

Payments to Normal Healthy Volunteers in Phase 1 Trials: Avoiding Undue Influence While Distributing Fairly the Burdens of Research Participation

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Clinical investigators must engage in just subject recruitment and selection and avoid unduly influencing research participation. There may be tension between the practice of keeping payments to participants low to avoid undue influence and the requirements of justice when recruiting normal healthy volunteers for phase 1 drug studies. By intentionally keeping payments low to avoid unduly influenced participation, investigators, on the recommendation or insistence of institutional review boards, may be targeting or systematically recruiting healthy adult members of lower socio-economic groups for participation in phase 1 studies. Investigators are at risk of routinely failing to fulfill the obligation of justice, which prohibits the systematic targeting and recruiting of subjects for reasons unrelated to the nature of the study. Insofar as we take seriously the obligation to engage in just subject recruitment and selection, I argue that we must acknowledge the implications low payments might have for subject recruitment and selection and examine the effect of low payments. If low payments de facto target the less well-off for phase 1 studies, we must defend the priority ranking of the obligation to avoid undue influence over the obligation of justice or adopt an alternative recruitment approach. This paper identifies a number of alternatives to the current system of low-value payments to research participants.

Keywords: *incentives, justice, normal healthy volunteers, payments, phase 1 studies, recruitment, respect for persons, undue influence*

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I. INTRODUCTION

To conduct clinical trials ethically, investigators must engage in just subject recruitment and selection and avoid unduly influencing research participation. There may be tension between the practice of keeping payments to participants low to avoid undue influence and the requirements of justice when recruiting normal healthy volunteers (NHVs) for phase 1 drug studies. Phase 1 studies are the early human studies of a new agent conducted to evaluate the safety and tolerability of an investigational agent and to explore how the agent functions and is metabolized in humans. Phase 1 studies of new agents to treat cancer enroll patients with cancer, but phase 1 studies for many other types of drugs enroll healthy people. The latter are the focus of this paper. It is a widely, though not universally (Savulescu, 2001; Zink, 2001), held recommendation that low (Grady, 2001; Dickert and Grady, 1999), or no (McNeil, 1997; Reame, 2001) payments be offered to potential research participants to avoid unduly influencing them. The term “payments” refers to transfers of money or its equivalent (e.g., gift cards) not intended as reimbursement for actual expenses, for example, cab fare or parking. It is neutral on the important question of whether those payments should be treated as incentives or wages. (For further discussion of incentives versus wages, see Dickert and Grady, 1999.) By intentionally keeping payments low to avoid unduly influenced participation, investigators, on the recommendation or insistence of institutional review boards (IRBs), may be targeting or systematically recruiting healthy adult members of lower socio-economic groups for participation in phase 1 studies. Investigators are at risk of routinely failing to fulfill the obligation of justice, which raises serious ethical concerns. Insofar as we take seriously the obligation to engage in just subject recruitment and selection, I argue that we must acknowledge the implications the no- or low-payment approach may have for subject recruitment and selection and examine the effect of low payments. If low payments *de facto* target the less well-off for participation in phase 1 studies, we must defend the priority ranking of the obligation to avoid undue influence over the obligation of justice or identify an appropriate alternative.

We have limited data on who participates in phase 1 studies, though it appears that the less well-off, including the homeless, may participate at higher rates than the better off (Beauchamp et al., 2002; see also McNeil, 1997). We also have limited data on payment practices in research, though it seems that financial payments often are offered to encourage healthy adults to participate in phase 1 studies (Dickert, Emanuel, and Grady, 2002). Finally, we have limited data on what motivates NHVs to participate in phase 1 trials. In the United States and elsewhere, money appears to be a significant motivating factor for some research participation, and the less well-off may be more motivated than others to participate in phase 1 trials (Hassar et al., 1977; Novak, Seckman, & Steward, 1977; Robertson, 1986;

Bigorra and Banos, 1990; Dooley, 1991; McNeil, 1993, 176; Tishler and Bartholomae, 2002; Tishler and Bartholomae, 2003). For example, Kirkpatrick found that “money is the primary reason young [mean age 28] and elderly [mean age 72] volunteers participate in their first drug study and the primary reason young volunteers participate in subsequent studies” (1991, 109). There is no evidence to suggest that most NHVs who enroll in phase 1 studies do so for primarily idiosyncratic reasons, such as an interest in science, a relationship with someone who has the condition a new agent may be meant to treat, a concern with promoting research on conditions they have, or because they are altruistic (Kirkpatrick, 1991, 109–113).

