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What's the Price of a Research Subject? Approaches to Payment for Research Participation

[Sounding Board]

Dickert, Neal; Grady, Christine.

National Institutes of Health; Bethesda, MD 20892

Successful clinical research depends on the ability to recruit research subjects. Tension between the need to recruit subjects and the obligation to offer them certain types of protection has made recruitment a persistent ethical challenge. One important and difficult issue involves whom investigators should enroll in research studies. A different but equally crucial issue concerns the types of inducement investigators should use to recruit subjects.

For decades, many investigators have paid subjects for participating in research studies, and this practice remains one of the most controversial methods of recruitment. [1] Despite discussions over many years, ethical issues about payment remain unresolved. The predominant concern expressed is that payment of subjects might represent "undue inducement," by leading to a decrease in either the voluntariness or the understanding with which subjects agree to participate. [2-6] A second concern is that the payment of subjects may result in economically disadvantaged populations' bearing an unduly large share of the risks and burdens of research participation. [2,4,5] Many people also worry that the use of money as a recruitment tool will lead to putting subjects at risk who do not care about or support the goals of the study. [2-4,6,7] Finally, some believe that the payment of subjects violates the ethical norms of the investigator-subject relationship by turning it into a commercial relationship. [6,8,9] This worry is particularly apparent when subjects are very ill.

Although some argue that the payment of subjects is never ethical, this practice has long been an integral part of the recruitment of research participants. In fact, the payment of subjects is likely to become even more pervasive as the need to recruit grows along with the capacity for technological discovery and the level of commercial funding for clinical research. The frequency of payment may also increase in response to requirements for greater inclusion of women, minorities, and children in research studies. [10,11] As this practice becomes more frequent, it is essential to recognize that payment can be made in various ways, some of which are more ethically acceptable than others.

No consensus has emerged on when and in what manner it is ethical to pay subjects. Although federal regulations and guidelines call attention to some of the moral issues that payment raises, they offer little substantive guidance for clinical investigators, institutional review boards, or contract research organizations on how to pay subjects ethically. The federal "common rule" [12] never mentions the payment of subjects, and the guidelines of the Office of Protection from Research Risks [13] and the Food and Drug Administration (FDA) [14] merely reflect the controversy over how to approach payment. For instance, FDA information sheets offer seemingly contradictory advice, suggesting that payment should be viewed as a "recruitment incentive" while simultaneously requiring institutional review boards to ensure that payment is not "unduly influential." [14]

Paying Patients or Healthy Subjects

Most of the literature on the payment of subjects reflects the common perception that only healthy subjects - those who do not have the condition under study - are paid for their participation in clinical research. It is true that patients are rarely or never paid in some types of research, such as clinical trials of cancer chemotherapy. However, listings and advertisements of ongoing clinical trials are evidence that patients with such diseases as asthma and human immunodeficiency virus infection are frequently paid for participating in clinical research. [15]

The ethical argument against the payment of patients rests on one or both of the following premises: patients are particularly vulnerable, and patients are deriving medical benefit in a way that healthy subjects are not. The special vulnerability of patients is most often attributed to two factors: the inability of patients to distinguish clinical care from research, often called the "therapeutic misconception," [16] and a perceived difference in power between patients and investigators, especially when an investigator is both the clinician and the researcher. In the absence of empirical data, however, it is not clear how payment exploits either source of vulnerability. Because patients typically pay for their clinical care, it seems plausible that paying patients for participating in research may, in fact, reduce the therapeutic misconception by distinguishing the procedures that are undertaken purely for research purposes from those that are performed as part of clinical care. Paying patients may also help to minimize the power differential by making participation seem less like a "favor" the patient is being asked to do for the physician-investigator.

The second premise - that patients are deriving benefit - also fails to justify an absolute prohibition against paying patients. After all, many studies enrolling patients offer little or no prospect of direct benefit. In fact, some of these studies also involve healthy subjects who are paid to participate. For example, a researcher may use positron-emission tomography to

study the differences in brain function between patients with obsessive-compulsive disorder and healthy controls. In cases in which neither patients nor healthy subjects would receive any immediate or direct benefit from the procedure, not paying patients while paying healthy subjects appears to violate the principle of justice, which demands that like cases be treated alike. [17] In studies that offer potential benefits, such as many phase 3 studies, there may be no reason to pay patients, but it is not clear why it would be unethical to do so simply because they may benefit from participating.

