

SOUNDING BOARD

A Framework for Ethical Payment to Research Participants

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Payments to research participants are ubiquitous and are made for a variety of reasons, both to healthy volunteers and to volunteers who are patients.¹⁻³ Nevertheless, such payments continue to engender controversy, and the payment-related policies and practices of institutional review boards (IRBs) often reflect some discomfort with payment.^{4,5} The central ethical question is whether a payment is “excessive” — whether it conflicts with the obligation, recognized in the U.S. regulations governing human-subjects research and bioethical guidelines, to minimize the possibility of coercion and undue influence during the informed consent process.⁶ There is substantial disagreement and confusion among investigators, IRBs, sponsors, bioethicists, and research participants over what constitutes an excessive payment, as well as about how to define the concepts of coercion and undue influence.⁷⁻¹² As a result, no practical framework has been widely adopted to guide investigators and sponsors in developing offers of payment or to guide IRBs in evaluating their acceptability.

In this article, we set our approach to this problem in a practical framework. It reflects input from a working group that comprised ethicists, members of IRBs, investigators, regulators, research participants, and industry representatives, who together considered payments in publicly and privately funded research, at academic institutions and elsewhere, and in various phases of research. Although the views expressed here are those of the authors, they have been substantially informed and sharpened by insights from members of the working group. The Supplementary Appendix, available with the full text of this article at NEJM.org, contains more information about the composition of the working group and the scope of its involvement.

First, we identify and address foundational concerns that have been expressed about offers

of payment to research participants. We then propose and defend a framework that distinguishes three rationales for payment: reimbursement for out-of-pocket expenses, compensation for time and burdens associated with research participation, and incentive to motivate participation. Payments that fall into any of these three categories can be ethically acceptable, and indeed desirable, but each rationale involves different considerations.

 CONCERNS ABOUT PAYMENT
TO RESEARCH PARTICIPANTS

U.S. regulations governing human-subjects research do not explicitly mention payment, but they do enjoin IRBs to minimize the possibility of “coercion” and “undue influence” in the consent process, concepts that regulatory guidance, in turn, links to payment.⁶ The Office for Human Research Protections (OHRP), for example, states that “IRBs should be cautious that payments are not so high that they create an ‘undue influence’ or offer undue inducement that could compromise a prospective participant’s examination and evaluation of the risks or affect the voluntariness of his or her choices.”¹³ Likewise, Food and Drug Administration (FDA) guidance ties payment to both “coercion” and “undue influence” and suggests that payment might undermine consent.¹⁴ Thus, IRBs have both ethical and regulatory reasons to scrutinize offers of payment, but there is variability and persistent uncertainty about how the concepts ought to be applied.

DEFINITIONS OF COERCION AND UNDUE INFLUENCE

Although various definitions of coercion and undue influence have been advanced in the research ethics literature, coercion is best understood as referring to situations that involve a threat to

harm someone or violate a person's rights, whereas undue influence is best reserved for situations in which an offer of something desirable influences decision making in inappropriate ways.^{15,16} These definitions sharply distinguish coercion (a threat) from undue influence (a type of offer). Although the regulations themselves do not define these terms, these definitions are consistent with those advanced in the Belmont Report, the foundational ethics document that undergirds the U.S. regulations, and by the OHRP.^{17,18} Because offers of payment always involve an offer of something desirable (i.e., money), rather than a threat, by definition they cannot coerce. These conceptual definitions thus make it clear that only undue influence is relevant in connection with payment. However, offers of payment do not always result in undue influence. This raises the question of what circumstances would cause offers of payment to unduly influence a person's decision to participate in research and how great this risk would be.

IDENTIFICATION OF THE RISKS OF UNDUE INFLUENCE

Several concerns might be captured under the umbrella of undue influence. Our focus in this section is on the possibility that payment might undermine research participants' valid informed consent, though we also identify two other concerns: the risk that payment might induce deception among participants and the risk that payment might disproportionately attract participants of lower socioeconomic status. Here we limit our discussion to cases in which payment is made to competent adults for their own participation in research; we do not consider cases in which payment is made to a third party on behalf of a vulnerable person who cannot consent for himself or herself, such as when payment is offered to the parent of a participant in pediatric research. These situations merit additional scrutiny.

