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Evidence for the Ethics of Incentivizing Clinical Trial Enrollment?

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In clinical research ethics, using monetary incentives for clinical trial enrollment has been controversial. Proponents argue that such incentives can accelerate recruitment in socially beneficial clinical trials, address problems of diversity and external validity in research participation, and appropriately compensate participants for trial-related burdens. However, many institutional review boards have limited the use or magnitude of such incentives out of concern that they could unduly influence prospective participants or unjustly shift the burdens of research participation to people with lower income levels.[1] Yet empirical data are lacking on whether incentives have these purported positive (eg, facilitating enrollment) or negative (undue or unjust influence) effects.

In this issue of *JAMA Internal Medicine*, Halpern et al[2] report results from 2 embedded randomized clinical trials (RCTs) intended to provide empirical evidence to inform these ethical questions. Prospective participants in 2 parent RCTs, an ambulation intervention for hospitalized patients and a smoking cessation intervention for people with major depressive disorder, were first randomized to different enrollment conditions: no monetary incentive, a smaller incentive, and a larger incentive. Incentives increased the rate of consent to enrollment in the smoking cessation trial but not in the ambulation trial. The authors also evaluated whether inducement was undue or unjust, based on the magnitude of the interactions between incentive size and perceived research risk or self-reported income, respectively, on consent to enroll in the parent RCTs. The upper limit of the confidence intervals for the observed interactions excluded a prespecified noninferiority margin (an interaction odds ratio of 2.0), which the authors interpreted as being not compatible with the presence of undue or unjust inducement.

This work is welcome, as it presents experimental data to a bioethical debate that so far has been largely driven by conjecture and competing suppositions. The authors regard their study as having settled the practical and normative debate, concluding, “Thus, research regulators should relax restrictions on the use of incentives designed to improve enrollment in low-risk trials.”[2] However, interpreting the authors’ findings is complex and illustrates some of the challenges inherent to applying empirical data to ethical problems.

An initial challenge is at the level of definitions. Among bioethicists, there is no consensus about what counts as undue inducement or an unjust distribution of research burdens. In this article,[2] the authors have operationalized these constructs based on their own interpretations of undue and unjust inducement, which may not capture all the concerns that scholars have raised about inducement. For example, other experts have argued that undue inducement exists when incentives are great enough to distort participants’ perception of research-related risk,[3] while

Halpern et al[2] interpret undue inducement as a change in the influence of perceived risk on decisions to enroll.

Other challenges are related to the authors' use of a noninferiority design, which may be unfamiliar to many bioethicists and can place substantial evaluative demands on readers.[4] In typical superiority analyses, researchers evaluate whether we can reject a null hypothesis that no difference between 2 conditions exists, which would be taken to show that a difference does exist. But in this case, the authors sought to affirm that undue or unjust inducement was not present. So they applied a noninferiority design testing a null hypothesis that undue or unjust inducement was present and interpreted the rejection of this null as showing that undue or unjust inducement was not present.

A problem is that noninferiority designs do not show that there is no difference between conditions. Instead, they help to evaluate whether one condition is not worse than another by more than some acceptably small margin. The choice of this noninferiority margin is crucial: choosing too large a noninferiority margin can increase the risk of falsely claiming noninferiority. The authors note that there was no evidence to guide the choice of a noninferiority margin of 2.0 for the odds ratio of the interaction term. But the main problem is not missing evidence, but a question for ethical argument: what extent of effect modification should we consider to be acceptably small? The authors' choice implies that undue inducement would be present if enrollment decreased from 40% to 25% with high risk perception in the no-incentive condition yet remained at 40% throughout in the incentive condition, but would not be present if enrollment had decreased from 40% to 26% with high risk perception in the no-incentive condition. To conclude that these results are not compatible with undue or unjust inducement depends on a particular threshold of how much inducement counts as undue or unjust, which is itself subject to ethical disagreement and argument.

Thus, the work of Halpern et al[2] illustrates that translating evidence to ethical guidance is not straightforward. Most ethical debates will not be conclusively resolved even by the best-designed experiment, but such debates can be clarified and reinvigorated by solid empirical findings. For instance, given the potential benefits of monetary incentives for clinical research participation, those who would limit their application may owe us an applicable criterion for what makes an inducement undue or unjust. Presumably, exorbitant incentives or incentives specifically targeted at vulnerabilities for the most underserved could qualify, but it seems less likely for the $100 to $500 range of incentives considered in this trial.

More research would also be helpful to understand when incentives are scientifically beneficial (eg, why incentives improved enrollment in a trial of smoking cessation but not in a trial of ambulation). We welcome further work to improve the evidence base for bioethical discourse and carefully address how experimental evidence can be applied to the ethical conduct of clinical research.

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