The Journal of Infectious Diseases

REVIEW

Paying Participants in COVID-19 Trials

Emily A. Largent and Holly Fernandez Lynch

Department of Medical Ethics and Health Policy, Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania, USA, and Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, Pennsylvania, USA

Trials are in development and underway to examine potential interventions for treatment and prophylaxis of coronavirus disease 2019 (COVID-19). How should we think about offering payment to participants in these trials? Payment for research participation is ethically contentious even under ideal circumstances. Here, we review 3 functions of research payment—reimbursement, compensation, and incentive—and identify heightened and novel ethical concerns in the context of a global pandemic. We argue that COVID-19 trial participants should usually be offered reimbursement for research-related expenses, and compensation for their time and effort, as for other types of research under usual circumstances. Given increased risk of undue influence against pandemic background conditions, incentive payment should be avoided unless essential to recruitment and retention in important trials whose social value outweighs this risk. Where essential, however, incentives can be ethically permissible, so long as reasonable efforts are made to minimize the possibility of undue influence.

Keywords. research ethics; payment; undue influence; informed consent; COVID.

With much of the globe rushing to respond to coronavirus disease 2019 (COVID-19), clinical trials to evaluate safe and effective options for treatment and prevention are critical. The trials are diverse, examining new and repurposed drugs and vaccines at various stages of development, and involving a variety of designs with a range of opportunity for direct benefit. A wide variety and number of research participants are needed to enroll in these trials, reflecting a spectrum of experience with COVID-19—including healthy individuals, individuals exposed to the virus, individuals experiencing different levels of disease severity, and recovered individuals—as well a diversity of age, sex, race and ethnicity, socioeconomic status, medical comorbidities, and more.

We have already seen that many individuals are eager to try nearly anything that has exhibited some promise against this disease, which may facilitate trial recruitment [1]. But what role will payment play in encouraging trial participation—and what role should it play? Paying research participants is ethically contentious under ideal circumstances and pandemic circumstances are far from ideal. Concerns about offering payment are therefore likely to be heightened in this context [2].

Existing frameworks for evaluating the ethics of paying research participants offer a strong foundation for assessing the acceptability of payment in COVID-19 trials. Nonetheless, consideration must be given to the unique medical, financial, and institutional circumstances wrought by the pandemic. We argue that participants in COVID-19 trials should be offered reimbursement for research-related expenses and compensated for their time and effort, just as they should be for any other type of trial. Given the pandemic's devastating economic effects, as well as the fact that risks may be higher or more uncertain in COVID-19 trials than in nonpandemic research, there is an increased likelihood of undue influence stemming from incentive payments. Still, it may be permissible to offer incentives when necessary to recruit and retain participants for important trials offering the possibility of social value sufficient to outweigh these concerns, so long as steps are taken to minimize the risk that participants will be unduly influenced.

OFFERS OF PAYMENT

Paying research participants serves several discrete functions [3]. First, participants may be reimbursed for out-of-pocket expenses incurred as a result of research participation, such as copayments or travel costs. Second, payment can compensate participants for the fair value of their time and effort expended in research participation. Third, incentive payments go beyond what is necessary to either reimburse or compensate, with the intention of improving recruitment or retention. Offers of payment that fall into any of these categories can be ethically acceptable; however, each function raises distinct ethical considerations influenced by the pandemic.

Reimbursement

Offering reimbursement for reasonable, research-related expenses to restore participants to their financial baseline should be viewed as the ethical default in COVID-19 trials, as in research more broadly. This treats participants fairly by preventing

Received 13 April 2020; editorial decision 20 May 2020; accepted 22 May 2020; published online May 29, 2020.

Correspondence: Emily A. Largent, JD, PhD, RN, Department of Medical Ethics and Health Policy, University of Pennsylvania, 423 Guardian Drive, Philadelphia, PA 19104 (elargent@pennmedicine.upenn.edu).

