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Promoting Ethical Payment in Human Infection Challenge Studies

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Abstract:

To prepare for potential human infection challenge studies (HICS) involving SARS-CoV-2, we convened a multidisciplinary working group to address ethical questions regarding whether and how much SARS-CoV-2 HICS participants should be paid. Because the goals of paying HICS participants, as well as the relevant ethical concerns, are the same as those arising for other types of clinical research, the same basic framework for ethical payment can apply. This framework divides payment into reimbursement, compensation, and incentives, focusing on fairness and promoting adequate recruitment and retention as counterweights to concerns about undue inducement. Within the basic framework, several factors are especially salient for HICS, and for SARS-CoV-2 HICS in particular, including the nature of participant confinement, anticipated discomfort, risks and uncertainty, participant motivations, and trust. These factors are reflected in a payment worksheet created to help sponsors, researchers, and ethics reviewers systematically develop and assess ethically justifiable payment amounts.

Key words: challenge study, SARS-CoV-2, COVID-19, payment

Promoting Ethical Payment in Human Infection Challenge Studies

Safe and effective vaccines are widely viewed as the most likely means of curtailing morbidity and mortality due to COVID-19, especially given fatigue around social distancing and avoidance of public gatherings. In November 2020, early analysis of results for Pfizer's investigational mRNA vaccine showed 90% efficacy in preventing symptomatic COVID-19, although questions remain about durability of protection, efficacy against severe disease, and impact on viral transmission (Herper 2020); several other vaccine candidates are expected to complete Phase 3 studies before the end of the year (Garde 2020). Despite unprecedented speed in conducting this research (Joseph 2020), interest in SARS-CoV-2 human infection challenge studies (HICS) remains significant given open questions about vaccine efficacy, immune response, and viral-host interactions, among others.

Much of the discussion about HICS to combat COVID-19 has centered on whether trials that would intentionally infect healthy individuals with a pathogen for which we lack a proven cure could meet basic ethical requirements regarding risk and social value (Bull et al. 2020; Dawson et al. 2020; Eyal et al. 2020; Eyal 2020; Kahn et al. 2020; Shah et al. 2020a; Shah et al. 2020b; Singer and Martinez 2020; WHO Working Group 2020). Yet even skeptics have acknowledged that changed circumstances could alter the ethical equation. For example, the studies could become less risky as a result of the development of new curative therapies for COVID-19 or through a better understanding of how to confidently select lower-risk populations. They could also become more socially valuable. Several vaccines will be needed to fully combat the virus in different populations and settings, but there are growing concerns that if the U.S. Food and Drug Administration (FDA) grants emergency use authorization (EUA) to any COVID-19 vaccine, it could make continuation of large-scale blinded, randomized trials more difficult, especially for products that have not yet reached Phase 3 (Cohen 2020; Owermohle 2020). Therefore, in addition to learning more about the virus itself, SARS-CoV-2 HICS could have utility in continuing to narrow the field of vaccines worthy of further study and allowing direct comparison of efficacy between vaccine types and formulations should traditional trials become more difficult in the face of an EUA or a decline in natural infections to levels that make field

trials implausible (Nguyen et al. 2020). Despite continued debate about whether SARS-CoV-2 HICS should proceed, scientific, regulatory, financial, and ethical preparations for them have already begun.

As part of those preparations, in July 2020, 1Day Sooner – an organization working to advance the use of HICS in response to the COVID-19 pandemic – sought independent, expert guidance as to whether and how much SARS-CoV-2 HICS participants should be paid, as well as insight on the broader matter of ethical payment in HICS and how it should be considered in relation to payment for other types of research participation. At 1Day Sooner's behest, we convened a multidisciplinary working group composed of HICS researchers and prospective SARS-CoV-2 HICS participants, ethicists, attorneys, and economists to address these questions. Our group took no position regarding whether relevant ethical standards for SARS-CoV-2 HICS were satisfied at that time, nor do we take any such position now, but we assume that these studies could be deemed ethical in various plausible scenarios, since the alternative would render questions about payment moot. Given the extensive scrutiny likely to accompany any SARS-CoV-2 HICS, our goal was to offer a clear and defensible approach to payment to inform researchers, sponsors, ethics review committees, participants, and the public. However, we acknowledge that our expertise and perspectives are limited to the Global North and that additional considerations may be relevant when research is conducted elsewhere in the world.

Our working group released a report in August 2020, with 52 distinct recommendations regarding ethical payment, the key points of which are highlighted here (Fernandez Lynch et al. 2020). Since then, the question of payment for SARS-CoV-2 HICS participation has become more urgent. In September, it was reported that the UK government plans to fund the conduct of these studies beginning in January 2021(Cookson 2020). Reporting in October confirmed plans to enroll between 30 and 50 healthy adults aged 18 to 30 in a SARS-CoV-2 HICS testing the lowest viral dose capable of infecting most participants, in preparation for subsequent HICS testing vaccine candidates (Callaway 2020). Although it is unclear whether these HICS will in fact proceed given additional rounds of necessary approvals, other protocols are also in development and progress toward launch is clear.

Our group concluded that because the goals of paying HICS participants, as well as the relevant ethical concerns, are the same in kind as those arising for other types of clinical research, the same basic framework for ethical payment can apply; there is no need for a unique payment framework specific to HICS. However, because the basic framework requires considering a variety of factors when setting payment amounts, which may take on more or less significance depending on relevant context, we identified several considerations likely to be especially salient for HICS — and for SARS-CoV-2 HICS in particular. Those factors are reflected in a practical worksheet created to help sponsors, researchers, and ethics reviewers systematically develop and assess ethically justifiable payment amounts for SARS-CoV-2 HICS, with relevance to other HICS and clinical research more broadly.

I. Considering a Distinct Framework for HICS Payment

Concerns about payment for clinical research participation typically cluster around the following issues: preserving the integrity of participants' informed consent; treating participants fairly, both individually and across populations; encouraging adequate recruitment and retention; avoiding participant deception around eligibility and adverse events; and preserving public trust (Fernandez Lynch et al. 2020; Fernandez Lynch and Largent 2020). The basic framework for ethical payment, described in Section II.A below, is designed to be responsive to each of these concerns by assessing payment offers according to the various functions they are intended to serve, whether reimbursement, compensation, or incentive.

