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Paying for Fairness? Incentives and Fair Subject Selection

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In their Target Article, "Promoting Ethical Payment in Human Infection Challenge Studies," Lynch et al. (2021) propose a framework for ethical payment to research participants and apply it to the case of human infection challenge studies (HICS) involving SARS-CoV-2. In addition to the purposes of reimbursement and compensation, they argue that payment may be used as an incentive to ensure adequate recruitment for clinical trials, and even to "promote the just distribution of research burdens" (Lynch et al. 2021, 18). In this Open Peer Commentary, we first develop a claim that we take to be implicit in Lynch et al.'s article, namely, that payment may be used to ensure fair subject selection. We then investigate this claim's implications for Phase I studies with healthy volunteers, focusing on whether incentive payments should be used to promote the fair sharing of research burdens and to advance the goals of fair inclusion. We argue that trial sponsors and clinics should proceed cautiously with the category of "incentive" payment. Instead, we suggest improving Phase I study payment in keeping with standards of fair compensation *may* also incur a fairer distribution of burdens, while the issue of fair inclusion is orthogonal to payment incentives.

PAYING FOR FAIRNESS?

Lynch et al. (2021) argue that payment may be used as an incentive to not only ensure adequate recruitment for clinical trials, but also to affect the types of participants who enroll. For example, they state that payment may be used to incentivize wider participation from people of different socio-economic classes and to ensure the enrollment of a sufficiently diverse study population. At the same time, they define incentive payments as those, "needed to address anticipated or actual recruitment and retention shortfalls" remarking that these "may help promote the just distribution of research burdens" (Lynch et al. 2021, 18). An important question then is whether incentives, which are paid to move the science forward, sometimes also impact the just distribution of research burdens as a beneficial side-effect, or whether incentive payments may be made directly to enhance fairness. We suggest here that Lynch et al.'s discussion of the use of incentives can be fruitfully reconstructed as the claim that it is permissible to use payment to ensure fair subject selection.

MacKay and Saylor (2020) distinguish four dimensions of fair subject selection, with each corresponding to a particular benefit or burden of clinical research the distribution of which is influenced by participant selection. The chief benefit of clinical research is clinically relevant generalizable knowledge, and the selection of participants has implications for which subpopulations stand to benefit from it. As such, *fair inclusion* requires that members of clinically distinct populations be included in research to ensure that research results fairly benefit members of society. Where participation is ex ante net beneficial for participants, participation is itself a benefit and so prospective participants should have a *fair opportunity* to participate. Where participation is ex ante net burdensome for participants, *fair burden sharing* requires the fair sharing of the burdens of participation. Finally, since prospective participants may differ in terms of

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the risks their participation imposes on others, *fair distribution of third-party risks* requires that participants be selected with an eye to ensuring that such risks are fairly distributed.

Lynch et al. (2021) argue that payment may be used to recruit a more diverse study population. Doing so may involve realizing fair inclusion by targeting members of clinically distinct groups to ensure generalizability, or better realizing fair burden sharing by increasing payments overall to ensure that it is not merely low-income people who participate. However, payment may also be used to realize fair opportunity and fair distribution of third-party risks. For studies with a prospect of a direct benefit, higher payments may smooth participation for those facing obstacles due to financial constraints. Similarly, in cases where a study imposes risks on third parties, payment could be increased to encourage people to enroll whose participation will not pose sizeable risks on others.

Reconstructed in this way, Lynch et al.'s (2021) potential suggestion that it is in principle permissible to use incentives to fulfill fair subject selection raises several questions deserving of further investigation. For example, which dimensions of fair subject selection are important enough to warrant the devotion of greater resources in the form of higher payments? In addition, is it ever permissible to use *differential* payments to incentivize some prospective participants and not others to enroll in a study? Persad, Lynch, and Largent (2019) argue in favor of differential payments to realize fair inclusion, but what about for fair opportunity or fair burden sharing? To further explore the use of incentive payments, we turn to the context of Phase I studies with healthy volunteers and consider their use to promote fair burden sharing and fair inclusion.

PAYING FOR FAIRNESS IN PHASE I HEALTHY VOLUNTEER STUDIES?

Participants in Phase I healthy volunteer studies carried out in the USA are disproportionately low-income racial and ethnic minority men (Chen et al. 2018; Fisher and Kalbaugh 2011; Grady et al. 2017). These studies pose health risks with no potential for benefit, typically include days to weeks of confinement in a clinical trial facility, and involve activity restrictions as well as bodily monitoring procedures. If fair burden sharing requires that the burdens of participation in clinical research are widely distributed, Phase I studies in the USA currently violate this dimension of fair subject selection. Additionally, given the overrepresentation of men, these trials also fail to meet standards of fair inclusion. One possible solution to these problems is to increase payments for some Phase I trials specifically to incentivize higher-income Americans (Iltis 2009) and women to participate. The "incentive" payment approach to these dimensions of fair subject selection is troubling, however, and potentially also misses the mark.

Increasing payment specifically to incentivize higher income individuals to participate in Phase I trials raises the specter of differential individual payments. Healthy volunteers who face economic precarity and a number of steep barriers to participating in the labor market (including lacking legal immigration status, possessing a felony record, or low educational attainment) are already "incentivized" to participate in these trials and frequently do so serially as a way to make ends meet (Fisher 2020; Grady et al. 2017; Walker, Cottingham, and Fisher 2018). So-called incentive payments would therefore be needed *only* for those not otherwise subject to the kinds of economic insecurity facing serial participants in Phase I trials. In this way fairly distributing the burdens of these trials may involve paying people who need the income more—and who are also more likely to be men of color—less for the same research burden. Such a result is not only perverse, but also unjust on its face.

In contrast, if fair compensation for Phase I trials accounts for many of the factors that Lynch et al. elaborate for HICS and that also apply to these trials—e.g. confinement, anticipated discomfort, risks, and uncertainty—payment amounts may also be raised for these studies, potentially in a way that more fairly distributes their burdens. The difference to an incentive payment (in their sense) is that the pay, as fair compensation, necessarily should apply equally to all participants regardless of their background incentive to participate.

What about the use of incentive payments to increase the participation of women in Phase I trials and foster fair inclusion? Targeted payments to women may well impact the demographic patterns in these studies; however, there are lower hanging fruit for addressing fair inclusion. To avoid fetal risk, women of childbearing potential are frequently excluded from Phase I trials. For women seeking enrollment in these trials as a means to earning an income, such barriers are cited as impeding their participation (Cottingham and Fisher 2020). Definitions of "childbearing potential" typically do not take into account individual circumstances that make the

likelihood of a woman's becoming pregnant extremely low—e.g. sexual orientation—but may instead insist eligible women are post-menopausal or surgically sterile (Cottingham and Fisher 2020). Additionally, other factors impeding women's participation in these trials such as lack of separate sleeping quarters (Jain, Cottingham, and Fisher 2020) may be better addressed by changes in clinic policies than by incentive pay.

Lynch et al. suggest that incentive payments may in some cases also ensure a fairer distribution of research burdens and that "payment might be used to make participation attractive to a wider pool" (21). We have interpreted this as a potential claim that incentive payments offer an in principle useful and permissible tool for promoting fair subject selection in clinical trials. This intriguing proposal is worthy of greater scrutiny. Here, we have explored the potential for such forms of payment in Phase I healthy volunteer trials. For these trials, incentive payments do not seem to be the right fix for the problems. Alternative solutions are to fairly compensate Phase I healthy volunteers for the significant burdens involved in their participation, and to adjust inclusion policies to better ensure that study participants represent patient populations.

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