The Journal of Infectious Diseases® 2020;XX:1–6

DOI: 10.1093/infdis/jiaa284

them from having to pay to contribute to socially valuable research that may not, or is not expected to, benefit them directly. Where direct benefit is possible, covering expenses can also promote distributive justice by making those potential benefits more widely accessible without regard to participants' financial need or wealth [4]. Considering that a high percentage of the population is likely to be infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the current absence of curative therapies or a vaccine, and the widespread financial hardship and exacerbation of economic disparities caused by the pandemic, COVID-19 trial participation must not be limited only to those who can afford it. Making participation widely accessible is especially important in light of the disproportionate impact this virus is having on minority communities [5, 6]. While there are of course many barriers to trial participation, financial barriers are among the most easily modified [7].

Although reimbursement should be the rule, there will be exceptional circumstances when it can be ethically acceptable to proceed without it. In the context of COVID-19, for example, investigators and institutions may be initiating trials without traditional sources of public research funding or with only limited support, such as the provision of product, by commercial companies. In these instances, there may not be adequate funding to reimburse participants. Lack of funding should not preclude important trials from proceeding, so long as participants are made aware of the financial implications of enrollment and reasonable efforts are made to minimize financial burden. If a limited budget is available for reimbursement, it may be acceptable to reimburse only select participants—such as those with the greatest financial need—or to cover expenses up to a prespecified limit without necessarily reimbursing them all [8].

Compensation

Compensation also should be viewed as the ethical default because it helps to minimize the chance participants will be exploited by receiving benefits that are disproportionately low compared to the burdens they undertake and the value they contribute to research. While the prospect of direct benefit is relevant to avoiding exploitation, research benefits are not always present and are never certain. Thus, it often makes sense to compensate participants for their work via a wage-payment model, using a fair local wage for similarly burdensome nonresearch endeavors as a benchmark [9, 10]. This is not intended to make participants better off as compared to their financial baseline or even to fully compensate for participants' opportunity costs but rather to acknowledge the value of their time and effort. Compensation can also help distinguish research activities, with their distinct goals and risks, from clinical care, signaling that participants are contributing to science and that individual benefit may not result from their research participation [11]. This is likely to be particularly important for COVID-19 patients, because the dearth of compelling treatment options means that clinical care will often incorporate experimental methods and research. Nevertheless, it may be ethically acceptable to proceed without compensation when reasonable budget constraints preclude it, as above.

When compensation is offered, 2 ethical concerns can arise, which sometimes point in opposite directions. First, if the amount is unfairly low, it will not adequately address the possibility of exploitation; this concern can be addressed by offering more compensation. Yet, relatively higher compensation may be linked to a second concern, which arises when circumstances extrinsic to a trial transform payments intended as compensation into de facto incentives. This is especially likely in the context of COVID-19.

Compensation is intended to render research participation as financially attractive as other, nonresearch opportunities that demand a similar amount of time, burden, and skill. However, the availability and type of those nonresearch opportunities can be impacted by a variety of factors. Even for those who have remained healthy, the COVID-19 pandemic is causing a human tragedy with significant economic impact, including widespread layoffs, small business closures, hiring freezes, and dramatic market fluctuations [12]. These challenges have exacerbated longstanding economic inequalities and laid bare the fragility and inadequacy of the social safety net in many countries, including the United States. These economic and social challenges are only likely to increase as the pandemic continues. Against this backdrop, many prospective COVID-19 research participants will no longer have meaningful alternatives for paid work, which may contribute to a perception—and perhaps reality—that paid research participation is their best opportunity to make money. This perception may be heightened if compensation is increased to the extent necessary to avoid exploitation, even if the total amount of money remains relatively modest.

These difficult background circumstances do not make offers of payment to COVID-19 research participants impermissible. It would be perverse to withhold fair compensation simply because participants are facing economic hardship [13]. Rather, in light of pandemic circumstances—similar features of which may be replicated in other contexts, including research conducted in low- and middle-income countries or with participants whose nonresearch options are limited even in the absence of a pandemic—offers of compensation may raise ethical concerns akin to incentives [14]. Thus, institutional review boards (IRBs) should consider whether it is sometimes appropriate to treat them as such.