It is reasonable to believe that altruism and idiosyncratic interests alone are unlikely to motivate a sufficient number of healthy persons to volunteer as subjects for phase 1 trials (Bevan et al., 1993; Resnik, 2001; Tishler and Bartholomae, 2002, 368). Without payments, recruitment may be slow and a sufficient number of subjects may never be found (Miller and Grady, 2001, 1032). It may be especially difficult to recruit based on altruism for phase 1 studies if investigators offer an honest appraisal of how likely it is that any individual’s participation will make a significant difference in someone else’s life. Phase 1 studies are distant from the development of therapeutic interventions, and Pharmaceutical Research and Manufacturers of America (PhRMA) estimates that only about one of every five compounds that enters a phase 1 trial becomes a Food and Drug Administration (FDA) approved drug (2006, 4). If we consider the likelihood of an investigational agent becoming an approved drug and discount the value of compounds that become FDA-approved but that do not significantly improve health outcomes for patients overall (e.g., a medication for a condition for which an effective treatment is available and that does not pose fewer or less worrisome side effects, does not have a better risk profile, and will not be priced significantly below its competitor drugs), then the significance of any given contribution may be so limited that it does not motivate altruists. In short, money appears to play an important role in recruiting NHVs into phase 1 studies. It might be impossible to maintain current levels of clinical research if NHVs are offered no money and we rely solely on altruism and idiosyncratic reasons to motivate participation. Insofar as the amount of money offered is modest, it is likely to motivate primarily the less well-off or persons who face an immediate need for cash. This combination of circumstances puts investigators at risk of targeting or systematically recruiting the less well-off by offering low payments to NHVs in phase 1 studies, raising questions about justice in subject recruitment.

Our assessment of the possible tension between the requirements of the principle of justice and actions taken to fulfill the principle of respect for persons, from which the obligation to avoid undue influence is derived, turns on our understanding of what these principles require. This paper offers an interpretation of the obligations grounded in these principles, argues that the current strategy for recruiting NHVs into phase 1 studies using low

payments puts investigators at risk of systematically targeting the less well-off and hence of violating the obligation of justice, and considers alternatives that might avoid this concern. This analysis involves a number of hypothetical claims about who is motivated to participate in research and what motivates them. Given the limited data we have that suggest that the less well-off may be over-represented in phase 1 studies, we are warranted in examining the ethical issues that emerge should these hypothetical claims be true. There has been little effort in the United States and elsewhere to document demographic characteristics of NHVs who participate in research or to study what motivates participants. This paper demonstrates that if the less well-off are the *de facto* targets of recruitment efforts for phase 1 studies, investigators and institutions may be routinely violating their obligation of justice. In light of this analysis, we should make a greater effort to pursue quantitative and qualitative research to determine who participates and why.

II. THE OBLIGATION TO AVOID UNDUE INFLUENCE AND THE OBLIGATION OF JUSTICE

The principles for the ethical conduct of research and the obligations implied by these principles as developed in the Belmont Report (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, 1979) serve as a starting point in this analysis because of the Belmont Report's authority in U.S. research ethics. The obligation to avoid undue influence is established in the Belmont Report as part of the duty to obtain participants' free and voluntary informed consent, which is derived from the principle of respect for persons. To obtain free and voluntary consent, investigators must avoid coercion and undue influence:

Coercion occurs when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance. Undue influence, by contrast, occurs through an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance (National Commission, 1979, C).

The Belmont Report does not offer an independent measure of what is "excessive, inappropriate, or improper," but we can conclude that some offers are acceptable because offers are not categorically prohibited (Emanuel, 2004). Persons who have adopted an understanding of undue influence compatible with the Belmont Report hold that undue influence involves offers that are irresistible and not merely attractive (Faden and Beauchamp, 1986, 356) or offers that render persons unable or unwilling to judge risks and benefits of participation (Macklin, 1981; Levine, 1986; Ackerman, 1989; McGee, 1997; Wilkinson and Moore, 1997; Emanuel, 2005; Grady, 2005; see also Dickert, Emanuel, and Grady, 2002; Tishler and Bartholomae, 2002). This view is different from one that would treat any situation in which a person is motivated by an offer as an instance of undue influence.

The potential for payments unduly to influence research participation has been thoroughly discussed, though not studied (see e.g., Rudy et al., 1994; see also Macklin, 1981; Levine, 1986; Ackerman, 1989; McGee, 1997; McNeil, 1997; Wilkinson and Moore, 1997; Dickert and Grady, 1999; Emanuel, 2005; Tishler and Bartholomae, 2002;). In addition to those who worry that substantial offers will be irresistible or render potential participants unable or unwilling to judge a study's risks and benefits, some worry that any level of payment will result in unduly influenced or coerced research participation (see e.g., Wartofsky, 1976; McNeil, 1997; Kuczewski, 2001, 49). Even when offering low-value payments, some warn, investigators must assess the motivations of individual volunteers to ensure that they were not unduly influenced by money or other advantages (Grady, 2001; Beauchamp et al., 2002; Tishler and Bartholomae, 2002). Concerns over the potential for money to unduly influence research participation have been especially pertinent to phase 1 studies enrolling NHVs.¹

If payments to NHVs in phase 1 studies are kept low to avoid having potential participants find the offers irresistible or be unable or unwilling to judge the risks of participation and an insufficient number of people are motivated to volunteer out of altruism or for an idiosyncratic reason, at least some participants will have to be recruited from among persons motivated by the low payments. If this is true, and those motivated by low payments are most likely to be from among the less well-off members of society, then payments are offered for the purpose of motivating participants and we expect that those most likely to respond to offers are the less well-off. This would render the less well-off the *de facto* targets of low-value payments, which would involve violations of investigators' obligations of justice, as described below. As noted earlier, this analysis turns on a number of hypothetical statements that are reasonable given current data but that have not been substantiated by the limited evidence we have about the NHVs who participate in phase 1 studies and what motivates them.