But might there be anything so exceptional about HICS as to indicate that they demand a distinct framework for ethical payment of their own? Especially given the promulgation of distinct ethical frameworks for the conduct of HICS more generally (Miller and Grady 2001; Bambery et al. 2016; Shah et al. 2017; Shah et al. 2020b; WHO Working Group 2020), this is a reasonable question and one that in part motivated 1Day Sooner to request our guidance. Yet after considering a variety of potentially unique features of this research design, we conclude that the basic framework applicable to payment for other types of clinical research participation can also accommodate HICS.

A. Public Trust

The idea of intentionally infecting healthy participants with potentially harmful pathogens, the key feature of HICS design, may be unfamiliar and uniquely disconcerting to the general public (Bambery et al. 2016; Shah et al. 2017; Shah et al. 2020b). Some have therefore suggested that missteps with regard to this research, whether real or perceived, could be particularly damaging to trust in the broader research enterprise — negatively affecting support for public research funding and willingness to participate in research, as well as eroding confidence in research outputs more generally. If true, perhaps this precarity suggests that a distinct approach to offers of payment for HICS participation is needed, in order to tread as carefully as possible.

Research payments could affect public trust in several ways. First, there might be concerns that high payment is being used to take advantage of disadvantaged research participants. For example, following rare instances of serious harm in Phase 1 trials, media reports have sometimes insinuated ethical impropriety by drawing attention to seemingly large dollar amounts without exploring the basis for these offers or how they were calculated (Rosenthal 2006; Emanuel and Miller 2007; Chan 2016; Largent and Fernandez Lynch 2017a). Payment offers in HICS, and SARS-CoV-2 HICS especially, may be subject to similar insinuations or outright critiques, exacerbated by the relative unfamiliarity and perceived risks associated with this type of research (Gathura 2018; KEMRI 2018). Of course, this does not mean that there is any actual impropriety, and it can help to contextualize offers of payment for HICS participation in relation to payment practices in research generally, as well as payment practices in non-research settings where people both assume risk and contribute to the social good. But most importantly, the basic framework for ethical payment in research is well-suited to explain how and why offers of payment are justified, even if they might appear high at first glance. Therefore, rather than being replaced for HICS, the basic framework can serve an important role in responding to distrust that might stem from payment for HICS participation.

A second way that payment could affect public trust is the opposite of the first: a concern that no or low payment for participation is unfair given the nature of what is being asked of research participants. This concern might be particularly pronounced for HICS given the burdensome and

uncertain nature of this type of research participation. In this regard, it is relevant to note that recent empirical data from the UK suggests that members of the public view payment as critically important in the context of HICS (Grimwade et al. 2020), such that failing to meet public expectations about payment in these studies could itself become a source of distrust. Here, too, the basic framework for ethical payment can help make sure that fairness considerations are given sufficient attention when setting payment offers for HICS.

Third, public trust might be at its most precarious in the event that HICS participants experience significant harm. Trust can be buoyed by demonstrating that these participants will have both their medical and financial needs met — and can be sunk if adequate provisions are not in place to address participant injury. Yet these considerations are also squarely within the purview of the basic framework for ethical payment, which incorporates an expectation of robust compensation for research-related harm.

Ultimately, the best way to promote trust in HICS is by helping the public understand why this design can be both scientifically important and ethically acceptable (KEMRI 2018), and then ensuring that HICS proceed only when those ethical standards are satisfied. If the risks associated with these studies are unreasonable in relation to their potential benefits, payment for participation cannot help achieve ethical acceptability and distrust is warranted. However, if the risks are reasonable in relation to benefits, participation does not become unreasonable simply because payment is offered. For HICS that are ethically acceptable, the basic framework for ethical payment need not be replaced by a HICS-specific approach but instead can help further support public trust by offering a clear and consistent justification for payment offers.

B. Risk Level

Another factor that might suggest HICS call for a special framework for ethical payment is concern that they are uniquely risky. Prior to recent consideration of HICS for emerging infectious diseases like Zika and COVID-19, modern ethical standards had restricted HICS to infection models causing mild or self-limiting disease or those with treatments proven to avoid serious harms (Miller and Grady 2001; Shah et al. 2017). In that context, participating in a Phase

1 toxicity study of a novel chemical entity could, for example, be expected to entail greater uncertainty and risk of harm than HICS participation (Johnson et al. 2016). Nevertheless, payment to participants is routine in Phase 1 studies.

Even as HICS are considered for pathogens capable of causing more severe symptoms or for which proven cures are not available, including SARS-CoV-2, efforts to minimize risks through careful participant selection and other safeguards could render the mortality risks to participants fairly low (WHO Advisory Group 2020), though other serious health concerns, including "long COVID," must also be considered (Carfì et al. 2020). Without suggesting that this analogy should drive payment decisions, 1Day Sooner has compared the risks of participation in SARS-CoV-2 HICS to the risks of live organ donation (Morrison 2020). Notably, US regulations have recently been amended to facilitate reimbursement and compensation payments to live organ donors in the form of dependent care costs and lost wages (HRSA 2020), although incentive payments for organ donors are still prohibited. Given this important constraint on payment for organ donation, risks in certain occupations — in which there are lower but no upper limits on permissible payment — may be a more apt analogy for HICS payment. In any event, even for higher risk HICS and HICS in which there is substantial uncertainty about the probability or magnitude of harm, the relevant ethical concerns about payment are the same as those noted above for payment in all clinical research and addressed in the basic framework, such as valid consent, fairness, and adequate recruitment. Thus, although certainly relevant to considerations regarding the ethical acceptability of HICS, including the importance of planning for research-related harm, heightened risks do not support adopting a novel framework for HICS payment as compared to other types of research.

C. Social Value

Opposite risk, perhaps HICS can be so socially valuable that payment should be analyzed differently for these studies on that basis. For example, Anomaly and Savulescu argue that, given the substantial potential of this study design "to save and extend millions of lives," it can be appropriate to pay "any amount to recruit and retain [HICS] participants." Although they note that their argument can extend to other types of research as well, Anomaly and Savulescu

suggest it is "especially compelling" for HICS (2019). But here too, the basic framework for ethical payment can manage this social value claim, as it highlights the ethical importance of using payment to achieve adequate recruitment and retention. No distinct approach is necessary on this basis, either.

