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THE IRB'S PERSPECTIVE

Determining Optimal Compensation for Clinical Trial Participants

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Paying participants for the essential role that they play in clinical trials is important, but the amount given, and how it is paid, require careful consideration.

Appropriately compensating clinical trial participants lessens the financial burden placed on them by participation in research and increases the pool of possible contributors. As a result, sponsors can increase diversity in their clinical trials, and make sure that they are truly representative of the patient population. Compensation increases recruitment, allowing studies to be completed efficiently, saving time, money, and staff resources. It also recognizes participants for their contribution to advancing medical science.

But how can sponsors strike the right balance between compensating research participants to achieve those benefits, while minimizing the potential for the payments to have an undue influence on their behavior?

The U.S. Food and Drug Administration (FDA) states that an investigator can only seek a person's consent to join a clinical trial if the prospective participant has "sufficient opportunity to consider whether or not to participate" under circumstances that "minimize the possibility of coercion or undue influence."[1] As coercion involves a threat of force, payments can never be coercive, but they could be unduly influential.

Primary concerns are that payments might interfere with participants' ability to give voluntary informed consent, by encouraging them not to fully consider the risks, burdens, and discomforts associated with the research, or to ignore side effects during the trial due to their desire to complete the study and get paid.

REGULATORY GUIDANCE

Fortunately, the FDA has provided an Information Sheet on this topic,[2] and the U.S. Department of

Health and Human Services' (HHS') Office for Human Research Protections (OHRP) has published responses to frequently asked questions.[3] The Secretary's Advisory Committee on Human Research Protections (SACHRP) has also provided some valuable recommendations.[4] While this guidance is helpful, there are still circumstances in which Institutional Review Boards (IRBs) need to rely on their experience and good judgement to make the best decisions.

RECRUITMENT ADVERTISEMENTS

It is generally acceptable for sites to state in clinical trial advertisements that people will be paid for participating and the amount. But the FDA guidance states that payments should look like the rest of the text and not be highlighted or in bold type.

Most clinical trial participant payments fall into one of four categories: reimbursement, compensation, bonus, or incentive.

REIMBURSEMENT

The FDA is generally comfortable with sponsors reimbursing clinical trial participants for costs they must incur. Its 2018 guidance states: "FDA does not consider reimbursement for travel expenses to and from the clinical trial site and associated costs such as airfare, parking, and lodging to raise issues regarding undue influence." But it adds that "IRBs should be sensitive to whether other aspects of proposed payment for participation could present an undue influence."

Reimbursement for some studies, particularly those for rare diseases, can involve substantial costs because they may require flying patients in from another country, include a one-week hotel stay, etc. If those costs were not covered, it could skew studies towards people with more resources because they could pay for themselves to get there, which is problematic from the justice perspective.

COMPENSATION

Compensating participants for lost economic opportunities during a study is a little more complicated because participants' income levels can vary significantly. IRBs typically require everyone to be paid the same amount, as a matter of equity. In multi-site trials, however, investigators are sometimes given the discretion to offer a payment that they feel is appropriate for their area, so the compensation in Alabama might be different from New York City due to differences in the relative cost of living.

Payments for participation are seen predominantly in studies for chronic conditions such as diabetes, obesity, or high blood pressure where people are not likely to suffer serious harm without the intervention. The payment is intended to compensate participants for the time and effort required to attend additional clinic visits outside the scope of their normal medical care.

Compensation in Phase 1 studies is generally higher than for later phase studies because it requires recruiting healthy individuals. It is more like a job for those participants than other types of research when the study drug is combined with medical care. Volunteers are typically required to spend the entire study confined to the Phase 1 Unit, so that researchers can better control their diet and other aspects of their environment. Compensation for Phase 1 studies usually works out to be about $10-$20 an hour. The only exception would be Phase 1 studies involving patients with cancer or another potentially deadly disease. Those studies generally do not pay for participation because they fall more in the clinical care continuum.

SACHRP suggests that payment for participation is prorated or evenly scheduled throughout the trial. For example, participants might get paid once a month or once every six months during a year-long trial. Paying a participant when the study ends for the number of meetings attended or study visits completed is also considered acceptable.

To further counter undue influence concerns, SACHRP recommends that the IRB evaluates the risk-

benefit ratio for the clinical trial, and the other IRB criteria for approval, before considering payment. Then, if the IRB considers that the study is acceptable, the money becomes less important because people cannot be drawn into a study that is not in their interest because the IRB has already deemed the risk-benefit ratio appropriate. In addition, the IRB will have determined that risks are minimized to the extent possible, and the research will provide benefit to society.

COMPLETION BONUSES & INCENTIVE PAYMENTS

Most of the unease relating to payments pertains to bonuses or participants receiving extra money at the end of a study for completing it. There are concerns that that payment structure might encourage a participant to stay in a study after they have had an adverse event or are experiencing a side effect of the drug because they are reluctant to lose the extra payment for the visits they have completed or miss the big bonus at the end of the study if they drop out. This is one of the remaining areas where concern exists at SACHRP and in IRBs about undue influence.

A small bonus payment is acceptable under the FDA guidance, but it does not give an actual figure or range for that payment. In practice, up to about 25% of the amount that the participant would be paid can generally be held over as a bonus. But anything more than 25% will raise eyebrows with an IRB. When pay is weighted too much toward completing the study, that is when it becomes inappropriate and potentially unduly influential.

SACHRP recommends keeping the level of financial and non-financial incentives low for clinical trials. Non-financial incentives might include entertainment, hairdresser appointments or a massage for participants in a Phase 1 study who must remain onsite for several weeks.

Another way to reduce the risk of introducing any undue influence with these benefits is to ensure that they are clearly described, without any exaggeration, in the consent documents. Situations in which a participant will receive only a partial payment, or no payment should be described there.

The payment schedule should also be clearly stipulated. If the study involves six visits, and a participant drops out after three visits, they will often want to be paid right away for the three visits. However, many sites wait until the study ends to pay everyone because it is more efficient from an administrative standpoint. Payments may be prorated throughout the study but not paid until the end. It is important to set expectations appropriately in the consent document.

CONCLUSION

It is acceptable to pay people to participate in clinical trials because they are making sacrifices to join research studies for the good of others. With careful consideration, it is possible to reimburse their costs, and compensate them for their time, effort, and other burdens without posing undue influence on their decisions. The IRB's objective review of the consent documents helps to ensure that occurs.

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1. FDA regulations 21 CFR Part 50.20. Definition of informed consent: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.20
2. FDA Payment and Reimbursement to Research Subjects information Sheet. January 2018: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/payment-and-reimbursement-research-subjects
3. OHRP FAQs: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/faq/informed-consent/index.html
4. SACHRP recommendations: https://www.hhs.gov/ohrp/sachrp-committee/recommendations/attachment-a-september-30-2019/index.html

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