The Belmont Report requires investigators and IRBs to ensure that subject recruitment and selection are just:

the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients ...) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied (National Commission, 1979, B.3).

Injustice may appear in the selection of subjects, even if individual subjects are selected fairly by investigators and treated fairly in the course of research. Thus injustice arises from social, racial, sexual and cultural biases institutionalized in society. Thus, even if individual researchers are treating their research subjects fairly, and even if IRBs are taking care to assure that subjects are selected fairly within a particular institution, unjust social patterns may nevertheless appear in the overall

distribution of the burdens and benefits of research. Although individual institutions or investigators may not be able to resolve a problem that is pervasive in their social setting, they can consider distributive justice in selecting research subjects (National Commission, 1979, C.3).

The obligation to respect the principle of justice is echoed in the Code of Federal Regulations, which requires that IRBs consider subject selection when reviewing a protocol and ensure that:

Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons (45 C.F.R. 46.111a3 and 21 C.F.R. 56.111a3).

The *de facto* targeting of the less well-off for participation in phase 1 studies enrolling NHVs would constitute a violation of the obligation of justice. Before defending this claim, I evaluate two arguments that could be made to deny it. First, one might note that the Belmont Report distinguishes between justice in the recruitment process and justice in outcomes. Even if investigators act fairly, there may still be an unjust enrollment pattern. The obligation of justice requires fairness in the recruitment and selection process but not necessarily in the outcome. It prohibits investigators from *purposely* seeking to recruit and select disadvantaged or otherwise vulnerable persons, but it does not require that investigators achieve or even actively try to establish just enrollment patterns. The obligation of justice is a negative one. Offering low incentives with the goal of avoiding undue influence, even if it happens to increase the likelihood that a disproportionate percentage of subjects will come from among the less well-off, is compatible with fulfilling the negative obligation of justice. This argument fails. In choosing actions aimed at a good, we must consider the potentially harmful implications or side-effects of the act. In some cases, we may conclude that the act is justified despite its side-effects, but such a conclusion must be defended. In many other cases, we may conclude that we should find an alternative that avoids the side-effects. Recognizing an act with harmful side-effects as justifiable is different from claiming that no obligation to avoid the harm exists. Moreover, the Belmont Report and the CFR call on investigators to avoid systematically recruiting or selecting participants for reasons not related to the matter under investigation. The Belmont Report and the CFR do not simply say that investigators must avoid targeting the disadvantaged *intentionally* but rather that they must avoid systematically targeting them.

Second, one could hold that the obligation of justice is fulfilled as long as the population of participants in human research overall appropriately represents various segments of society. No trial in particular, and no specific type of trial, must include a representatively diverse population as long as

the subject pool of any given study is sufficiently diverse to yield generalizable data. For some time we have been concerned that some populations may have disproportionate access to some potentially therapeutic clinical trials (Haynes and Smedlye, 1999; Gifford et al., 2002; Heiat, Gross, and Krumholz, 2002), whereas others may be over-represented in trials not expected to have therapeutic benefit (McNeil, 1997; Beauchamp et al., 2002) or that concern potentially stigmatizing conditions (McNeil, 1997; Beauchamp et al., 2002; Walsh and Ross, 2003). To suggest that representation of different socio-economic groups in research overall is sufficient to fulfill the obligations associated with the principle of justice is to ignore these concerns and discount the importance of the distribution of the benefits and burdens of research participation. Enrollment patterns that disproportionately benefit some populations and burden others are incompatible with the Belmont conception of justice when those patterns are not “directly related to the problem being studied” (National Commission, 1979, B.3).

It is reasonable to predict that low payments to NHVs in phase 1 studies will result in the disproportionate over-representation of the less well-off in such trials, and the limited demographic data we have on the healthy adults who participate in phase 1 studies support this prediction. To continue requiring low payments without making a substantial effort to determine whether the less well-off are *de facto* being systematically and predictably targeted and without exploring alternatives to correct the suspected imbalance is problematic. It is to accept as appropriate knowingly and willingly risking violations of justice. Two responses to this conclusion are possible. One is to defend the *de facto* targeting of the less well-off by defending the priority of the principle of respect for persons over the principle of justice. The other is to call for further research on who participates in phase 1 studies and why and to explore alternative recruitment strategies. Both are considered below.