Embedded in the concept of undue influence is the corollary concept of due or appropriate influence. For example, when a person is entertaining several reasonable job offers, there is nothing wrong with one employer offering a substantially higher salary in order to attract the candidate. This would be an instance of unproblematic or "mere" influence, rather than ethically problematic undue influence. Similarly, in the research context, payment may appropriately

influence the decision to participate in IRB-approved research, a view substantiated by the OHRP's statement that "compensation may be an acceptable motive for agreeing to participate in research."¹³

Offers of payment become problematic, however, when the attractiveness of the offer causes participants to unreasonably discount or fail to appreciate risks related to research, which would threaten the validity of consent.¹³ Unfortunately, however, there is no bright line delimiting what is merely influential from what is unduly so; because people evaluate offers of payment differently, the line will be different for each person. It is also not clear that offers of payment do, in fact, distort decision making. The limited available data suggest that payment may actually increase caution and perception of risks among prospective participants.¹⁹⁻²¹ Further empirical evaluation of the effects of payment on participant comprehension and decision making would be particularly helpful.

One response to these concerns would be for IRBs to take additional steps to safeguard the informed-consent process — for example, by requiring assessments of participant comprehension — rather than limit payment offers as a first-line defense against undue influence. Although such practices are unlikely to eliminate concerns that payment would compromise consent, they might help mitigate these concerns and reassure IRBs that consent is voluntary and informed, particularly as payment amounts and the risks of research rise.

IRBs are required to determine that the offer of research participation is itself reasonable for the target population, on the basis of the risks posed to participants and the benefits that may accrue to them and to society more generally. However, it is important to note that the regulators instruct IRBs to make this determination without counting payment as a benefit to research participants. IRB approval — which is premised on the minimization of risks and the assurance that risks are reasonable in relation to benefits — is no substitute for valid informed consent. However, IRB approval can lower the stakes of any deficiencies in informed consent by making it less likely that a decision by an eligible participant to enroll in research could be characterized as unreasonable.^{11,22}

Two additional concerns are worth noting.

Box 1. Considerations for Investigators Proposing Payment Offers

- Clearly communicate the rationale for payment amounts to the IRB by itemizing payments according to the following categories: reimbursement for out-of-pocket expenses, compensation for time and burdens, or recruitment incentive. Include justification for specific amounts proposed.
- Focus first on treating participants fairly by reimbursing and compensating them for participation before assessing whether incentive payments are needed.
- Plan to reimburse participants for out-of-pocket expenses unless there are strong countervailing reasons against doing so.
- Consult with the IRB on what types of expenses and amounts the IRB considers reasonable for reimbursement.
- Consider compensating participants for their time commitment and the burdens they assume.
- Provide justification for why the compensation rate proposed should be considered fair, drawing analogies to nonresearch contexts such as employment.
- Propose payment as a recruitment incentive only when proposing to offer more than would be justified for reimbursement and compensation.
- When possible, offer options for insurance coverage for participants (or other mechanisms of financial protection) in order to compensate for reasonable expenses arising from research-related injury.
- When compensation or recruitment incentive is offered, consider increasing safeguards around participant comprehension and informed consent, particularly as payment amounts increase. Include measures to assess comprehension (e.g., having participants explain key aspects of research in their own words) as appropriate.

Box 2. Considerations for IRBs Reviewing Payment Offers

- Keep in mind the distinction between “mere” and “undue” influence and recognize that payment can be an acceptable motivation to participate in research.
- Consider whether additional emphasis on the consent process, such as mechanisms for ensuring comprehension, would address concerns that payment might distort judgment or voluntariness and thereby undermine informed consent in particular cases.
- Recognize the importance of a risk–benefit determination in protecting participants and ensure that concerns about payment do not reflect underlying discomfort with the risk–benefit ratio.
- Recognize the positive ethical reasons in favor of payment that are based on fairness to participants and the importance of trial completion, which makes possible generalizable knowledge.
- Encourage or require investigators to itemize payments according to the following categories: reimbursement for out-of-pocket expenses, compensation for time and burdens, or recruitment incentive, with appropriate justification for the amounts proposed.
- Permit investigators to reimburse participants for reasonable out-of-pocket expenses or a reasonable estimate thereof.
- Consider developing standard operating procedures on the types of expenses and amounts considered reasonable for reimbursement.
- When evaluating compensation for time and burdens, focus on what would be considered a fair wage for similarly burdensome and risky nonresearch endeavors, such as employment, in the particular locale. Note that if a compensation rate is fair, it should not raise concerns about undue influence.
- Encourage or require investigators to offer payment as a recruitment incentive only when they wish to offer more than would be reasonable and fair for reimbursement and compensation.
- Recognize the positive ethical reasons in favor of facilitating recruitment through the use of recruitment incentives.

