembly, Seoul, October 2008, Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects, principle 27. Available at: http://www.wma.net/e/policy/b3.htm [Accessed: 15 July 2009].

[9]Tri-Council Policy Statement. *Ethical Conduct for Research Involving Humans*. 2005. Article 2.5(c).

[10]For purposes of evaluating the concept of direct benefits, we will bracket the possibility that there might be appropriate exceptions to this requirement. For example, it might be appropriate, in some instances, to allow adults who cannot consent to be enrolled in riskier research when there is compelling evidence that such participation is consistent with the individuals' competent preferences and values.

[11]C. Grady. Payment of clinical research subjects. *J Clin Invest* 2005; 115: 1681–1687; T. Chambers. Participation as commodity, participation as gift. *Am J Bioeth* 2001; 1: 48.

financial benefits in general are inappropriate in the context of clinical research.12 For example, it might be thought that clinical research is fundamentally a humanitarian enterprise that should be governed by altruism, not by the profit motive.

Alternatively, one might try to defend this concern based on the claim that potential benefits should be of the same type as the risks they justify. Since the risks subjects face in the context of clinical research typically involve clinical harms, the potential benefits should involve possible advancement of their clinical interests in particular. A risk to the immune systems or kidneys of individuals who cannot consent should be offset, on this view, by the potential to improve their health, not by the potential to increase their bank accounts. This view was endorsed in the US court case that, to date, has most explicitly addressed the ethics of clinical research with individuals who cannot consent, the case of *Grimes v Kennedy Krieger Institute.* In that case, the court expressed the view that investigators should not enroll individuals who cannot consent in risky research by offering them 'Gifts, trinkets, coupons for food…including coupons for things ranging from skating trips to groceries'.13

Second, one might argue that allowing any type of benefit to justify the risks subjects face would allow investigators to justify essentially any level of research risks simply by offering subjects more benefits.14 Investigators would be able to perform very risky research procedures on children, or adults who cannot consent, simply by offering them more money, or more clinically indicated counseling. The Kenyan guidelines for the ethical conduct of clinical research express a widely-endorsed response to this possibility:

> Extraneous benefits such as payment, or adjunctive medical services, such as the possibility of receiving a hepatitis vaccine not related to the research, cannot be considered in delineating the benefits compared with the risks, otherwise simply increasing payment or adding more unrelated services could make the benefits outweigh even the riskiest research.15

Third, ethics review committees make prospective and, hence, necessarily *preliminary* determinations, prior to the enrollment of any subjects, of whether the research offers an appropriate risk-benefit profile. The informed consent process then allows competent individuals to assess the risks and potential benefits for themselves, at the time of enrollment. Competent individuals can choose not to enroll when they judge that the potential benefits are not sufficient, given their personal interests, to justify the risks. The situation is very different when it comes to research with individuals who are not able to consent. In this case, subjects are not able to understand the studies and decide for themselves whether enrollment is consistent with their personal interests. This decision is made by someone else, the individual's surrogate decision maker.

Risk-benefit calculations, difficult enough to make for oneself, become increasingly difficult to make for others, especially for those who are unable to consent. Perhaps the greatest challenge and, hence, the greatest potential for mistakes, arises when one attempts to compare risks and potential benefits that are of very different types: how much payment is needed to justify three lumbar punctures? The difficulty making such determinations for

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12This objection faces the significant problem that a good deal of research is funded by private companies whose goal is ultimately to make a profit.

13*Grimes* v. Kennedy Krieger Institute, Inc., 782 A.2d 807 (Md. Ct. of App. 2001, reconsideration denied, Oct. 11, 2001). See pages 9 and 61, especially footnote 34.

14NIH Office of Human Subjects Research. Guidelines for Remuneration of research subjects Available at: http://ohsr.od.nih.gov/info/sheet20.html [Accessed 13 September 2009]. Some of the court's concern seems to trace to the potential for such offers to undermine the validity of parental permission and subject assent. The court also suggests that such offers are per se inappropriate in the context of clinical research.

15National Council for Science and Technology. Guidelines for ethical conduct of biomedical research involving human subjects in Kenya, 2004, page 6.

others lends support to the claim that the potential benefits which can justify risks to individuals who cannot consent should be limited to more clinical type benefits, where the comparison to clinical risks is at least more tractable. And this point lends support to the claim that investigators should not be able to simply add on whatever benefits they choose to justify the risks subjects face. Doing so would allow investigators to add types of benefits which are difficult to compare to the largely clinical risks of research participation, making the task of protecting vulnerable subjects more difficult and possibly less effective. More recent accounts of direct benefits recognize this concern and attempt to address it by limiting the types of benefits that can justify the research risks to which vulnerable subjects are exposed.