III. THE PRIORITIZATION OF THE PRINCIPLE OF RESPECT FOR PERSONS OVER THE PRINCIPLE OF JUSTICE

Sometimes actions that violate certain norms or values are permissible because they are overall the ethically best option. To evaluate whether it is justifiable to violate the principle of justice to fulfill the principle of respect for persons in recruiting NHVs for phase 1 studies, we may use a five-element framework developed by Childress et al. (2002) to evaluate the permissibility of overriding important values or norms, such as liberty or justice, to promote other values, such as public health. Here we use the framework to determine whether fulfilling the principle of respect for persons in part by avoiding undue influence warrants overriding the principle of justice by making the less well-off the *de facto* recruitment targets. The justificatory framework requires an affirmative answer to five questions to conclude that it is justifiable to infringe on some values for the sake of others.

First, is the practice of offering only low payments *effective* in avoiding undue influence? We do not know. We have no data telling us how many, if any, of the NHVs who enroll in phase 1 studies have found an offer of a low-value payment one they could not refuse or have been unable or unwilling to judge the risks of participation because of the offer. (Recall that these are common interpretations of what it means to avoid undue influence.)

Second, does the probable benefit of avoiding undue influence by offering only low payments *outweigh the infringement* on justice? The Belmont Report presents the principles of respect for persons and justice as two of three unranked important principles. There is no reason antecedently to hold that respect for one principle is more important than respect for any other, though it is not surprising that the goal of avoiding undue influence dominates attention in the United States given what some suggest is a preoccupation with autonomy in U.S. bioethics (see Callahan, 1994; Pellegrino, 1994). It is possible that we should be more concerned with avoiding undue influence and with intentional violations of justice rather than with unintentional injustices that emerge in research enrollment patterns. But this view has not been defended. Moreover, insofar as we are aware of potentially unjust enrollment patterns, at the very least we ought to evaluate whether there is an injustice and identify the conditions that lead to the injustice to determine whether we may avoid the injustice.

Third, to avoid undue influence, is it *necessary* to offer only low payments that may effectively target primarily the less well-off to participate, thereby violating the principle of justice? Perhaps not. Thus far we have not seriously explored alternatives that would enable investigators to honor both principles. Much of the remainder of this paper considers some alternatives.

Fourth, is offering low payments to all participants the mechanism for avoiding undue influence that *least infringes* on the obligations of justice? Again, we do not know. In the absence of serious consideration of alternatives and empirical data about research participation and motivation, it is not possible to assert that the status quo is the mechanism that least infringes on the obligation of justice. This supports the need for further empirical research on research participation.

Fifth, if the practice of offering low payments to all potential participants may result in a violation of the principle of justice, has *public justification* for the decision to offer uniformly low payments been given? In particular, is the decision transparent to those negatively affected by the decision, namely the less well-off who become the *de facto* targets of recruitment? The research ethics literature is full of defenses of low payments for research participation. However, rarely do we see recommendations for low payments directly address the issue of justice and the possible tension between efforts to avoid undue influence and justice. The decision to risk violating the principle of justice to fulfill the principle of respect for persons has not been publicly defended. Moreover, potential research participants are rarely, if ever, told why a particular offer is made.

It is possible that few trials, if any, will include a perfectly proportional representation of individuals from different socio-economic groups. This does not mean that investigators are not obligated to implement effective measures to recruit NHVs from different segments of the population so that the benefits and burdens of research are more equitably—even if not perfectly—distributed. We cannot assert definitively that our current pattern of enrollment of NHVs into phase 1 studies is inequitable because we have limited demographic data on participants and limited information on how much subjects are paid for specific studies. We also do not know whether any measures could effectively improve the representativeness of the subject population, or whether the only effective measures would violate other conditions for the ethical conduct of research. Nevertheless, we should take seriously the possibility that the current strategy of low payments, held up as the ethical approach to recruiting NHVs for phase 1 studies, may lead to routine violations of the principle of justice. If we take this possibility seriously, we will defend the ethical priority of the obligation to avoid undue influence over the obligation of justice and demonstrate that low payments meet all other criteria above, or we will investigate current recruitment and enrollment patterns to determine whether *de facto* the less well-off are systematically targeted. If they are, we must consider alternative strategies that might allow investigators to fulfill the obligation to avoid undue influence and to respect the principle of justice.

IV. ALTERNATIVE RECRUITMENT STRATEGIES

We should avoid presuming that uniformly low payments necessarily are the most appropriate mechanism for recruiting subjects and take seriously the possibility that low-value payments offered to NHVs in phase 1 studies may lead to failures of justice. If the current low-value payment strategy, which is meant to avoid unduly influenced research participation, results in failures of justice, then we must identify alternatives to the current strategy. Alternatives to the low payment strategy are considered here to assess whether we can satisfactorily resolve the tension between (1) the desire to avoid undue influence by restricting payments, which may result in the targeting and over-recruitment of less well-off healthy adults into phase 1 studies and (2) the obligation of justice according to which we must (a) avoid systematically recruiting particular groups of subjects for reasons not related to the problem under investigation, (b) avoid targeting stigmatized or vulnerable individuals, (c) avoid disproportionately recruiting and enrolling participants from specific groups except when necessary and appropriate to meet scientific goals, (d) engage in just subject selection such that the burdens of research are shared, and (e) ensure that those who are likely to benefit share some risk and burden and that those who participate are part of a group likely to benefit (Emanuel, Wendler, and Grady, 2000). Some alternatives merit greater consideration than they have been given thus far in the literature.