There is no inherent reason to treat patients and healthy subjects differently with respect to payment. Therefore, our analysis of payment generally applies to both types of participants.

Three Models of Payment

In this article, we evaluate three models of payment: the market model, the wage-payment model, and the reimbursement model (Table 1). Careful consideration of these models will help in choosing the most ethical approach. Other types of "payment," such as free medical services, do raise many of the same considerations, but this discussion refers only to payments in cash. Because cash payments are so pervasive and influential, and because they are more fungible than other forms of inducement, a careful analysis of their use is important.

Table 1. The Three Models of Reimbursement and Their Applications to a Hypothetical Case.

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The Market Model

The market model is grounded in traditional libertarian theory. [19] The principle of supply and demand determines whether and how much subjects should be paid for participating in a given study at a specific site. When research is arduous or risky and offers little or no prospect of direct benefit to subjects, there is little apparent reason for a person to participate. This model allows money to be the reason. For example, money may be an incentive for a healthy person to participate in a study of natural patterns of sleep, or in a phase 1 pharmacokinetic study of a treatment for a disease the person does not have. Similarly, it may be an incentive for a patient to participate in a nontherapeutic "challenge study" to examine the pathophysiologic features of a particular condition.

Use of the market model would probably result in high payment for participation in studies that offer subjects no prospect of direct benefit but involve risky or uncomfortable procedures. Payment may also be high when investigators want to recruit subjects very quickly, or when few people are eligible to participate. In addition, the market model

sanctions the use of large completion bonuses and other incentives to encourage compliance with the protocol. After all, the value of a subject's participation is often dependent on the subject's completion of the study. The market model would, however, suggest that there be little or no payment when people are eager to enroll in a study, as may be the case for studies involving such agents as trastuzumab (Herceptin) and antiangiogenesis factors for the treatment of cancer.

The Wage-Payment Model

The wage-payment model operates on the notion that participation in research requires little skill but does require time, effort, and the endurance of undesirable or uncomfortable procedures. This model adopts the egalitarian position that subjects performing similar functions should be paid similarly. Participating in research is similar to many other forms of unskilled labor in that it requires little skill or training, may involve some risk, and often involves relatively little "labor." [2,4,20] The wage-payment model thus involves the payment of subjects on a scale commensurate with that of other unskilled but essential jobs. Application of the wage-payment model would lead to the payment of a fairly low, standardized hourly wage, augmented by increases for particularly uncomfortable or burdensome procedures. [2,3] The payment of completion bonuses is also consistent with this model; however, they should not constitute a large proportion of the payment, because this model bases payment primarily on the time subjects spend "working" (i.e., participating in the research).

The wage-payment model is not entirely distinct from the market model, but there are two fundamental differences between them. First, in the wage-payment model, payment is set according to the unskilled-labor market rather than the supply of persons eligible for participation. Second, the wage-payment model requires standardization, both among different protocols and between research and other forms of unskilled labor.

The Reimbursement Model

According to the reimbursement model, payment is provided simply to cover subjects' expenses. This model reflects a different form of egalitarianism, and it is based on the view that research participation should not require financial sacrifice but should be "revenue neutral" for participants. One application of this model would involve reimbursing subjects only for expenditures such as travel, meals, and parking. Alternatively, use of this model could involve reimbursing subjects for their time away from work at whatever rate the subjects are typically paid in addition to reimbursement for expenses. With either version, each subject would be paid according to his or her own expenses.

The reimbursement model differs from both of the other models in three important ways. First, it precludes subjects' making a profit. Second, it does not use money to compensate for nonfinancial "expenses," such as effort or discomfort. Third, payment does not depend on any market, either for research participation or for unskilled labor.

Applying the Models to a Case

Delineating the practical implications of each model is crucial; people who appear to agree in theory often use different models in determining payment for a particular study,

resulting in widely divergent payment practices. Consider a study testing the effect of a protease inhibitor on the bioavailability of a narcotic pain medication. The subjects are healthy persons, and the study requires them to take the protease inhibitor daily for 12 days and to come to the clinic eight times. For two of the visits, the subjects must remain at the clinic all day. Overall, the study takes 29 hours and involves a screening examination, administration of the pain medication with serial blood collections, and follow-up. This protocol offers no direct benefit, involves the discomfort of serial blood collection, and requires taking medications that may cause diarrhea, nausea, or other side effects.