Incentives

Rather than aiming to satisfy obligations of fairness to participants or to set research on a par with other payment-generating activities, incentives aim to push trial enrollment higher on an individual's choice set—or incidentally have that effect based

on available alternatives. As such, incentives are not ethically obligatory. However, to the extent incentives can contribute to recruitment and retention, and thus to efficient trial completion with adequate statistical power, they can be ethically important [15]. Incentives may also advance distributive justice by increasing willingness to enroll, thereby spreading the burdens of research participation over a larger swath of the population and avoiding concentrating those burdens exclusively on individuals who are the least well off financially by making research more broadly attractive. Yet, incentives can be ethically fraught.

Some people worry that incentives may coerce research participants. The prevailing view is that coercion entails a threat to violate an individual's rights or not fulfill an obligation to her unless she complies with some request, in a circumstance in which she has no reasonable alternative but to comply [16]. By this definition, genuine offers of payment are not coercive because they are not threats [17]. Importantly, feeling that there is no reasonable alternative to make a similar amount of money—a feeling likely to arise for at least some prospective COVID-19 trial participants—is not the same as being coerced.

A more salient ethical concern is that incentives may unduly influence participants, although this is more complex than just making a decision motivated by a desire for financial benefit. Undue influence occurs when an excessive reward leads the recipient to make a choice that is *unreasonably* against her self-defined values, interests, or responsibilities [16, 18].

A decision would be *objectively* unreasonable if it reflected a level of risk an IRB would not or should not approve for participants in the target population. For example, it would be objectively unreasonable for persons with a known hypersensitivity to hydroxychloroquine to participate in a trial assessing that drug's effect on the progression of COVID-19 [19]. Approval of a trial protocol by a well-functioning IRB should generally eliminate concerns that incentives will lead to objectively unreasonable decisions.

In contrast, research participation may be *subjectively* unreasonable if it is discordant with an individual's particular values and interests or if the risks (should they materialize) would be particularly burdensome for the individual to bear [20]. Because IRBs are tasked with making population-level judgments, they cannot be expected to assess the subjective reasonableness of trial participation for every individual. Thus, IRB review cannot eliminate the possibility that that incentives will lead to subjectively unreasonable decisions—and, therefore, to undue influence. For instance, a Jehovah's Witness considering participation in a trial of intravenous immunoglobulin—a blood plasma product—for COVID-19 might have conscience-based concerns. Similarly, someone who is highly risk-averse may prefer to avoid the uncertainties associated with research participation. Either of these individuals could be encouraged by offers of incentive payment to set aside those concerns.

While this may seem worrisome, in practice, it is quite hard to distinguish between cases in which an offer of payment has unproblematically tipped the balance in favor of an otherwise undesirable but not unreasonable choice and those in which it has problematically tipped the balance in favor of an unreasonable or irrational choice. In many cases, a decision to enroll in research will reflect a participant's reasoned judgment that, in these circumstances, participation is aligned with her overall interests, even if certain considerations might have weighed in the other direction. Decisions are often multifactorial, with various pros and cons; the fact that all cons have not been resolved does not necessarily render a decision subjectively unreasonable.

Acknowledging this challenge, the best IRBs can do is to minimize the possibility of undue influence for trial participants *on the whole* by making it unlikely for research participation to constitute an objectively unreasonable choice for members of the target study population. They should also make sure the consent process alerts participants to factors that might make participation subjectively unreasonable [20].