Differential Payments

One alternative to uniformly low payments is to offer payments to individuals based on what is likely to motivate them without unduly influencing them. Different offers could be determined by how much money persons typically make in the time required for study participation or another baseline. Some participants might be offered something other than or in addition to money because they might be more motivated by, for example, gift cards to expensive stores or an opportunity than by cash. A differential payment system could take many forms. The possibility is introduced here to evaluate whether it is a potential alternative to the current recruitment and payment system that would satisfy (a) the need to enroll a sufficient number of subjects, (b) the obligation not to unduly influence participants, and (c) the obligation to avoid systematic recruitment of subjects from specific groups without a valid scientific reason for doing so. This approach raises significant concerns, twelve of which are discussed below. Nevertheless, it should not be dismissed without due consideration or without demonstrating that it is inherently wrong to pay people differently, that it is morally better to over-recruit the less well-off than to offer unequal payments, or that for some other reason the proposal is morally unacceptable, as some have done (see e.g., Newton, 1982).

The first concern is that paying people different amounts for entering the same study is discriminatory; it involves treating similarly situated people differently (see Beauchamp et al., 2002, 556). To discriminate means “to make a distinction” or “to make a difference in treatment or favor on a basis other than individual merit” (Merriam-Webster Online, 2007). Numerous widely accepted practices in our society involve discrimination against people who are very similarly situated for purposes of achieving some other goal. Schools sometimes apply different admissions standards for students with particular racial, ethnic, or socio-economic profiles or students whose parents are alumni. Parents who are enrolling a child in a school may be given preference for enrolling a younger sibling over parents who have no children in the school. Where a person lives may play a role in determining whether the person will be given priority for an organ that becomes available for transplantation. Our society holds that some forms of differential treatment are legitimate even when the basis for treating similarly situated people differently is not individual merit. Differential payments for research participation might be a case of appropriate, justified discrimination aimed at fulfilling some of the obligations of the ethical conduct of research as set forth in the Belmont Report and the CFR, namely the participation of a wider range of people in research to achieve a better distribution of benefits and burdens of participation and the avoidance of unduly influenced participation or of the systematic targeting of particular groups. The claim that differential payments constitute illicit discrimination depends on the truth of

two claims: (1) equals are being treated unequally and (2) it is wrong to treat equals unequally in this case. To know whether differential payments constitute wrongful discrimination, we need to know what makes people unequal and equal and which differences legitimately may be considered in determining how to treat people.

The charge that unequal payments constitute illicit discrimination is more plausible if payments are treated as wages than as incentives and there is no difference in the quality or value of the work different participants provide. Nevertheless, different wages for participation could be defended by arguing that some people's time is worth more than other people's time on the labor market. Insofar as one wants to hire people who command higher pay, one will have to pay them accordingly. Insofar as investigators are trying to meet enrollment goals established as part of achieving justice in recruitment, finding ways to enroll those who will be motivated only by more money or other privileges without unduly influencing other participants is important. If payments are treated as incentives, the charge of illicit discrimination is less plausible. If different persons require different offers to motivate them and one's goal is to motivate various individuals to participate without unduly influencing any participant, then it may be legitimate to offer different incentives to different persons. Incentives are, by their nature, subjective. Motivating a wide range of persons to respond in the same way might require different offers. Insofar as one holds that it is important to motivate those different parties, it may be legitimate to treat people's motivational structures and their anticipated responses to offers as legitimate differences among them that justifiably warrant differential treatment.

A second objection to unequal payments is that the practice would penalize the less well-off (see Beauchamp et al., 2002, 556). If "penalty" refers to "disadvantage, loss, or hardship due to some action" (Merriam-Webster Online, 2007), unequal payments are not penalties. They do not involve imposing a hardship or disadvantage or withdrawing a privilege. Different offers are made and no one is required to accept any offer. Currently, people in different studies that involve comparable amounts of time and inconvenience or in the same study at different sites, may be paid differently. Generally, we do not hold that those who are paid less despite comparable inconveniences are being penalized. In the new system, some persons in the same study at the same site would be paid differently not as a penalty but in an effort to promote other ends.

A third objection to unequal payments is that they are exploitative or potentially exploitative (Beauchamp et al., 2002, 556). Presumably, the concern is that differential payments would exploit the less well-off because they would be offered less money than the better off to participate in the same research. To exploit is "to make use of meanly or unfairly for one's own advantage" (Merriam-Webster Online, 2007). Several accounts of exploitation in biomedical research echo this definition. According to De Castro

“[e]xploitation involves the taking advantage of someone by another. It is a relational concept that seems to suggest an intention on the part of one party to make use of another for her/his own purposes” (1995, 260). On this account, unequal payments are not necessarily exploitative. If differential payments are offered to avoid unduly influencing participation while recruiting people from different socio-economic groups to participate, unequal payments are not aimed at taking advantage of others and are not exploitative.