D. Susceptibility to Financial Influence

There is also no evidence to suggest that HICS participants are uniquely susceptible to having their capacity for good judgment negatively impacted by offers of payment in ways that would merit a special approach compared to other types of clinical research. Healthy research participants in general tend to have mixed motivations, with financial reward necessary but not sufficient for their decision to enroll; other motivations include altruism, pursuit of scientific interests and curiosity, and even thrill-seeking, among others (Tishler and Bartholomae 2002; Stunkel and Grady 2011; Grady et al. 2017; Fisher et al. 2019). Importantly, even when healthy participants are motivated by money, available data indicate that perceived risk is their ultimate deciding factor, and they will avoid studies they perceive to be too risky. These findings about motivation and decision-making among healthy participants in general are largely replicated in studies specific to HICS (Njue et al. 2018; Kraft et al. 2019; Oguti et al. 2019; Jao et al. 2020). HICS participants report that they engage in substantial deliberation before deciding to enroll, are not worried about study risks (perhaps unsurprisingly, given low risk of serious long-term harm in traditional HICS involving treatable diseases), and would consider participating again. The only study we are aware of to examine the perspectives of HICS participants compared to non-participants found that a substantial majority of non-participants would not participate in any HICS, even if payment was doubled; non-participants who would consider participating in HICS largely indicated that they would not do so if both risks and compensation were doubled (Hoogerwerf et al. 2020). Taken together, these data indicate the research payments are resistible even in the context of HICS, eliminating another potential concern that might have supported a distinct approach to HICS payments.

Importantly, there is even less reason to believe that SARS-CoV-2 HICS participants would be uniquely susceptible to financial influence. Although it is not yet possible to assess the

motivations of actual SARS-CoV-2 HICS participants, since no such study has yet been launched, anticipatory hypothetical evidence is available from individuals who have expressed their interest in participation via 1Day Sooner. In public statements (Kleinwaks 2020; Morrison and Rose 2020; Phillips 2020), explanations of why they signed up with 1Day Sooner, and a small focus group conducted for our report, prospective participants emphasize altruism, a desire to do something in response to the historic pandemic, and willingness to accept even significant study risks given the perceived importance of the research. Although some do identify offers of reimbursement and compensation as logistically necessary for them to be able to participate, they do not appear to be motivated by money and express a desire to avoid any type of payment that could compromise the science (e.g., by inducing deception amongst participants). Based on these limited insights, concerns about poor or distorted judgment resulting from offers of payment seem even lower in this context than they might be for other research, despite the financial challenges that have hit many people in the wake of the pandemic (Largent and Lynch 2020). Apart from payment, however, we note that the zeal with which prospective SARS-CoV-2 HICS participants hope to enroll on altruistic grounds may call for the sorts of consent protections typically associated with offers of payment, especially to help make sure that these individuals have a realistic understanding of the likelihood of these studies to dramatically influence the course of the pandemic (Shah et al. 2020a).

* * *

Overall, we find no reason to conclude that the basic framework for ethical payment applicable to other types of clinical research cannot also be applied successfully to HICS, which is not to say that the considerations discussed in this section are irrelevant to HICS payment, but only that they do not merit a wholly unique approach. This is in line with available ethics literature regarding HICS, which indicates some familiar concern about financial influence on informed consent, while acknowledging the importance of fair compensation, the need to avoid both exploitation and deception, and analogies to paid employment – and which generally agrees that payment for HICS is not necessarily of unique concern (Miller and Grady 2001; Bambery et al. 2016; Shah et al. 2017; Anomaly and Savulescu 2019; Grimwade et al. 2020; Jamrozik and Selgelid 2020; Shah et al. 2020b).

II. The "Payment Funnel"

Simply resolving that HICS do not call for a distinct payment framework does not resolve important questions about how HICS participants in fact should be paid. To do that, we must actually apply the basic framework for ethical payment, a broad conceptual approach described in more detail in our full report and elsewhere. The basic framework arrays research payment into the functional categories of reimbursement, compensation, and incentive in order to specify the ways in which payment might both raise ethical concerns and be used to respond to them (Gelinas et al. 2018).

Although this approach facilitates critical understanding of why payment should be offered and why traditional concerns about high payment may be inappropriately masking problems associated with low payment, additional work is needed to move from the framework towards an ethically defensible dollar amount for participant payment. The next step, then, is to consider a number of factors that can help stakeholders apply the basic framework to the particular clinical research studies in front of them, and finally, to focus even more specifically on factors likely to be especially relevant in developing payment offers for HICS participation. Taken together, these factors — which may overlap and converge in specific cases — should not be viewed as standing outside the basic framework for ethical payment, but rather as part of it, with the basic framework serving as the broad end of a funnel that moves toward increasingly specific assessments based on study-specific features that help determine whether more or less payment is needed and appropriate (see Table 1). Each step toward the base of the funnel is described in the sections that follow.

A. The Basic Framework for Ethical Payment to Clinical Research Participants

Separating payment offers according to the function they are intended to serve provides a systematic approach for both specifying and justifying those offers — and helps to make plain the tradeoffs between no, low, and high payment amounts. Starting with this strong foundation will be important given the scrutiny likely to face payment offers in SARS-CoV-2 HICS.

1. Reimbursement

Reimbursement of actual and reasonable out-of-pocket expenses, such as those incurred for travel, meals, and dependent care, should be offered as a matter of fairness to avoid participants having to pay in order to contribute to socially valuable research (CIOMS 2016). It can also help make research participation feasible for a broader range of people by removing financial barriers, a particularly important consideration when research bears the prospect of direct medical benefit or when it is scientifically important to include a diverse research population (Largent and Fernandez Lynch 2018). Offers of reimbursement raise no ethical concerns because these payments entail no net benefits to participants.

2. Compensation

Compensation for participants' time, as well as their assumption of research-related burden and inconvenience, should also be offered as a matter of fairness, as these are critical contributions experienced as losses by participants; they are giving something up or accepting something unfavorable as a result of participation. Thus, the same justifications applicable to reimbursement apply here.