Although careful IRB review generally constitutes a critical bulwark against undue influence, there are additional considerations when evaluating the potential for undue influence in COVID-19 trials. First, given that there is still much to be learned about SARS-CoV-2 and so little is known about the various interventions under study in this context, we may justifiably be concerned that it will be difficult for IRBs to make risk-benefit determinations confidently. Therefore, participation even in IRB-approved studies may not always be truly objectively reasonable for the target study population, or there may be disagreement about what is objectively reasonable. Moreover, the challenge of evaluating this research may be exacerbated by the heightened burdens currently facing IRBs. The sheer volume of COVID-19 research proposals being put forward [21] and the dire need for clinical advancement mean that members are being asked to review a tremendous number of protocols as quickly as possible, often while meeting remotely to promote social distancing, all of which may influence the quality and nature of review.

Second, the global scale of the pandemic and associated morbidity and mortality may render even quite risky research objectively reasonable on the basis of high social value. For example, we have already seen vaccine trials proceed without the usual animal trials, and there is increasing discussion of using challenge trial design to speed vaccine development, a design far riskier for SARS-CoV-2 than for viruses used in other recent challenge trials given the lack of a proven cure [22–25]. It is widely accepted that trials can be justified on the basis of benefits to society; in the absence of direct benefits, it may be desirable to offer larger incentive payments similar to hazard pay offered to emergency workers or others performing dangerous work—as noted above, this can help make participation

attractive across a wider socioeconomic swath [26]. Yet, larger incentives might also increase the likelihood of undue influence by making it more likely that people will make subjectively unreasonable decisions [20].

A third concern is that incentives, because they go beyond amounts available through participating in other activities, may cause individuals "to lie, deceive, or conceal information that, if known, would disqualify them as participants in a research project" [27]. Such obfuscation can have 2 effects [20, 28]. First, it may expose individuals to research-related risks that exclusion criteria were designed to shield them from. Second, it may jeopardize the scientific integrity of the research. This can be of particular concern when it is not possible to rely on objective, independently verifiable measures to confirm trial eligibility [29].

In response to these challenges, one might consider the most conservative course of blocking incentives for COVID-19 trials. However, this approach could inhibit recruitment, retention, or both, impeding the conduct of critically important research, in turn creating a greater possibility that participants will be exposed to research risks without realizing the social benefits that initially justified them. There are 2 potential errors here: (1) inhibiting ethically acceptable trials out of an abundance of caution, or (2) risking undue influence and deception by incentivizing participation in COVID-19 trials [30]. Given the importance of research in response to the pandemic, as well as limited, albeit encouraging, empirical data suggesting that higher offers of payment increase participants' perceived risk as well as time spent reviewing research-related risks [11, 31–33], our view is that incentive payments can be ethically permissible, despite the residual risk of undue influence and deception.

Rather than blocking incentives for COVID-19 trials due to the concerns raised above, the better approach is to differentiate those circumstances in which incentive payments are truly essential to boost recruitment and retention for important research. If they are not, as may be the case for COVID-19 research that offers participants other benefits or that can rely on altruism born of social solidarity, it is best to avoid incentive payments. This is also the more efficient approach; why spend resources on incentives that are unneeded?

However, incentives sometimes will be critical. For example, COVID-19 trials that offer no or low potential for direct benefit and impose substantial burdens and risks, such as early phase trials focused on dosing and safety, may otherwise fail to adequately enroll participants. Of course, the fact that participants may have qualms about participating that need to be overcome by offering incentives might suggest that concerns about undue influence are highest in these circumstances. Yet these are also the COVID-19 trials for which IRB attention is likely to be most intense and focused, potentially reducing concerns about objectively unreasonable decisions to enroll. Risks of subjectively unreasonable decisions remain, but should be viewed in a similar context to other research risks, meaning that they can be justified when both minimized and reasonable in relation a study's potential for benefit.