First, the offer of payment might induce potential participants to deceive investigators about their eligibility for study participation, which

would raise concerns about the safety of the participant and about the scientific integrity of the research.^{23,24} The relation between payment and deception in research is another area that is in need of systematic empirical analysis. That said, it is likely that certain types of studies (such as phase 1 research with healthy volunteers) are more susceptible to deception than others. Given this, investigators should assess the risks of deception on a case-by-case basis; it would be overbroad to restrict payment in all cases on the basis of concerns about deception.

Second, offers of payment might disproportionately influence people of lower socioeconomic status to participate in research, which would raise concerns about unfair distribution of risks and burdens related to research. It may exacerbate economic injustice, however, to offer prospective research participants less because they are already impoverished. Instead, corrective measures, such as recruitment strategies that target wider populations and that better distribute risks and burdens across the population, should be sought. Similarly, it is important to ensure that the potential benefits of participation are distributed fairly, which may entail offering compensation to make participation feasible for more people. Ultimately, what matters and what should be sought is fair payment for participants, in accordance with the framework below.

A FRAMEWORK FOR DESIGNING
AND EVALUATING OFFERS OF PAYMENT

With this background, it is possible to provide a framework for designing and evaluating offers of payment.²⁵ The intent is to provide IRBs and investigators a practical tool to facilitate a transparent explanation of how offers of payment have been designed and why they are — or are not — reasonable. Summaries and points to consider are included in Boxes 1 and 2.

REIMBURSEMENT FOR OUT-OF-POCKET EXPENSES

Reimbursement for reasonable expenses incurred by research participants is generally acknowledged to be an ethically acceptable way to restore participants to their financial baseline before participation, thus rendering such payment both fair and appropriate. The guidelines of the Council for International Organizations of Medical Sciences (CIOMS), for example, state that

“participants should not have to pay for making a contribution to the social good of research.”²⁶ Expenses for which reimbursement is ethically appropriate may include reasonable costs of travel and parking, meals, accommodation, and childcare. When payment is categorized as reimbursement, rates should reflect true (or reasonably estimated) out-of-pocket costs. As long as this rule is observed, reimbursement does not constitute a net benefit to participants and thus cannot be unduly influential. Indeed, in response to inquiries from stakeholders about appropriate reimbursement practices, the FDA updated its information sheet on payment and reimbursement to research subjects in January 2018 to clarify that reimbursement of travel expenses and associated costs do not raise issues regarding undue influence.¹⁴

Although reimbursement is acceptable — indeed, desirable — it is not always strictly obligatory. Some participants may be willing to bear the costs of research participation for altruistic reasons. In addition, the presumption in favor of reimbursement can be overridden by study-specific considerations, such as cases in which research visits overlap with participants’ routine medical visits. The prospect of direct medical and ancillary benefits may also weaken the presumption in favor of financial reimbursement, since these nonmonetary benefits offer alternative ways to make participants “whole” (i.e., to balance any burdens or losses resulting from participation in research). Although it is generally fair and desirable to offer reimbursement, and we think that reimbursement should be the default expectation (and should be considered during the process of establishing study budgets), it may be ethically acceptable to proceed if there is no budget for reimbursement or if there are other ways to make the participant whole. However, given the importance of reimbursement, when it is not offered, investigators should explicitly justify that approach to the IRB.