## MORE RECENT ACCOUNTS

Recent accounts define ‘direct’ benefits as the potential benefits of receiving the intervention being tested in the study. The US National Bioethics Advisory Commission, for example, claims that direct benefits ‘stem from the research interventions themselves’.16 And Nancy King, who has developed perhaps the most important account, defines direct benefits as benefits ‘arising from receiving the intervention being studied’.17 This way of defining direct benefits has the distinct virtue of helping to address the 3 concerns we considered in the previous section.

First, by limiting direct benefits to the benefits of receiving the experimental intervention this account effectively limits direct benefits to clinical benefits, thus eliminating the need to compare risks and potential benefits that are of very different types. Second, this approach limits investigators’ ability to add in extra direct benefits on top of the potential benefits of the intervention being tested. As Nancy King notes, benefits ‘arising from being a subject, even if one does not receive the experimental intervention (for example, a free physical exam and testing, free medical care and other extras, or the personal gratification of altruism)’ are not direct.18

Third, to be ethical, clinical research should have sufficient social value. Intervention trials satisfy this requirement when they test interventions which have the potential to improve clinical care for future patients. When this requirement is satisfied, there is reason to think that receiving the intervention that is being tested offers some potential for benefit that is important, even for individuals who are unable to provide informed consent. If the intervention being tested has the potential to benefit future patients it often will offer some, albeit often uncertain and low, potential to benefit to those who receive it during the testing process.19

To evaluate accurately the recent accounts it is important to note that they do not have the implausible implication that investigators should never offer added benefits to individuals who cannot consent. Providing additional benefits, such as free medical care or testing, may be appropriate in some cases and offers one way to help vulnerable subjects who are contributing to the research enterprise. The recent accounts allow such provision, provided the associated benefits are not taken into account when evaluating whether the research poses excessive risks to those who cannot consent.

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16Research Involving Persons with Mental Disorders That May Affect Decisionmaking Capacity. 1998. *Volume I: Report and Recommendations of the National Bioethics Advisory Commission*: 45.
17N. King. Defining and Describing Benefit Appropriately in Clinical Trials. *J Law Med Ethics* 2000; 28: 332–343.
18Ibid: 333.
19There are exceptions, of course. A single administration as part of an early phase trial may well offer no potential for clinical benefit.

## CLINICALLY INDICATED PROCEDURES

Clinical trials often include diagnostic procedures—additional scans, blood draws, or biopsies—to help answer the scientific question(s) posed by the study. These procedures are in the clinical interests of subjects in some cases, but not others. The latter possibility is the more common one, and arises when the additional procedures provide information that is important for research purposes, but which has no bearing on the subjects' clinical care. An example would be the performance of an extra blood draw to obtain samples that will be stored for future research. Less frequently, these procedures may be in the clinical interests of the subjects. For example, the procedures might provide information that is relevant to the care of subjects, perhaps offering additional information on the status of their disease that would not be available in the clinical setting.[20]

Because these interventions are not being tested themselves, the potential benefits they offer subjects do not qualify as 'direct' on recent accounts. It seems to follow, on these accounts, that the potential benefits of these procedures cannot justify the risks they pose to subjects. And this conclusion suggests that if such interventions pose more than minimal risk (or more than a minor increase over minimal risk under some regulations) they cannot be included in research with individuals who are unable to consent, even when the procedures are in the subjects' clinical interests.

The problem with this conclusion is that use of these procedures does not involve investigators taking advantage of subjects' circumstances by adding risky and unrelated interventions merely for the investigators' benefit. Moreover, the fact that these procedures offer clinical benefits suggests that their benefits can justify the risks they pose. These considerations point to the possibility of a somewhat broader account which defines direct benefits as benefits that result from the interventions that are needed for scientific reasons to test the experimental intervention.

To see how this proposal differs from the recent accounts, imagine that an investigator needs to perform 2 lumbar punctures to evaluate the experimental treatment. On recent accounts, the potential benefits of receiving the experimental intervention are the only ones that qualify as direct. It follows that, if the ethics review committee judges the risks of the lumbar punctures to be greater than minimal (or greater than a minor increase over minimal), the investigator would not be allowed to conduct this research with individuals who cannot consent, even when the lumbar punctures would provide clinically useful information to the extent that undergoing them is in subjects' clinical interests. This result does not protect individuals who cannot consent so as much as it precludes them from the possibility of receiving certain clinical benefits.