Thus, incentives should be limited to COVID-19 trials with adequate time and research personnel to facilitate robust informed consent processes that can help prospective participants carefully consider the risks, burdens, and discomforts of participation, as well as those that can adopt objective measures of eligibility and adherence. They should also be limited to those trials with sufficient importance to the battle against COVID-19 that their potential benefits can overcome residual concerns about undue influence. Relatedly, care should be taken to avoid incentive payments being used to draw participants into lower priority trials [34]. IRBs are tasked with minimizing—not eliminating—the possibility of undue influence; we should accept that minimization may look different for COVID-19 trials compared to other research.

CONCLUSION

Offering payment for trial participation intended to combat a pandemic that is coupled with economic distress raises unique considerations. We argue that reimbursement and compensation should be offered in COVID-19 trials as a matter of fairness, as is true for other types of clinical research. Yet the economic stressors of the pandemic may cause compensation to be experienced as an incentive, raising concerns about undue influence, while the usual protections against undue influence may also be weakened by pandemic circumstances. Rather than abandoning the utility of incentives, we recommend that they be limited to those COVID-19 trials that truly need them, that will permit undue influence to be minimized, and whose social value and importance can outweigh residual risks of undue influence. This suggests that financial incentives will be most appropriate for COVID-19 trials without the prospect of direct benefit, although in the face of such a massive global threat, altruism and a call to duty may render incentives even less critical.