The three models would lead to very different payments for participation in this study (Table 1). True application of the market model would depend on the current market. On the basis of amounts commonly offered today, it is reasonable to estimate that subjects might be paid $25 an hour, $200 for taking the medications, and a $200 completion bonus, leading to a total payment of $1,125. The wage-payment model would lead to payment of about $10 per hour, just below the 1998 total national average for nonfarm production workers, [18] as well as $50 for the inconvenience of taking the drug for two weeks and $50 for the more invasive serial blood collection. Total payment would be $390. One formulation of the reimbursement model would involve payment only for travel, meals, and parking expenses. If parking cost $3 per hour, lunch cost $6 for each of the two days the subject was required to remain at the clinic all day, and the subject traveled 40 miles round trip and was reimbursed at $0.30 per mile, total payment would be $195. Alternatively, in addition to reimbursement for their expenses, subjects could also be paid their regular wages for 29 hours. A professor might then be paid $50 per hour for a total of $1,645. Yet, a student who worked outside of class for $7 per hour would receive $398. Applying the three models to this case illustrates that different models can lead to large variations in the amount paid to subjects for participating in the same study.

Advantages and Disadvantages of Each Model

The market model has four potential advantages. First, it is likely to ensure a sufficient number of subjects in the time frame in which they are needed. Similarly, large completion bonuses are likely to ensure that the subjects complete the study. A third advantage is that the market model may allow subjects to make money while making a socially beneficial contribution. [2,21] Finally, this model is likely to reduce or eliminate the financial sacrifice of participation. The latter two advantages depend, of course, on the study's popularity, because this model will lead to little or no payment for participation in studies in which many subjects are eager to enroll without being paid.

Conversely, there are several possible disadvantages. One potential problem is that payment may be so high that all other factors become irrelevant to subjects' decisions to participate or to remain in research studies. Whether escalating payment can really compromise voluntariness is controversial. [4,5,21-23] But, it may be ethically problematic to commercialize research participation by "hiring" subjects who are motivated only by profit [8,9,24,25] or to offer very high payments to economically vulnerable groups. In addition, large total payments and completion bonuses may provide an incentive for the subject not to explore carefully the risks and benefits of the research or to conceal important health information in order to become or remain eligible for the study and thus receive payment. [1,5] Finally, the market model is likely to lead to situations in which researchers are

competing with each other for subjects on the basis of the amount they pay their subjects.

There are five potential advantages of the wage-payment model. First, the possibility of undue inducement or exploitation is lessened if subjects have other options for earning similar amounts of money. [5] Second, this model would lead to the standardization of payment among studies, lessening interstudy competition based on payment and potentially creating an incentive for investigators to minimize risks to subjects. The wage-payment model reduces the financial sacrifice of participation for subjects. In addition, the wages offered by similarly risky unskilled jobs serve as a lower limit on the amount offered for paid studies. Finally, the wage-payment model allows people to be paid for work that is valuable to society. [2,21]

This model may be less likely than the market model to yield a sufficient number of subjects in the desired time frame. The wage-payment model could also make paid studies attractive primarily to people with low incomes, particularly because it might involve financial sacrifice for wealthier participants. [2,4,5] Finally, treating the subject's role as an unskilled job may be seen as inappropriately commercializing participation in research. [8,9,24,25]

The reimbursement model has four potential advantages. By prohibiting monetary inducement, it not only alleviates any concern about undue inducement, but it also presents no incentive to conceal information or remain uninformed about risks and benefits. Furthermore, the reimbursement model does not preferentially induce vulnerable populations to participate. Finally, this model lessens the financial sacrifice of research participation to some degree.

The most obvious disadvantage of the reimbursement model is that it may yield an insufficient number of subjects within the desired time frame. [26] After all, in the current climate of commercialization, it provides no incentive to participate, and it will actually require financial sacrifice for almost all subjects if time away from work is not reimbursed. The only people who would not incur additional expenses if their time were not reimbursed would be those who are already hospitalized or who are unemployed. On the other hand, if time as well as other expenses are accounted for, different people will be paid unequally for the same contribution to research, a disparity that seems unfair. [5] The latter formulation is also likely to lead to either exorbitant costs or the targeting of low-income people in order to avoid paying higher participation costs.