The present proposal, in contrast, would count the potential benefits of the lumbar punctures as direct since they are scientifically necessary to evaluate the intervention being tested. This approach raises the question of how ethics review committees should evaluate interventions that are needed for a valid study, but which themselves do not offer subjects the potential for clinical benefit. How should ethics review committees handle the lumbar punctures if they are necessary for scientific reasons, but do not offer any potential for clinical benefit? To answer this question, we will need to consider the process for evaluating the risks and potential benefits of research interventions, sometimes called 'component' analysis.

[20]To be clear, this claim is not intended to cover clinical care interventions that sometimes are included in clinical research studies. Rather, the point is that research studies sometimes include interventions that are not part of clinical care, but nonetheless offer some potential for clinical benefit.

## COMPONENT ANALYSIS

Most guidelines and commentators agree that the individual interventions which make up a given study should be evaluated separately with respect to risks and potential benefits.[21] This approach is important because it helps to ensure that each intervention that subjects undergo is evaluated carefully to ensure that its risks are minimized and the remaining risks are justified by the intervention's potential to benefit subjects, if any, and its potential to provide important information that cannot be collected in a less risky way.[22]

Some guidelines and many commentators go further and specify that each intervention in a given study must either pose low risks or itself offer a compensating potential for direct benefit. For example, a US Institute of Medicine report holds that: 'the potential benefits from one component of the research should not be held to offset or justify the risks presented by another'.[23] This approach is intended to avoid what has been termed the 'fallacy of the package deal'. In particular, it is widely considered a fallacy to allow the potential benefits of one intervention to justify the risks of a different intervention in the same study.[24] In the words of the US National Bioethics Advisory Commission, this requirement prevents investigators from including:

> additional procedures such as biopsies, blood tests or scans, that are unlikely to yield any information of benefit to society by justifying them on the basis of including an intervention that holds the prospect of direct benefit such as an experimental oncology treatment.[25]

Consider a research protocol designed to test an experimental medication for cancerous tumors. Imagine that the medication has shown real promise in prior studies to the extent that the ethics review committee finds that it offers subjects significant potential for clinical benefit, and relatively low risks. If the ethics review committee were to evaluate the overall risks and benefits of the entire study only, the investigator might be able to add in a purely research biopsy that is of little value and justify its inclusion on the grounds that the potential benefits of the experimental medication are sufficient to justify its own risks, as well as the risks of the added biopsy. Component analysis is intended to block this potential for exploitation. Since the direct benefits of one intervention cannot justify the risks of other interventions, the added biopsy would be allowed only if its risks were minimal or it offered the potential for clinical benefit which justifies its risks.

## SCIENTIFICALLY NECESSARY PROCEDURES

Now consider a variation on the cancer study in which the biopsy still does not provide any information that is relevant to the subjects' clinical care, but it will provide information that is necessary for a valid assessment of the experimental medication, and there is no less risky way to obtain this information. For example, the biopsy might be needed to assess whether the medication is penetrating the tumor. This biopsy poses risks to subjects and offers them no potential for clinical benefit. Thus, assuming the biopsy poses greater than minimal risk (or a minor increase over minimal risk under some regulations), it could not be performed in individuals who are unable to consent. And, assuming the biopsy is needed for a valid study,

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[21] C. Weijer. The ethical analysis of risk in intensive care unit research. *Crit Care* 2004; 8: 85–86; A. McRae & C. Weijer. U.S. Federal Regulations for emergency research: a practical guide and commentary. *Acad Emerg Med* 2008; 15: 88–97.

[22] See, for example, the US National Commission. 1977. Report and recommendations: research involving children. Washington, DC: U.S. Government Printing Office., pages 6–7.

[23] Institute of Medicine. Ethical conduct of clinical research involving children. Field MJ, Behrman RE (eds). 2004. Washington, DC: National Academies Press, page 138.

[24] R.J. Levine. The Need to Revise the Declaration of Helsinki. *New Engl J Med* 1999; 341: 531–534.

[25] National Bioethics Advisory Commission. Ethical and policy issues in research involving human participants. Bethesda, MD: Report and recommendations of the National Bioethics Advisory Commission, 2001, chapter 4, page 78.

it follows that this study could not be conducted in individuals who are unable to provide informed consent.

For the purposes of protecting those who cannot consent from excessive risks this result seems potentially problematic because it effectively precludes them from access to the experimental medication. Yet, in this case, the investigators are not simply adding on additional and purely research procedures to be performed on a captive audience. As a result, it seems that this study might be appropriate for individuals who cannot consent, despite the fact that it includes a procedure which poses greater than minimal risk and itself offers no potential for clinical benefit. One way to address this possibility would be to compare the total potential clinical benefits of the interventions necessary for scientific purposes to the total risks these same interventions pose to individuals who cannot consent.