Notes

Potential conflicts of interest. H. F. L. receives research funding from the Greenwall Foundation; received travel costs and honorarium for a lecture to WCG Clinical in 2017; and consulting fees from Hueston Hennigan in 2019 on matters related to research compliance. E. L. reports no potential conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Silverman E. Hospital orders for old malaria drugs have spiked amid coronavirus pandemic. STAT, **24** March **2020**. https://www.statnews.com/pharmalot/2020/03/24/hospitals-covid19-coronavirus-shortages-malaria/?utm_source=STAT+Newsletters&utm_campaign=ab32187c22-Pharmalot&utm_medium=email&utm_term=0_8cab1d7961-ab32187c22-150575837. Accessed 1 June 2020.
2. Larson GS, Baseler BR, Hoover ML, et al. Conventional wisdom versus actual outcomes: challenges in the conduct of an Ebola vaccine trial in Liberia during the international public health emergency. Am J Trop Med Hyg **2017**; 97:10–5.
3. Gelinas L, Largent EA, Cohen IG, Kornetsky S, Bierer BE, Fernandez Lynch H. A framework for ethical payment to research participants. N Engl J Med **2018**; 378:766–71.
4. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA **2000**; 283:2701–11.
5. Yancy CW. COVID-19 and African Americans. JAMA **2020**; 323:1891–2.
6. Kirby T. Evidence mounts on the disproportionate effect of COVID-19 on ethnic minorities [published online ahead of print 8 May 2020]. Lancet Respir Med doi:10.1016/S2213-2600(20)30228-9.
7. Largent EA, Lynch HF. Addressing financial barriers to enrollment in clinical trials. JAMA Oncol **2018**; 4:913–4.
8. Persad G, Fernandez Lynch H, Largent E. Differential payment to research participants in the same study: an ethical analysis. J Med Ethics **2019**; 45:318–22.
9. Dickert N, Grady C. What's the price of a research subject? Approaches to payment for research participation. N Engl J Med **1999**; 341:198–203.
10. Lynch HF. Human research subjects as human research workers. Yale J Health Policy Law Ethics **2014**; 14:122–93.
11. Cryder CE, John London A, Volpp KG, Loewenstein G. Informative inducement: study payment as a signal of risk. Soc Sci Med **2010**; 70:455–64.
12. Krizinger A, Kearney A, Hamel L, Brodie M. KFF health tracking poll - early April 2020: the impact of coronavirus on life in America. Kaiser Family Foundation, **2** April **2020**. https://www.kff.org/other/poll-finding/kff-health-tracking-poll-early-april-2020/. Accessed 1 June 2020.
13. Gelinas L, White SA, Bierer BE. Economic vulnerability and payment for research participation. Clin Trials **2020**; 17:264–72.
14. Alenichev A, Nguyen VK. Precarity, clinical labour and graduation from Ebola clinical research in West Africa. Glob Bioeth **2019**; 30:1–18.
15. Halpern SD, Karlawish JH, Berlin JA. The continuing unethical conduct of underpowered clinical trials. JAMA **2002**; 288:358–62.
16. Largent EA, Fernandez Lynch H. Paying research participants: regulatory uncertainty, conceptual confusion, and a path forward. Yale J Health Policy Law Ethics **2017**; 17:61–141.
17. Wertheimer A, Miller FG. Payment for research participation: a coercive offer? J Med Ethics **2008**; 34:389–92.
18. Emanuel EJ. Undue inducement: nonsense on stilts? Am J Bioeth **2005**; 5:9–13; discussion W8–11, W17.
19. Sanofi. Hydroxychloroquine in outpatient adults with COVID-19. ClinicalTrials.gov, **2020**. https://clinicaltrials.gov/ct2/show/NCT04333654. Accessed 1 June 2020.
20. Largent EA, Lynch HF. Paying research participants: the outsized influence of "undue influence". IRB **2017**; 39:1–9.
21. Thorlund K, Dron L, Park J, Hsu G, Forrest JI, Mills EJ. A real-time dashboard of clinical trials for COVID-19 [published online ahead of print 24 April 2020]. Lancet Digit Health doi: 10.1016/S2589-7500(20)30086-8.
22. Boodman E. Researchers rush to test coronavirus vaccine in people without knowing how well it works in animals. STAT, **11** March **2020**. https://www.statnews.com/2020/03/11/researchers-rush-to-start-moderna-coronavirus-vaccine-trial-without-usual-animal-testing/. Accessed 1 June 2020.
23. Eyal N, Lipsitch M, Smith PG. Human challenge studies to accelerate coronavirus vaccine licensure. J Infect Dis **2020**; 221:1752–6.
24. Shah SK. Ethical considerations for Zika virus human challenge trials. February **2017**. https://www.niaid.nih.gov/sites/default/files/EthicsZikaHumanChallengeStudiesReport2017.pdf. Accessed 1 June 2020.
25. Shah SK, Miller FG, Darton TC, et al. Ethics of controlled human infection to address COVID-19. Science **2020**; 368:832–4.
26. Anomaly J, Savulescu J. Compensation for cures: why we should pay a premium for participation in 'challenge studies.' Bioethics **2019**; 33:792–7.
27. Macklin R. On paying money to research subjects: 'due' and 'undue' inducements. IRB **1981**; 3:1–6.
28. Fernandez Lynch H, Joffe S, Thirumurthy H, Xie D, Largent EA. Association between financial incentives and participant deception about study eligibility. JAMA Netw Open **2019**; 2:e187355.
29. Kraft SA, Duenas DM, Kublin JG, Shipman KJ, Murphy SC, Shah SK. Exploring ethical concerns about human challenge studies: a qualitative study of controlled human malaria infection study participants' motivations and attitudes. J Empir Res Hum Res Ethics **2019**; 14:49–60.
30. Largent EA, Fernandez Lynch H. Making the case for completion bonuses in clinical trials. Clin Trials **2019**; 16:176–82.
31. Halpern SD, Karlawish JH, Casarett D, Berlin JA, Asch DA. Empirical assessment of whether moderate

payments are undue or unjust inducements for participation in clinical trials. Arch Intern Med **2004**; 164:801–3.
32. Slomka J, McCurdy S, Ratliff EA, Timpson S, Williams ML. Perceptions of financial payment for research participation among African-American drug users in HIV studies. J Gen Intern Med **2007**; 22:1403–9.
33. Bentley JP, Thacker PG. The influence of risk and monetary payment on the research participation decision making process. J Med Ethics **2004**; 30:293–8.
34. Gelinas L, Lynch HF, Bierer BE, Cohen IG. When clinical trials compete: prioritising study recruitment. J Med Ethics **2017**; 43:803–9.