The Model of Choice: Wage Payment

We recommend the adoption of the wage-payment model for three principal reasons. First, the wage-payment model greatly reduces the common worry about undue inducement. Because most potential subjects are likely to have other options for earning similar amounts of money, they will presumably choose participation in research when they prefer it to other options for earning an unskilled-labor wage. Given the prevalent view that subjects should to some extent support the goals of research, [7] money should not be the only factor influencing participation. Although money may be a motivating factor in subjects' decisions, it will not have such a predominant role as to negate the influence of other considerations. Because this concern is especially important when a study is very risky, not allowing payment

to escalate according to risk constitutes a crucial safeguard.

Second, standardization among studies is extremely valuable for several reasons. The minimization of competition for subjects on the basis of payment will help to contain the cost of research. Standardization also averts the creation of barriers to the success of less well funded studies and the encouragement of research on potentially lucrative drugs over equally important research on disease mechanisms and rarer diseases. Because the level of funding of a research study often correlates most closely with the commercial potential of the drug or device under study and not necessarily with its quality or social value, it is important to adopt practices that do not favor only well-funded studies. Standardized payment schedules will also be extraordinarily helpful to institutional review boards and investigators as a means of determining payments. Furthermore, not altering payments on the basis of risk creates an incentive for investigators to minimize risks in order to recruit subjects effectively.

Third, because payment is based on the contribution subjects make, the wage-payment model adheres to a basic assumption of the principle of justice: that similar people should be treated similarly. [27] This feature represents a great advantage over the reimbursement model, according to which already well-paid subjects would be paid more than those with lower incomes enrolled in the same study. It is also an advantage over the market model, which would allow site-specific markets to lead to very different levels of payment at different sites in multicenter studies.

The disadvantages of the market model are too serious for it to be the best approach. The chances that money would overshadow such factors as risk would be greatest in the studies with the greatest risks. Even for people who believe that subjects need no protection from monetary influence, [18,21] there are important reasons to reject the market model. Its likely effect on which studies are conducted and on the cost of research is profound. In addition, the potential effect of large completion bonuses on subjects' willingness to report side effects or withdraw from studies is problematic. Such an effect could compromise the validity of study data, thereby placing future patients and subjects at risk.

The reimbursement model is too restrictive, unfair, and unworkable. The mere payment of expenses incurred without reimbursement for time spent would no doubt hamper recruitment. Although reimbursement for these expenses may be incorporated into some versions of the wage-payment model, such reimbursement on its own would still entail considerable financial sacrifice for most participants. Alternatively, paying subjects the equivalent of their salaries for the time they spend participating appears unjust and will either drive up the cost of research or lead to the selection of only low-income people.

Conclusions

We believe that the wage-payment model represents the most ethical approach to paying research subjects, and we think it is an approach that can be successfully implemented through several key steps. To ensure local standardization of payment, research institutions and institutional review boards should develop specific policies or guidelines outlining how investigators should determine in which cases and in what manner to pay subjects who enroll in their studies. We also encourage the FDA and the Office of Protection from Research Risks to publish guidelines suggesting this model of payment, so that there will be more national

standardization of payment practices. Finally, we encourage pharmaceutical and biotechnology companies to develop industry standards conforming to the wage-payment model.

Although we recommend the broad implementation of this model, it is important to emphasize that further investigation of the payment of research subjects is critical, given the current lack of data. Four types of research will be particularly helpful in refining this model. First, it is crucial to evaluate the extent to which the cognitive, social, and physical status of potential subjects should alter decisions about payment for research participation. Second, there is a need for empirical research to determine the ways in which offers of money affect the quality of subjects' informed consent. Third, it is important to study whether payment leads to the recruitment of a disproportionate number of poor subjects. Finally, there is a need for data on the importance of payment with respect to successful recruitment; little is known about the effect of different amounts or methods of payment on recruitment efforts. [26]

For the present, the wage-payment model, coupled with a commitment to rigorous research, will most effectively balance the increasing need for human research subjects with adequate protection of the subjects who make such research possible.

Neal Dickert, B.A.

Christine Grady, Ph.D.

National Institutes of Health; Bethesda, MD 20892

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