## THE MODIFIED APPROACH

The present analysis suggests that direct benefits might be defined as the clinical benefits of the procedures that are scientifically necessary to test the experimental intervention under study. This includes the potential benefits of the experimental intervention and any potential benefits of the interventions needed to test the experimental intervention. To implement this modified approach, ethics review committees would sum the potential clinical benefits of all the scientifically necessary interventions in the study, and compare these potential benefits to the total risks posed by the same set of interventions. The study would qualify as prospect of direct benefit only if the potential benefits justify or outweigh these risks.

This modified approach seems to protect individuals who cannot consent from the three concerns considered previously without having the potential to inadvertently block important research that offers an appropriate risk-benefit profile. Investigators would not be able to perform unnecessary procedures solely for research purposes, nor would they be able to simply include additional benefits in order to offset otherwise uncompensated risks. For example, the benefits of payment do not qualify as direct on this approach because payment is not needed for scientific purposes, even though it sometimes may be necessary for practical purposes (e.g. it might be needed to recruit enough subjects). Similarly, investigators would not be able to justify the risks of an added research procedure that is not needed scientifically on the grounds that the intervention being tested offers significant potential benefits.

To implement the modified approach it will be necessary to determine which procedures or interventions included in a given study qualify as scientifically necessary. Most importantly, scientifically necessary procedures should not be defined as any procedures that are necessary to answer a scientific question posed by the study. Under this definition, investigators could simply add to the protocol a scientific question regarding the results of tissue biopsies and then argue that additional tissue biopsies are scientifically necessary to answer this question. In effect, investigators could include as many procedures as they wish simply by adding a question that would be answered by each of the added procedures.

This approach seems problematic to the extent that the added biopsies are irrelevant to the testing of the experimental intervention. One way, then, to block this possibility would be to stipulate that the potential benefits of experimental interventions can justify the risks of only those procedures that are relevant to testing the experimental intervention. If a study is designed to evaluate a new treatment for lymphoma, the scientifically necessary procedures would be only those that are relevant to evaluating the new treatment.

The strictest way to implement this approach would be to stipulate that only those procedures which are scientifically necessary to provide a valid test of the experimental

treatment offer direct benefits. A slightly less strict approach would also cover procedures that are scientifically necessary to answer questions which are related to the evaluation of the experimental intervention but which, strictly speaking, are not scientifically necessary for the purposes of that evaluation. Imagine that an additional blood draw would allow the investigators to answer an important question related to the experimental intervention, but not one that is directly relevant to the overall purpose of the study. Perhaps the study is designed to assess the safety of the intervention, but the added blood draw could provide important information for future efficacy testing. The second approach, but not the first, would regard this blood draw as scientifically necessary.

The previous analysis of the protections needed for research subjects who cannot consent seems to support the latter approach. This approach limits direct benefits to ones that are clinical and that are important to evaluating the intervention under study. This approach would not allow investigators to simply add in interventions that are of interest to them. It would allow only those interventions that, for scientific reasons, are important for evaluating the experimental intervention and which offer the potential for socially valuable information that cannot be obtained in a less risky way. The present analysis also suggests that necessity in this sense should be treated as transitive across procedures. If a scan is necessary to evaluate the experimental intervention, and the scan will provide the necessary information only if subjects first ingest a contrast agent, the administration of the contrast agent would also qualify as scientifically necessary to evaluate the experimental intervention.

## IMPLEMENTATION UNDER EXISTING REGULATIONS

This modified definition of direct benefits can be adopted by review committees which are subject to the many regulations which do not explicitly prohibit them from allowing the benefits of one procedure to justify the risks of a different procedure. For example, the International Conference on Harmonization guidelines do not limit ethics review committees to evaluating the risks-benefit profile of individual interventions.26 Thus, committees reviewing research under these guidelines could evaluate the individual procedures to make sure that their risks are minimized and justified by the potential benefits to subjects, if any, and the potential to collect important information. The committee could then determine either that the risks of the scientifically necessary procedures are low, or the risks of these procedures are justified by the potential direct benefits of other interventions in the study which are scientifically necessary.

Implementation of the present approach will be more difficult under regulations that explicitly require ethics review committees to employ component analysis. As we have seen, inclusion of a scientifically necessary procedure does not involve exploitation of subjects' circumstances – the investigators are not, in effect, saying: 'Since we've got you here anyway, and there is a prospect of direct benefit to you that outweighs the risks and discomforts of a biopsy, we might as well have you undergo a biopsy for our own purposes'. This suggests that ethics review committees which are operating under component analysis might find that a scientifically necessary procedure that itself offers no potential for clinical benefit nonetheless offers direct benefits in terms of making available to subjects the potential benefits of receiving the investigational therapy. In such cases, it may, therefore, be permissible to conduct research with children or adults with severe dementia that involves a necessary research procedure that poses greater than a minor increase over minimal risk.

