Payment of COVID-19 challenge trials: underpayment is a bigger worry than overpayment

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One way to test vaccines is through human challenge trials in which participants are intentionally infected with a contagious organism to expedite the process of assessing the vaccine's effectiveness. Some experts believe challenge trials may play an important role in fighting COVID-19, especially if the vaccines under current study do not demonstrate sufficient efficacy, if spread of COVID-19 is controlled to a point that radically slows down traditional trials, or if new vaccines need to be rapidly developed for specific subpopulations.[1]

Challenge trials involve significant time, burden and risk, requiring participants to spend 3–6 weeks in legal quarantine for 24 hours a day in a high-security facility. During this time, no inperson visitors will be allowed, except for very limited inperson contact from researchers collecting necessary data and checks. Following the quarantine period, participants will be asked to attend numerous outpatient follow-up visits over the course of months, to further monitor their response to the vaccine. Participation involves being away from family who may themselves become sick during the global pandemic, as well as potential fear and mental anguish around being a 'first' subject. Because there is no definitive treatment for COVID-19, participants could experience serious illness. But even with milder illness, medical experts know very little about the long-term consequences of COVID-19 infection.

This raises the question of how much people should be paid for their participation in COVID-19 challenge trials. Most think participants should be paid something, but many contend that we should be cautious about incentivising people with large amounts of money.[2–4] In short, they are concerned about overpayment of research participants. Grimwade *et al* have the opposite concern—that researchers will underpay challenge trial participants. We agree.

Grimwade *et al*'s survey of investigators involved in 25 challenge trials for diseases other than COVID-19 found that the maximum payment offered was $4446 and the average amount was $1770, with an average hourly payment of $13.77.[5] Among the investigators surveyed, 84% believed that the amount their trial paid was appropriate—only 16% believed the amount was too low. While that amount is more than the US current federal minimum wage ($7.25/hour), it is less than the suggested fair minimum wage of $15/hour. Even more concerning, it fails to account for the extra risks and burdens of COVID-19 challenge trial participation that go beyond a typical minimum wage job. Hazard pay for exposure to virulent biologicals is recommended to be 25% extra on top of base pay, for example. And that extra 25%, if provided, does not even account for the burdens associated with challenge trial participation—only the hazards. In sum, these data raise significant concerns about underpayment, exploitation and unfair treatment of challenge trial participants.

Grimwade *et al* argue that participants should be offered higher payment that accounts for participant time, and for pains, burdens and willingness to take risk. They also recognise and respond to several arguments against higher payment, including the most common concern of undue inducement. Undue inducement occurs when people do not pay full attention to the risks and benefits of research participation because they are myopically focused on the money. We agree with Grimwade *et al* and others[6] that the remedy for making sure people pay attention to the risks of research participation is not to pay them less; it is to strengthen informed consent processes and for institutional review boards (IRBs) to take steps to make sure that risks associated with research participation are minimised as much as possible. There are, however, two additional ethical concerns associated with high payment that Grimwade *et al* do not discuss: unjust inducement and crowding out of altruism. Below, we address both of these concerns to further bolster Grimwade *et al*'s defence of higher payment.

Some think that even if undue influence can be avoided, larger compensation amounts might be more attractive to those who have lower incomes and/or who have lost work during the pandemic. This is essentially a concern about justice—that the risks and burdens of challenge trials will disproportionately fall on already disadvantaged groups. Some have called this 'unjust inducement'. In response to this concern, there is little evidence to support the hypothesis that paying people more for research participation will result in the disproportionate enrolment of low-income populations. In fact, research supports the opposite—higher payment strongly influences wealthy people's willingness to participate.[7] In the context of COVID-19 in particular, it is worth nothing that over 30 000 participants from 140 countries have indicated a willingness to participate in challenge trials on 1DaySooner. Examples include nurses, scientists, parents, journalists, historians, members of the armed forces. While we do not know details about these potential participants' vulnerabilities and incomes, they come from all walks of life. Furthermore, recruitment for challenge trials could be designed to ensure diversity in enrolment so that one group (such as one income strata) does not bear significantly more risk or burden than others. Early challenge trials will be relatively small with 5–25 participants, so monitoring this will be easier, and doing so is important for public trust.

Another ethical concern some might have is that offering substantial payment waters down the altruistic motives of those involved. Of the more than 30 000 people who have indicated their hypothetical willingness to volunteer for COVID-19 challenge trials, the main motivation expressed is altruism. That is truly admirable. But altruism and payment frequently coexist. Teachers, physicians, public defenders—they all dedicate their lives to helping people, but few do that without compensation. Some, in fact, do it with quite generous compensation. Participants who do not want money to muddy the water could elect to donate the money they receive for participation to fund future COVID-19 research or recovery

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measures. In short, payment need not cancel out the presence of altruism in participants.

Instead of asking whether generous payment for challenge trials is ethically inappropriate, consider another question. Once an IRB determines a research study poses an acceptable ratio of potential risks and benefits, and has determined that informed consent processes are in place to help potential participants understand those risks and benefits, how is anyone participating in the trial made better off by receiving less money, rather than more? What harm is done when someone, otherwise hesitant to expose themselves to these acceptable risks and burdens, chooses to participate in the trial because of generous reimbursement? Given the potential burdens and risks accompanying challenge trials, we shouldn't worry about whether we are overpaying people for their participation. We should concern ourselves about whether we are underpaying them. In this respect, we may go a bit further than Grimwade *et al*. While they are concerned with underpayment, they do hint that some amount would be 'too much'. We do not share that concern.

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