Fairness does not call for compensation based on participants' opportunity costs (i.e., the benefits they have forgone by not pursuing their best alternative option), which might for example lead to paying lawyers $400 for an hour of their time but paying baristas only $15. Rather, research compensation is an acknowledgement of participants' contributions to research, which leads to the conclusion that there generally should be equal pay for equal work. Depending on a study's demands, however, fair compensation may be substantial and, for at least some individuals, higher than their opportunity costs, rendering research participation more financially attractive than their alternative options. This is a key difference from reimbursement, raising the possibility of undue influence, a concern that is likely to be particularly pronounced the greater the risks involved in research participation.

One definition of undue influence in research emphasizes outcomes, namely an offer so attractive that it leads prospective participants to make a decision against their self-defined

interests (Largent and Fernandez Lynch 2017b). Importantly, independent ethics approval substantially limits this concern by making sure that research participation represents a reasonable offer to a study's target population independent of payment – in other words, that research risks and burdens are acceptable (Emanuel 2005). We acknowledge, however, that this protection is incomplete (Largent and Fernandez Lynch 2017b). For example, there may be individuals who are enticed by offers of money to deceive study staff about their eligibility to participate or their experience of adverse events, thereby exposing themselves to unreasonable risk or compromising the science (McManus and Fisher 2018; Fernandez Lynch et al. 2019). However, additional safeguards, such as using objective enrollment criteria and adverse event metrics rather than subjective self-reports, can help diffuse these concerns. There may also be concerns about the capacity of ethics reviewers to truly protect participants by successfully ensuring that only reasonable research is approved, but this is a larger issue that should preclude research from proceeding altogether, not only paid research.

Other undue influence concerns are more procedural in nature, emphasizing autonomous decision-making processes rather than decisional outcomes. Here, the issue is that, regardless of whether research participation is ultimately a reasonable choice, ethical research typically also demands valid (voluntary, informed) consent (SACHRP 2019). Therefore, if payment were to impair a person's judgment regarding the decision to participate in research, for example by causing them to ignore important risk considerations, that would also be ethically problematic. Yet empirical evidence offers little support for this concern, even amongst those who are financially worse-off (Halpern et al. 2004; Slomka et al. 2007; Singer and Couper 2008; Cryder et al. 2010; Ambuehl and Ockenfels 2017; Fisher et al. 2018; Anomaly and Savulescu 2019; Ambuehl et al. 2020b; Ambuehl et al. 2020a; Gelinas et al. 2020). Where concerns remain, additional safeguards can be implemented to buttress informed consent, including added time and attention to the consent process and key features likely to be material to a reasonable person's decision-making (Gelinas et al. 2018; SACHRP 2019).

No solution will eliminate all possibility of undue influence in the face of payment amounts that extend beyond participants' opportunity costs. Nevertheless, it is critical to recognize that people with limited financial opportunities can be exploited *either* by taking advantage of a willingness

to engage in unreasonable activities in exchange for money *or* by taking advantage of a willingness to accept less than is fairly owed to them for undertaking otherwise reasonable activities. Given substantial protections against the former, as just described, the potential for unfairness through insufficient compensation is of greater concern than ethical challenges that may be associated with higher payments. Accordingly, fair compensation for participant time, burden, and inconvenience should be the priority, alongside appropriate safeguards against undue influence (Iltis 2009). This is especially important given the routine expectation and acceptance of fair compensation for non-research activities even for individuals whose options may be limited.

Fairness and participant protection further demand compensation for any significant research-related harms that may befall participants, which should generally be guaranteed through no-fault insurance coverage of short- and long-term medical costs, lost wages, pain and suffering, and death. The specific parameters of appropriate compensation for research-related harms have been well-covered elsewhere (PCSBI 2011; Henry et al. 2015). The persistent failure to legally require such compensation in the U.S. is a major ethical concern, obligating researchers, sponsors, ethics reviewers, and institutions to fill the gap before allowing research entailing risk of harm to proceed (Lamkin and Elliott 2018). Should they fail to do so, however, refraining from offering participants reimbursement and compensation for time, burden, and inconvenience would not ameliorate the situation but only compound the failure to treat participants fairly. In contrast, offering incentive payments, discussed next, despite such failure would make things worse. Yet rather than theorize about second-best alternatives, it is most critical to emphasize that compensation for research-related harms should be guaranteed as an ethical requirement, even where not a legal one.

Importantly, this type of compensation, paid only once harms actually materialize, does not constitute a net benefit to the recipient and therefore raises no ethical concerns; it is the failure to offer this payment that is a problem. Since assumption of risk that never materializes into harm is not a loss, however, fairness does not demand that risk itself be compensated. Risk-based payments may nonetheless be acceptable under other rationales (Fernandez Lynch and Largent 2020; Grimwade et al. 2020).

3. Incentives

Treating participants fairly can have the additional benefit of helping to promote recruitment and retention, but incentives go beyond what is owed to individuals as a matter of fair reimbursement or compensation. Incentives are paid as needed to address anticipated or actual recruitment and retention shortfalls, including those that may stem from the risks and uncertainty associated with research.

Empirical examination can help clarify the precise effects of incentive payments and whether they are likely to achieve their goals. Ideally, they broaden the range of individuals willing to consider participation, which may help promote the just distribution of research burdens. Unjust inducement is the concern that offers of payment will disproportionately appeal to worse-off populations. The solution should not, however, be to pay less or withhold fair payment altogether, but rather to offer incentives in hopes of encouraging wider participation across economic groups. Incentives may also be paid specifically to encourage enrollment of diverse populations that are scientifically important to include.

Because incentives are offered with the direct intention of making research relatively more attractive than other alternatives available to prospective participants, including those that may entail less risk (whereas this is only the incidental impact of fair compensation), they entail the highest potential for undue influence. Yet this is not enough to demand their avoidance. Insufficient — and insufficiently diverse — recruitment and retention are known problems in research with numerous ethical consequences, including unnecessarily exposing participants to burdens and risks in research that fails to answer critical research questions (Halpern et al. 2002). Given the safeguards available to minimize undue influence and the findings indicating that it is likely less of a concern than it might appear, as noted above, our view is that to the extent incentives can help address inadequate recruitment and retention in socially valuable, ethical research, they are justifiable on balance. This is true even if some concern about undue influence remains in particular cases (Largent and Fernandez Lynch 2017b; Gelinas et al. 2018).