[26]Specially, the International Conference on Harmonization specifies that non-therapeutic trials (i.e. a trial in which there is no anticipated direct clinical benefit to the subject) may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled: (a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally; (b) The foreseeable risks to the subjects are low; (c) The negative impact on the subject's well-being is minimized and low.

To take a specific example, the US regulations allow institutional review boards to approve pediatric research interventions or procedures that pose more than minimal risk when the intervention or procedure holds out the prospect of direct benefit that justifies it risks.27 To implement the present approach in this context, ethics review committees might regard the scientifically necessary procedures as providing a prospect of direct benefit in the sense that undergoing these procedures is necessary for subjects to have the opportunity to gain the clinical benefits offered by receiving the experimental intervention. This approach seems to capture the spirit of component analysis by prohibiting investigators from adding in procedures to take advantage of subjects' circumstances and their need for treatment.

This way of implementing the modified approach to direct benefits will not be possible under some regulations. For example, the Indian Council of Medical Research guidelines of 2000 state that ethics review committees may approve pediatric research only when 'the risk presented by interventions not intended to benefit the individual child' are low. This regulation allows purely research biopsies to be included in research with children only when the risks of the biopsy itself are low.28 As a result, this requirement is inconsistent with the approach endorsed here in which the risks of riskier, but scientifically necessary research procedures may be justified by the potential clinical benefits of the intervention being tested (assuming its potential clinical benefits are sufficient to justify its own risks as well as the risks of the purely research biopsy). Barring some argument for why it would be unethical to enroll in such research individuals who cannot provide informed consent, the present analysis implies that such regulations should be modified along the lines considered here.

## CONCLUSION

Early accounts of direct benefits were designed to ensure that individuals who cannot consent are enrolled in riskier research only when it offers them sufficient potential to benefit. These accounts defined direct benefits based on either the likelihood or the magnitude of the potential benefits. A better approach stipulates that individuals who cannot consent may be enrolled in riskier research only when the potential benefits are sufficient, taking into account their probability and magnitude, to justify the risks. This conclusion raised the question of whether there was further normative work to be done by the concept of 'direct' benefits.

To answer this question we considered what additional protections might be needed for individuals who cannot consent, such as children and incompetent adults, in the context of riskier research. It was argued that it makes sense to include protections to minimize the chances of error when evaluating whether the potential benefits to these subjects justify the risks they face. In this regard, recent accounts limit direct benefits to the potential benefits of the intervention being tested. This approach addresses the concerns raised by enrolling individuals who cannot consent, but has the potential to preclude scientifically necessary procedures that happen to be in the interests of these individuals. This approach, combined with some versions of component analysis, also would prohibit the enrollment of individuals who cannot consent in research that needs to include riskier procedures in order to test the intervention under study.

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[27]Specifically, subpart D of the US regulations state that 'HHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual subject' when the IRB finds that 'the risk is justified by the anticipated benefit to the subjects'. U.S. Code of Federal Regulations. 45CFR46.405

[28]We are assuming here that the intentions of the investigators who perform the biopsies roughly track the potential that the biopsies will benefit the subjects.

These concerns point to the possibility of a modified approach, one that defines ‘direct’ benefits as the benefits of scientifically necessary procedures, and which allows the potential benefits of one scientifically necessary procedure to justify the risks of other scientifically necessary procedures. This approach suggests that the ‘Fallacy of the Package Deal’ is not a fallacy in all cases. It is not a fallacy to allow the benefits of an investigational therapy to justify the risks of a procedure that offers no chance of benefits, but which is necessary for a valid test of the investigational therapy. Such research seems ethical even when it enrolls subjects who cannot consent.

## Biographies

**Alex Friedman** received his Ph.D. in philosophy from MIT and completed a post-doctoral fellowship at the NIH Department of Bioethics. His research deals primarily with ethical issues in distribution of scarce resources, as well as harms and benefits.

**Emily Robbins,** M.D., is an intern at the Children’s Hospital of Philadelphia where she will complete her residency in pediatric neurology.

**David Wendler** is head of the Unit on Vulnerable Populations in the Department of Bioethics at the NIH Clinical Center. He is a philosopher trained in the philosophy of science and epistemology. His current work focuses on the ethics of research with individuals who are unable to give informed consent.