Wertheimer argues that exploitation involves the unfair taking advantage of one person by another (1987). Building on this understanding, Resnik argues that “A exploits B in a transaction or relationship if and only if: (1) A takes advantage of B and (2) A harms B, A disrespects B, or A acts unjustly toward B” (2003, 235). The first condition, that A takes advantage of B, generally does not apply to the case of differential payments. If payment levels are set by asking “how low can we go and still get enough people to participate?” investigators may be taking advantage of the less well-off. But if the scale is developed with the goal of offering payments that will motivate but not unduly influence participants, the charge of taking advantage of the less well-off is misplaced. Investigators merely are offering payment for participation commensurate with a participant’s overall socio-economic status. Participation is not required of anyone and failure to participate does not entail loss of other benefits to which a person is entitled. Differential payments would take advantage of the less well-off if they were forced to participate for less money, but no one is obligated to participate. Even if in offering differential payments investigators were taking advantage of the less well-off, we would have to demonstrate that they also harmed, disrespected, or acted unjustly toward participants to claim that they exploited persons. Here one’s views of harm, disrespect, or injustice will determine whether one deems differential payments exploitative. For example, Resnik holds that “[p]aternalistic actions involve exploitation even when they benefit the exploitee” (2003, 236). If one offers low payments to persons one believes are likely to be unduly influenced by higher payments, one may be accused of acting paternalistically and hence of disrespecting those who receive lower payments. Others might argue that if the payment structure is transparent, in offering different payments for participation one merely is extending different offers and respecting the authority of individuals over themselves. Persons are free to accept or reject these offers. One is not tricking or manipulating anyone into participating, much less into participating for less money.

Even if one holds that paying participants in the same trial differently is exploitative, it may be permissible. Resnik argues that exploitation must be evaluated in the context of all the reasons for and against performing an act. Although exploitation is wrong and to be avoided, exploitation may be permissible if “the moral reasons in favor of X ... outweigh the wrongfulness of its exploitative features” (2003, 250). Even if differential payments were deemed exploitative, it might be permissible to adopt the practice if it were

necessary to fulfill morally worthy goals or obligations. We could once again use the five-element justification framework developed by Childress et al. (2002) to determine whether it is permissible to exploit in an effort to achieve justice. Again we would find that in the absence of data, it is impossible to assert definitively that the current system or any other approach is justified.

Fourth, someone might object to unequal payments because they lead to an unfair distribution of benefits and burdens of research. For this objection to be valid, money would have to be treated as a benefit of research participation. This would be a departure from the FDA and Office for Human Research Protections (OHRP) policies that disallow investigators and IRBs from considering payment as a benefit of research (OHRP, 1993, chapter 3; FDA, 1998). Unequal payments would aim to decrease the burden of participation that currently might be borne by a segment of the population that appears to be over-recruited into phase 1 studies and they would not affect the benefits of participation.

A fifth objection is that it would be impractical to offer unequal payments (Beauchamp et al., 2002, 556). This may be true, but it is not an in-principle objection to unequal payments. At one time we may have thought that other requirements for the ethical conduct of research would be too impractical, and some would argue that our current system of IRB review is impractical. Judgments about whether a plan is “too impractical” turn in part on the value we assign to different goals and how creative we are in imagining different mechanisms to execute a particular practice. If our current practices violate obligations of justice and unequal payments are the best mechanism to correct the injustice while still respecting persons, we should develop an effective plan to implement unequal payments or we must defend the claim that it is more important to have an easy payment system than a just one.

A sixth objection to unequal payments is that they may be ineffective at broadening the participant pool while avoiding undue influence. The majority of participants might come from among the less well-off despite unequal payment offers because some individuals may not be motivated to participate under any circumstances or would respond only to offers many deem exorbitant or inappropriate, such that there might not be appropriate representation from all members of society. Or, some participants could be unduly influenced even if we enacted an unequal payment system. If unequal payments will not fulfill the goal of representative participation of people who are better off in phase 1 studies, then unequal payments should not be employed. While differential payments are unlikely to achieve equitable representation of all socioeconomic groups, if they were to expand significantly the range of participants, we would be closer to fulfilling the obligation of justice. That we cannot fulfill the goal perfectly does not mean that we should not attempt to improve our aim. The effect of unequal payments would have to be studied. If another plan would be more effective in broadening the range of people who participate in phase 1 studies without violating other

important values and goals, then it would be appropriate to consider that alternative instead of unequal payments.