* * *

Overall, each of these functions of payment helps to explain why low payments for research participation may be more ethically concerning than high payments, since low payments may be unfair and lead to inadequate enrollment, even while concerns about undue influence may be overblown and addressed in other ways. Although concerns about research payment often seem to serve as a proxy for deeper concerns about the acceptability of research risks, these considerations must be disaggregated. In all circumstances, payment for research participation is only ethically acceptable if the research itself is ethically acceptable. Withholding or reducing payment cannot fix unethical research and, when research is ethical, doing so raises additional ethical concerns. Like other socially valuable, burdensome, potentially risky endeavors, research participation is worthy of generosity and appreciation (Largent and Fernandez Lynch 2017a; McConnell and Wilkinson 2020). Participants should be paid accordingly.

B. Further Specifying the Basic Framework for Ethical Payment

Once the categories of reimbursement, compensation, and incentive are set forth, the next step moving down the payment funnel is to consider how factors relevant to a wide variety of clinical research, including HICS, should influence specific payment offers within each payment category, perhaps calling for higher or lower amounts depending on the circumstances.

1. Direct Medical Benefit

Thinking about clinical research in general, one question that sometimes arises is whether the prospect of direct medical benefit from study participation should influence payment. In circumstances where such medical benefit is possible, it may suffice to encourage adequate participation, reducing the need for financial incentives.

Direct medical benefit cannot, however, be guaranteed in research, and so it should not be relied upon to compensate for participant losses undertaken for the purposes of generating social value. More importantly, even if direct medical benefits do accrue, they are incommensurate with and therefore do not fully account for the financial impacts of research participation. Non-financial benefits do not mitigate out-of-pocket costs associated with participation or render participation less time-consuming, burdensome, or likely to result in research-related harms. Moreover, in

addition to requiring that the burdens of research participation be fairly distributed, justice demands fair distribution of potential benefits. This requires reducing financial barriers to participation, lest benefits be available only to those who can afford to participate (Nipp et al. 2016; Unger et al. 2016; Largent and Fernandez Lynch 2018). For each of these reasons, the prospect of direct medical benefit generally cannot justify reducing or eliminating reimbursement and compensation payments. Further, there is no reason to conclude that offers of payment to participate in research with a prospect of direct benefit are problematic.

2. Early Withdrawal or Termination

Another question is how to pay participants in the event of early withdrawal or termination from clinical research. Reimbursement and compensation payments should be prorated, since they are intended to cover costs and contributions that accrue over time and that are not reduced to zero simply because participation does not continue for as long as initially expected. Research-related harms should also be fully compensated regardless of whether participation was completed, since their costs will be experienced by participants in full.

In terms of incentive payments, completion bonuses are acceptable when needed to minimize early withdrawal that could jeopardize a study's scientific validity, long-term data collection, and the contributions of other research participants (Largent and Fernandez Lynch 2019). In general, completion bonuses should be limited to studies in which fair reimbursement and compensation are offered in order to avoid pressure to remain in a study in order to receive any payment at all. Ethics review should also ensure that appropriate conditions are in place to terminate participation in the event it becomes unreasonable, and participants who are terminated in those cases should be entitled to any completion bonus since they have in fact completed their commitment to the study (which cannot extend beyond the point of unreasonable risk). When completion bonuses are offered to participants for completing follow-up visits that are inconvenient but not risky, they raise little concern.

3. Study Location

How should study location influence participant payment? To start, investigators must comply with local restrictions, requirements, and norms applicable to paying research participants, whether stemming from legal obligations or institutional policies. For example, some localities may allow payment only in certain types of research or may allow only certain types of payment (Albuquerque and Barboza 2016; Jamrozik and Selgelid 2021). If fair payment is precluded, other research locations should be considered.

Study location is also relevant in other ways. With regard to compensation, local minimum wage is often suggested as a benchmark (Dickert and Grady 1999), which may not itself be fair in the context of a "living wage" (Ravenscraft 2019), but has the benefit of being easy for researchers to identify and apply, while aligning research with the non-research alternatives available to participants (Gelinas et al. 2020). Wages from other employment settings may also be considered, as well as using multiples of the local minimum wage, depending on what research demands of participants (Dickert and Grady 1999; Fernandez Lynch 2015; Grimwade et al. 2020). As a practical matter, it is also important to consider other research opportunities at and around a given study site, since this can provide information about what incentive payments may be needed to attract sufficient numbers and types of participants.

4. Economic Vulnerability

Study location may also correspond to an additional consideration potentially relevant to research payment, which is the economic vulnerability of prospective participants. Economic vulnerability can be found at any study site around the world, although it is concentrated more heavily in certain locations. There can be justifiable reasons to conduct studies in these locations, such as a high prevalence of the condition under study (Jamrozik and Selgelid 2020), but sites should not be selected for the simple exigency of economically vulnerable local participants' perceived willingness to accept research-related risks and burdens in exchange for payment (Emanuel et al. 2004). The same is true with regard to individual participants, who should not be targeted due to their economic vulnerability, but also should not be excluded on that basis. In either context, withholding or reducing payment for otherwise ethical research is not an appropriate response, as it "aggravates a bad situation and is unfair" (Gelinas et al. 2020). Instead, the focus should be on fairness and consent supports, as discussed above.

5. Study Budget

In practice, study budgets are highly salient to setting payment amounts. The critical question is whether payment needs should dictate study budgets or vice versa.

Reimbursement of out-of-pocket expenses and compensation for time and burden are important, but we do not go so far as to suggest that a study necessarily should be disapproved if its budget precludes offering these payments in adequate amounts. Volunteers are permitted to forgo payment for causes they find sufficiently important, although such altruism should not be expected or demanded of participants contributing to socially valuable research. Thus, payment in these categories should be treated as the ethical default, such that justification is needed should researchers or sponsors propose to deviate from this norm (Gelinas et al. 2018). Careful consideration should be given to the tradeoffs involved and whether it is better to offer no payment at all rather than low payment in these circumstances. For example, offering low payment may exploit those who lack better alternative options, as noted above, while offering no payment avoids that concern by removing financial motivations altogether. However, some payment may be better than none when it is important to make research opportunities more widely available, such as when they offer the prospect of direct medical benefit.

In contrast, adequate compensation for research-related harm should be viewed as an absolute ethical requirement and not merely as an ethical default. This is at least in part because it is much more difficult for participants to account for and bear the costs of harms, particularly significant harms, than the burdens of participation itself, which are likely to be more predictable and manageable. Thus, just as employers are required to finance workers' compensation for workplace injuries, study sponsors and investigators must budget to compensate participants for research-related injuries, through paying for insurance policies or otherwise (Fernandez Lynch 2015).