COMPENSATION FOR TIME AND BURDENS

Payment may also be offered to compensate research participants for the fair value of their time, their willingness to accept research-related burdens, and their contributions to research. In this regard, research participation can be usefully equated with other activities that are compensated, such as employment, in which it is

widely accepted that treating people fairly and avoiding exploitation requires adequately recompensing people for their efforts; this is particularly true when those efforts contribute to socially valuable activities.²⁷ As with reimbursement, compensation for time and burdens is the ethical default, but there may be overriding considerations that can justify proceeding with the research even in the absence of compensation.

The analogy between employment and research endeavors supports a presumption in favor of similar compensation rates between them. When developing and evaluating offers of compensation, investigators and IRBs should consider what would constitute fair remuneration for analogously time-consuming and burdensome, albeit unskilled, employment. Compensation rates should be the same for all research participants and should reflect the general value of the time and burdens associated with study participation; they should not, for instance, be based on participants’ particular earning potential outside of research.²⁵ In short, there should be equal pay for research participants’ equal “work.”

In addition to research-related burdens, participants also accept research-related risks. Whereas burdens are foreseeable hardships associated with study participation (e.g., required blood drawings), risks may or may not materialize into real harms (e.g., bruising from blood drawings).²⁸ Regulatory guidance and ethics guidelines differ on whether the level of risk associated with a study is an appropriate basis for determining compensation rates. OHRP guidance states explicitly that although IRBs, when deciding whether to approve a study, may not consider payment to be a benefit that offsets risks, “[r]emuneration to subjects may include compensation for risks associated with their participation in research.”^{13,29} In contrast, CIOMS guidelines state that compensation should not be based on risks.²⁶

Because the main justification for offering compensation is fairness to research participants, it is important to recognize that this is better achieved by compensating participants if and when harms actually occur, either through appropriate insurance or other mechanisms, than by compensating for the possibility of harm (i.e., risk) before any harm materializes. Although an investigator may want to offer payment for a person’s willingness to accept the prospect of

risk as a type of incentive (of the kind discussed in the next section), doing so is not a requirement of justice. In contrast, when risks materialize into actual research-related injury, compensation is required as a matter of justice. Programs that provide such compensation have been widely recognized as essential to ethical research, even though such compensation is not currently required by U.S. research regulations.³⁰

INCENTIVES FOR PARTICIPATION

Whereas offers to reimburse and compensate participants are motivated by considerations of fairness, when payment is offered as an incentive, the goal is simply to improve recruitment and retention rates. Reimbursement and compensation may also provide incentives for participation, insofar as some people may not be willing to participate without them, but we use the term incentive to refer to payment beyond what would be justified for reimbursement and compensation.

Although we acknowledge that incentives are probably the most controversial category of payments, regulatory guidance recognizes incentives as legitimate in principle.¹⁴ Like reimbursement and compensation, incentives should be understood to have an ethical dimension, in that many studies do not meet recruitment targets and, as a result, are underpowered or are terminated early.^{31,32} This is problematic for a number of reasons, but a key issue is that IRB approval assumes that the study will answer its principal research question and will deliver socially valuable knowledge. Participants in studies that cannot answer the research question (or that answer it with compromised statistical power) are exposed to research-related risks for limited — or perhaps even no — offsetting social benefits. The problem of unsuccessful trial accrual probably requires multiple responses, including, perhaps, limiting or prioritizing research in thoughtful ways to ensure feasibility; however, one important component will be improving research participation rates among the public.³³ Higher offers of payment will probably help in this regard.^{34,35} Overall, we urge IRBs to recognize that it is appropriate to encourage people to enroll in studies that IRBs have approved as socially valuable and reasonable for participants, and offering incentives is one such way to do so.

CONCLUSIONS

Given the ambiguity in the bioethics literature and regulatory landscape, the design and evaluation of offers of payment to research participants can be challenging. The practical framework offered here could help reduce uncertainty and confusion around payments to research participants. Itemizing payments according to the proposed categories can give both investigators and IRBs a better understanding of the rationale for total payment amounts and make evaluating them more manageable. It can also help contextualize the practice and ultimately contribute to fair treatment of research participants and better stewardship of their contributions by facilitating timely completion of research.

The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic health care centers, or the National Institutes of Health.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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DOI: 10.1056/NEJMs1710591

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