A seventh objection is that unequal payments are unjust or perpetuate past injustices. For example, Newton, agreeing with Macklin (1981) claims that “offering a different amount of money to each person, for the same work, [is] so clearly in conflict with justice as not to merit further consideration ...” (Newton, 1982, 5). Newton does not define and defend a conception of justice under attack. I have argued here that the current practice of equal low payments for all may violate the conception of justice articulated in the Belmont Report and reflected in the CFR’s discussion of equitable subject selection (45 C.F.R. 46.111.a.3). Some of the mechanisms that might be adopted to determine how much participants would be paid could reflect previous sources of inequality and injustice. Although not all persons who are in lower socio-economic groups are there because of past injustices, some may be, and offering such persons less money for research participation could be seen as reflecting past injustices. As a society we often treat people differently in ways that are not necessarily in their interest because they are less well-off and we accept such differential treatment even when they are less well-off because of past injustices. For example, people who are in a nursing home and whose care is being covered by Medicaid often are denied a private room. Surely some of them may be poor at least in part because of past injustices. Even if they strongly prefer a private room, generally we do not insist that they all receive private rooms because their circumstance reflects a past injustice. Differential payments for research participation may be another form of justified differential treatment.

An eighth concern is that adopting differential payments might motivate investigators and sponsors to actively recruit those who are less well-off into research. Research could be conducted for less money if primarily those who will be paid less enroll. This motivation to recruit participants who will “cost” less is a species of conflict of interest concerns and should be avoided. Although it is desirable to avoid such conflicts, they have thus far not been treated as absolute impediments to research because of the potential for more harm to result from their complete elimination (Goldner, 2000). Should differential payments generate a new conflict, we may choose to tolerate and manage the conflicts rather than disallow them if the advantages of differential payments are significant.

Ninth, subjects who are being paid less may become angry if they learn of the differential payments. The possibility of subject anger and its implications, for example, erosion of trust or future difficulty in recruitment, should be taken seriously. The concerns may be too grave to warrant unequal payments, but potential discontent among subjects is not necessarily a reason to disregard the option of unequal payments. Other taken-for-granted practices in research, such as the use of placebos in some studies, paying subjects in the same study at different sites differently, and the possibility of companies

and investigators making large sums of money by using subject's tissue samples, may make subjects angry and erode trust. This potential anger is not treated as a reason to alter study design or to distribute earnings differently in most cases. If unequal payments are necessary fully to respect the principle of justice and avoid unduly influencing participants, differential payments may be appropriate even though they might anger some persons.

Tenth, increasing payments or increasing some payments could increase the cost of research. Many of the requirements for the ethical and compliant conduct of research add costs to the research enterprise. We should ask of each of these: is it worth the cost? If we think we should aim to fulfill the Belmont conception of justice while avoiding undue influence, that the current use of low, equal payments to all NHVs fails in this regard, and that unequal payments will achieve these goals, then the additional costs associated with unequal payments may be worthwhile. It also is possible that higher payments to some participants could lower overall costs of research or not affect the overall costs because they could increase the speed of recruitment or improve retention rates.

An additional concern is that offering different payments is paternalistic; it assumes some people are less capable than others of evaluating a study's risks or refusing offers. The charge that a practice is paternalistic does not speak definitively against it. Human research is subject to codes of ethics and government regulations that require paternalistic practices. Moreover, the current insistence on uniformly low payments based in part on an interest in avoiding undue influence also is paternalistic. If one finds paternalism to be a wrong-making condition, not only are differential payments unacceptable but so are many other standard requirements for the conduct of research, including reliance on uniformly low payments.

Finally, some might hold that it is perverse to offer more money to the rich than the poor or to persons who are less willing to make personal sacrifices than to those willing to participate in the same study for less money. If the goal of differential payments is to enable investigators simultaneously to fulfill the requirements of the principle of justice and the obligation to avoid undue influence, then we may accept this implication. If this arrangement is deemed unacceptable and in fact the less well-off are over-represented in phase 1 studies and are the *de facto* targets of low payments, we must alter our conception of justice, find another way to increase participation of NHVs from among the better off or demonstrate that it is more important ethically to avoid undue influence than to fulfill the obligation of justice and that offering low, equal payments to all is effective in avoiding undue influence.

These concerns may be legitimate and should be considered in evaluating options for recruiting NHVs to participate in phase 1 studies. However, if current strategies result in the *de facto* systematic targeting of the less well-off and hence in violations of the principle of justice, alternatives to the current approach, including unequal payments, should be considered. None of

the concerns associated with unequal payments clearly is morally more serious than the *de facto* systematic targeting and over-recruiting of healthy adults who are less well-off into phase 1 studies. None is a reason for absolutely rejecting unequal payments. We should not presume the obligation of justice is so insignificant as to justify routinely failing to fulfill it in the name of equality.

Higher, Equal Payments For All Subjects

A second alternative to address the possible tension between the obligation to avoid undue influence and the obligation of justice is to offer equal but higher payments or to offer alternative forms of payment of equal but higher value to all participants (Menikoff, 2001).² As in the present system, investigators would have to avoid enrolling unduly influenced participants (Grady, 2001). If one paid all participants more, one might motivate more persons who are better off to participate while not discouraging the less well-off from participating. We would be more likely to achieve the goal of having a sufficient number of subjects and the goal of achieving a just distribution of the benefits and burdens of research. A number of possible concerns with this proposal are considered.