Incentives are the most discretionary payment type, since participants can be treated fairly without them and they may not be needed to achieve recruitment goals. However, when recruitment goals are likely to be achieved only if incentives are offered, it would be ethically

problematic to proceed without them. Moreover, when incentives could help critically important research proceed faster to produce significant social value, which may for instance be measured in healthcare costs averted or lives saved, blaming budgetary constraints for low participant payment makes little sense (Anomaly and Savulescu 2019). Overall, participant payment should not be treated as an afterthought in study budgets, but rather carefully considered and built into budgets to promote both adequacy and utility.

6. Participant Perspectives

Participant perspectives and expectations also should be taken into account when determining offers of payment. Most critically, participants may face costs and burdens that researchers are unaware of, which may impede recruitment and retention and are relevant to fairness. Prospective participants might also find certain types of payment or other benefits highly motivating, or there may be certain cultural considerations that would make payment more or less effective.

C. Key Factors to Consider in Payment for HICS Participation

The next step in the payment funnel is to move from the considerations likely to arise across clinical research to those likely to be especially salient when designing payment offers for HICS in particular.

1. Participant Isolation and Confinement

The first of these features is the length and intensity of participant isolation and confinement, both to avoid participants acquiring the infection of interest in the community rather than via challenge and also to prevent them from infecting others. Also relevant are where and how isolation and confinement are expected to occur, whether at home or at an inpatient facility (Lambkin-Williams et al. 2018). Confinement for a SARS-CoV-2 HICS, for example, may last for several weeks and may require participants to socially distance even from each other, a significant psychological burden (Gbesemete et al. 2020).

Reimbursement should account for the full duration of self-isolation and/or inpatient confinement, ideally including all relevant costs to the participant. Compensation should also be designed to reflect the heightened burdens of lengthier and more intense isolation and confinement. Incentives, including completion bonuses, may be necessary as the burdens of confinement and the timeframe for follow-up visits increase. Especially since total payments may be substantial, consent supports to help participants understand the potential difficulties associated with lengthy confinement are recommended. These might include test periods of confinement prior to challenge and involvement of prior HICS participants in the consent process to share their real experiences and perspectives (Fernandez Lynch 2020).

2. Anticipated Discomfort and Risk

Another feature of particular importance to payment for HICS participation is anticipated discomfort, since participants can be expected to experience at least some degree of illness, although this may vary substantially, especially for SARS-CoV-2 given the number of people who experience only asymptomatic infection or mild symptoms. Payment should compensate for anticipated median discomfort, rather than being adjusted based on participants' actual discomfort, both due to subjectivity in experience and the need to avoid exaggeration or fabrication of symptoms in order to secure greater payment. Incentives may also be needed as anticipated discomfort increases in likelihood and intensity.

Since the risk of lasting harm beyond discomfort is fairly low in most traditional HICS, risk-based compensation or incentives are likely unnecessary, although provisions must be in place to compensate for any research-related harms that do arise. For riskier and less certain HICS, such as those that would involve SARS-CoV-2, comprehensive no-fault insurance to address participant harms is essential and should be sufficient to cover the costs of medical care, lost wages, and death; under no circumstances should such research be allowed to proceed without this guarantee. Whether heightened incentives will be needed to account for heightened risk and uncertainty depends on participant motivations, but so long as the research itself is ethically acceptable and appropriate protections are adopted to minimize the possibility of undue influence, as described above, heightened risk should not impede greater payment.

3. Participant Motivations

Where HICS participants are expected to be predominantly motivated by altruism, as is likely for SARS-CoV-2 and potentially other pandemic circumstances, incentive payments are probably unnecessary. However, as noted above, it is essential to make sure that participant altruism is not rooted in mistaken beliefs about the potential social impact of the research. In contrast, even where altruism predominates, fair reimbursement and compensation remain important. If compensation is substantially more than participants might otherwise have the opportunity to earn, there may be less reason for worry that altruistically-motivated participants will be induced by payment to engage in deceptive behaviors likely to harm the study's ability to achieve scientific goals. Where participants are more financially motivated, safeguards against deceptive behaviors will be more important.

Some HICS participants may also be motivated by the anticipation of direct medical benefit, despite being healthy enrollees (Jamrozik and Selgelid 2021). For example, some prospective SARS-CoV-2 HICS participants, especially those who believe that SARS-CoV-2 infection is inevitable in the community, may feel it is safer to be infected in a controlled setting with access to close monitoring and priority for the highest-quality care even if the study does not offer access to any investigational vaccine. Yet as various precautions such as masking and social distancing can be taken so that viral exposure is not in fact inevitable, it is difficult to characterize the challenge exposure itself as a benefit, even during the current pandemic. To the extent that HICS involve access to investigational vaccines, which not all do, that is more reasonably characterized as a potential benefit for individuals at risk of viral exposure in the community. However, some participants may receive placebo, and especially because HICS are often used to down-select between early vaccine candidates, vaccine efficacy is far from guaranteed. In addition, the potential for a more severe SARS-CoV-2 infection due to antibody-dependent enhancement is an important element of risk disclosure for current vaccine trial participants. As in other types of research, any prospect of direct benefit from HICS participation should not reduce fair reimbursement or compensation levels. Perceived potential for benefit may reduce the need for incentives in practice, but again where these perceptions may be inaccurate, they should be addressed during the consent process.

4. Diverse Recruitment

Payment may sometimes be useful for recruiting a more diverse study population, depending on whether the reasons driving non-enrollment can be influenced by payment or are appropriate to influence by payment (Wendler et al. 2005; Durant et al. 2014; Beskow 2016; Niranjan et al. 2020). For example, payment might be used to make participation attractive to a wider pool, without targeting any particular groups, or it could be offered more strategically in hopes of encouraging the enrollment of certain populations of interest (Persad et al. 2019). Absent scientific reasons for focusing study on a particular group, participant diversity is generally desirable (Bierer et al. 2020). However, HICS — due to their typically small size and imperfect replication of natural infection — inevitably have limited generalizability (Jamrozik and Selgelid 2021). As a result, increasing participant diversity across traditional demographic parameters including race, ethnicity, and gender may not be scientifically impactful unless the effect size of such factors is especially large. Stated otherwise, even if HICS enroll highly diverse participants, they likely will not suffice to indicate how a vaccine studied using this method should be expected to perform at the population level.

Accordingly, scientific considerations regarding diverse enrollment are probably less relevant for HICS than they might be in other types of research. What about diversity for social reasons, such as fairly spreading the benefits and burdens of study participation across groups (Bierer et al. 2020)? As just noted, HICS often entail no or low prospect of direct medical benefit, potentially making it less critical — whether through payment or other recruitment efforts — to ensure that individuals who might otherwise face barriers to participation have an opportunity to enroll than would be the case if the likely benefits were high. In contrast, the burdens of participating in HICS are substantial and should not be disproportionately concentrated in those already facing various types of social disadvantage. Higher payment might help minimize this problem by making participation competitive with the options available to those who are economically better off, although consideration should also be given to factors like where and how participants are being recruited to make sure that burdens are not being concentrated on certain communities for reasons that extend beyond economics. Overall, absent benefit or scientific utility, there seems to

be less need to use payment levers to specifically target the inclusion of those who have been historically underrepresented in research.

Another reason sometimes supporting efforts to improve diverse recruitment is to encourage broader trust in research and research outcomes. Yet although trust in vaccines and vaccine trials is proving to be a serious concern in the context of COVID-19, especially among communities of color (Boodman 2020a; Boodman 2020b), it is not clear that trust will be improved by the intentional inclusion of these communities in SARS-CoV-2 HICS, especially if that enrollment is achieved through financial incentives (Kahn et al. 2020). To the contrary, it is reasonable to worry that financial incentives to encourage people of color to enroll in these studies may exacerbate worries of some that they are being "used as a guinea pig for white people" (Hoffman 2020).

Where trial diversity is important and lacking, payment should be considered as one tool among many to address those concerns, alongside attention to root causes of inadequately diverse enrollment, which may include distrust in research and systematic exclusion stemming from both historical and current racism. In the context of HICS, we anticipate that diversity goals, where relevant, can be best achieved by reducing financial barriers to participation and emphasizing fair compensation rather than using payment to specifically incentivize the enrollment of historically underrepresented groups. This approach should also suffice to promote fair access to any perceived benefits of HICS participation, tenuous as they may be.

5. Stigma

Another consideration when setting payment offers may be the stigma that sometimes accompanies HICS participation. Some HICS participants, for instance, report experiencing negative responses from family and friends or keeping their participation secret due to concerns about how it may be perceived (Roth 2007; Njue et al. 2018; Kraft et al. 2019; Oguti et al. 2019; Hoogerwerf et al. 2020; Jao et al. 2020). Even if the stigma is associated with perceived mercenary risk-taking for money, however, that would be insufficient reason to reduce fair payment; the same is true to the extent that paying HICS participants might negatively influence public trust in this type of research. The better response, as noted in Section I, is to encourage

public understanding of HICS, their risk levels, importance, and associated participant protections. Perhaps in contrast to other types of HICS, public attention to potential SARS-CoV-2 HICS and associated characterization of prospective participants as "heroic" suggests that any such stigma or lack of public trust is less likely to be a relevant factor for these studies.

6. Independent Ethical Approval

Finally, to promote confidence that participants are only being offered payment in ethically acceptable HICS, it is advisable to rely on ethics review boards that have experience with this design and that are able to adequately evaluate risks and burdens, efforts to minimize both, and potential social value, especially in relation to other ongoing and planned studies. Each of these considerations is made more difficult for potential SARS-CoV-2 HICS, given the substantial uncertainty about both risks and the utility of this type of study as traditional vaccine development moves at "warp speed" (Shah et al. 2020b; Shah et al. 2020a). Since the current approach to ethics review is ill-suited to handle these critical assessments, we agree with recommendations that research programs with "contentious risk" and "highly contingent social value" be reviewed by specially constituted "Comprehensive Ethics Review Committees" capable of engaging with the relevant literature, consulting with experts, and gathering evidence, far beyond what is usually expected of traditional protocol-specific review committees (Shah et al. 2018).

III. Putting It All Together: Setting Payment Amounts for SARS-CoV-2 HICS

After determining that HICS do not call for their own special payment framework, we began at the broad end of the funnel with the basic framework for ethical payment, narrowing to factors relevant to payment in clinical research generally, and further to factors relevant to HICS payments most specifically. This payment funnel offers a systematic approach with guidance that can be used by sponsors and researchers as they work to produce a justifiable dollars and cents figure based on the characteristics of their particular study, which ethics reviewers must then evaluate. However, because each study's particular characteristics are so integral to justifying payment amounts, we cannot identify an amount or even a range that would be appropriate for

HICS or SARS-CoV-2 HICs in the abstract. Stakeholders must therefore take the final step between conceptual guidance and actual payment offers on their own.

It may be helpful for sponsors and researchers at this final stage of the payment funnel to consider what participants are being paid in similar trials — in this case, other HICS. Yet, current payments to HICS participants cannot be the ultimate arbiter of acceptable amounts, as it is not clear that they have been based on application of any systematic ethical framework. Perhaps it is for this reason that these payments are highly variable, with differences between them not entirely explained by salient differences between the studies.

Grimwade et al. recently surveyed HICS investigators and, upon reviewing complete payment practices from 25 studies provided by those investigators, found a payment range from "£0 (no payment) to £3393 (mean (SD) = 1,325.9 (1,206.15)) and the range of hourly payment varying from £0 to £30 GBP (mean (SD) = 10.51 (8.82))." In USD as of October 2020, that range is about $0-$4388, with an hourly rate of $0- $38.80. Importantly, a majority of the investigators surveyed indicated that they took into account payment offers from previous studies when setting their own study's payment amounts (Grimwade et al. 2020).

In our own review of HICS payments, we searched ClinicalTrials.gov for HICS conducted between January 1, 2015, and June 1, 2020; this search returned 109 hits. We were, however, only able to collect information about payments to participants from 18 of the studies, using a combination of publicly available information and contact with select study investigators (see Table 2). This is indicative of a problematic lack of transparency about payment practices, even in protocols and consent forms, a problem that is not unique to HICS. We refrained from calculating maximum possible payment totals within our sample, as this was not always clear from the information available to us. But like Grimwade et al., we observed substantial variability in payment amounts. Participant payment was most commonly referred to as compensation, with a focus on time spent in study visits and during any inpatient phase; some studies also provided distinct payment for receipt of an investigational medical product, pathogen challenge, blood draws, additional procedures and visits, and study completion. Reimbursement of participant travel and time away from work was also mentioned in some

cases. No study in our sample specifically referenced incentives. Compensation for study-related injury was not always explicitly guaranteed, was sometimes disclaimed, and was — from our perspective — discussed in insufficient detail. Although investigators and sponsors may have non-public channels for identifying index payment amounts, such as their own prior studies or studies conducted by colleagues, greater transparency would be useful to promote consistency where appropriate and to allow critical examination, particularly by ethics review boards and participants.

The payment amounts and variation revealed by both Grimwade et al. and our analysis likely reflect investigators' best judgments in the face of limited guidance, as well as their perceptions of what ethics reviewers are likely to accept. Due to longstanding concerns that payment can constitute an undue influence, and a general lack of consideration of the ethical consequences of paying too little (Largent and Fernandez Lynch 2017b), using current payment amounts as a benchmark may result in merely replicating payments that are unnecessarily and inappropriately low. As more systematic approaches are adopted in line with the guidance herein, however, payment amounts from other similar HICS should eventually become a more useful heuristic. In the meantime, they should not be treated as conclusive, but can nonetheless offer helpful context.

To help researchers and sponsors move beyond reliance on prior examples, we have translated the basic framework for ethical payment into a worksheet to facilitate systematic and justifiable approaches to setting payment amounts (see Table 3). This worksheet could be easily modified for use in other types of clinical research, but here, we have highlighted factors of particular salience to SARS-CoV-2 HICS. Importantly, the worksheet does not offer a formula or algorithm into which one can plug information to arrive at a singular answer. Rather, it invites reflection on relevant factors and benchmarks, implicitly acknowledging that there can be a range of reasonable payment amounts for any given study.

The worksheet consists of two tables. The first of these is organized by payment type – reimbursement, compensation, and incentive. For each payment type, the worksheet notes the goal, as well as whether amounts should be expected to vary across participants in the same study (Persad et al. 2019), the extent of coverage, factors to consider, and relevant benchmarks.

We favor using publicly available benchmarks — for example, reimbursement rates used by governments and minimum wage rates — as these should be readily accessible to researchers and will therefore facilitate application of the framework, as well as transparency. Further work on benchmarks that can be easily used to calculate research payment based on relevant analogies from outside the research setting should be treated as a high priority for interdisciplinary work between researchers, bioethicists, economists, participants, and others.

The second table focuses exclusively on compensation for harm, which will be provided if and only if harm materializes. Accordingly, it is separated from the first table in order to avoid these amounts being included in calculations of payment totals. That payment for harm is not presently guaranteed in clinical research is an ethical failing of the global research enterprise (Henry et al. 2015; Chingarande and Moodley 2018; Lamkin and Elliott 2018). As noted above, SARS-CoV-2 HICS should not be allowed to proceed in any setting in which there have not been adequate provisions made for compensating research-related harms.

Conclusion

The basic framework for ethical research payment divides payment into three categories — reimbursement, compensation, and incentive — and emphasizes the importance of fairness and adequate recruitment and retention, with efforts to minimize undue influence, participant deception about their eligibility and adverse events, and negative impacts on public trust. High offers of payment are sometimes met with scrutiny and concern, but this basic framework suggests that it can be ethically appropriate to offer substantial payment for research participation and highlights that low payment also raises significant ethical concerns.

The basic framework is relevant to payment for all types of clinical research, including HICS. Nonetheless, there are factors within that basic framework likely to be particularly salient to setting payment amounts for HICS, including participant isolation and confinement, anticipated discomfort, risk of lasting harm, and participant motivations. Based on these factors, HICS – and potential SARS-CoV-2 HICS, in particular – will likely be on the high end of the payment spectrum. Researchers and sponsors should be expected to transparently and systematically

justify payment amounts to ethics reviewers, participants, and the public, which can be facilitated through the use of the payment worksheet.

Our work was spurred by concerns that payment for SARS-CoV-2 HICS might require a novel ethical framework, which we ultimately determined to be unfounded. Our hope is that our analysis — here and also in the comprehensive report prepared for 1Day Sooner, which addresses each of the relevant considerations in substantially greater detail — will serve both to ease concerns about payment in these studies, should they proceed, and to advance the broader project of ensuring ethical payment to participants in all clinical research.

Tables

Table 1. The Payment "Funnel" — Factors Relevant to Ethical Payment for Participation in Human Infection Challenge Studies

Table 2. Payment in selected Human Infection Challenge Studies identified through ClinicalTrials.gov, 2015-2020, as well as investigator contacts

Table 3. SARS-CoV-2 Human Infection Challenge Studies: Payment Worksheet

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Tom Darton reports involvement in conducting human challenge studies, in high- and low-resource settings, which may be influenced by the recommendations described in this manuscript, although he has no plans to be involved in such studies for SARS-CoV-2. He reports an honorarium provided by the Greenwall Foundation for work led by Seema K. Shah and Annette Rid on the ethics of human infection challenge studies (2017-2019). He has also been involved with the 1Day Sooner Research Team, co-authoring a manuscript evaluating use cases for a SARS-CoV-2 challenge study and in surveying the attitudes and motivations of human challenge volunteers. He reports no additional relevant disclosures beyond the honorarium from 1Day Sooner.

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Thomas Smiley reports that he is a 1Day Sooner volunteer ambassador. As described on the 1Day Sooner website, "Volunteer Ambassadors are unpaid volunteers who help workshop 1Day Sooner's media talking points and speak with the press about their decision to take part in a potential COVID-19 challenge trial. Volunteer Ambassadors share their personal perspectives as potential challenge trial volunteers and are expected to maintain a high standard of scientific accuracy and historical awareness. They are entirely free to disagree with any of 1Day Sooner's institutional views, including the above talking points." He reports an interest as a prospective participant in future COVID-19 challenge trials that may be influenced by the recommendations described in this manuscript, but otherwise has no financial conflicts of interest to disclose beyond the honorarium from 1Day Sooner.

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