First, some might hold that to increase payments would increase unduly influenced participation, particularly among the less well-off. Concerns with undue influence emerge as soon as any payment or any other advantages are offered because there are some persons for whom any amount of money or any benefit is irresistible. One justification for offering low payments might be that they minimize the number of persons who cannot resist the offer or whose capacity to evaluate risks and benefits is compromised in light of the offer. Some supporters of low payments argue that investigators must assess the motivations of each subject to screen out those who volunteer because they feel unable to turn down the money (Grady, 2001, 2005). Although some have criticized this screening approach as paternalistic (Vanderpool, 2001) and one could argue that investigators have conflicts of interest that could affect their assessment of participant motives, I grant this recommendation for the sake of argument. Once investigators are in the business of assessing participants' motives, it is plausible that they might offer higher payments and, just as they would do if they offered lower payments, assess the motives of potential subjects to ensure that they are freely choosing to participate and that their ability or willingness to evaluate risks and benefits has not been compromised. Higher payments might raise the stakes of this assessment because more people might find the offer irresistible or be unable or unwilling to judge the risks of participation in light of the offer. Nevertheless, insofar as payments or any other offer or advantage, such as meals and lodging, may unduly influence some potential subjects and investigators must avoid unduly influencing anyone, researchers are not

obligated to minimize the number who *might be* unduly influenced. Rather, they must not enroll persons who *have been* unduly influenced. Low payments do not solve the problem of undue influence; careful enrollment does.

Second, increased payments could render a greater proportion of the less well-off ineligible to participate. If higher payments are more likely to unduly influence the less well-off and such persons are screened out, then the less well-off could be under-represented or we could see enrollment shortfalls in research. The validity of this concern turns on the extent to which money renders potential participants unable to understand and appreciate information about risks, which remains an open question (Grady, 2005; see also Russell, Moralejo, and Burgess, 2000; Bentley and Thacker, 2004; Halpern et al. 2004), and the extent to which money would be more likely to unduly influence the less well-off than other persons. Insofar as persons remain willing and able to judge the risks of participation to refuse an offer, they remain *prima facie* eligible. It is plausible that among the less well-off we will find potential participants capable of making informed decisions in light of offers of payment and that among the well-off we will find persons who are unable or unwilling to evaluate risks and benefits or resist the opportunity to make money.³ It is important to recognize that a willingness to do something for money in itself does not indicate that a person was unduly influenced.

Third, offering higher payments overall might not be effective in encouraging the better off to enroll. If so, then the potential risks of higher payments, such as the possibility that more participants will be unduly influenced, will not be offset by the hoped-for benefit of increased participation among the better off. As with several other issues discussed here, the validity of this objection turns on empirical evidence currently unavailable. If this is a valid concern and the current approach of equal, low payments for all leads to the *de facto* systematic targeting and recruitment of the less well-off, we should identify a satisfactory alternative that enables investigators to conduct research ethically.

Fourth, to offer higher payments to all participants could increase the overall costs of conducting research. Increased costs might be offset by other advantages, such as the possibility that recruitment will be speedier. If higher research costs are not offset, we must ask whether such costs are worthwhile. As noted earlier, a number of the mechanisms in place to promote the ethical conduct of research most likely add costs to the research enterprise. Higher costs do not necessarily mean we should not pursue the option if the new system makes it possible to fulfill the principles of respect for persons and justice in research.

Insofar as any one or combination of the above concerns regarding unequal payments or higher overall payments is offered as a definitive reason for choosing equal, low payments for all participants, such concerns should be evaluated against the need to fulfill the principle of justice.

No Payments

A third possibility is to disallow payments to participants and recruit based on altruism or special interest alone. We do not know on balance what the subject population would look like if no financial incentives were offered to NHVs who participate in phase 1 studies. It is plausible that disallowing payments would not lead to a fair distribution of the burdens of research participation and that most subjects would come from (a) the worst off among us who are enticed by food and shelter or other advantages of participation and (b) the mostly older members of society who, according to some research (Kirkpatrick, 1991, 109–113), are more likely to volunteer for altruistic reasons. Relying on altruism to recruit NHVs for phase 1 studies could require exaggerating claims about the impact any individual's participation would have on the well-being of others. An honest assessment of the expected benefit of phase 1 trial participation might not motivate altruists because, as noted earlier, only approximately one of five agents tested in a phase 1 study becomes an FDA-approved agent (PhRMA, 2006). Relying on altruism raises another question: is there something about acting altruistically that makes a decision more likely to be free and voluntary than one made with the goal of earning money? Relying on altruism by offering no incentives may not improve the chances that persons will not be unduly influenced to participate. Participants may be influenced, and some unduly influenced, by the desire to do good or to be seen as people who do good for others. It also is possible that in the absence of payments, recruitment would fall short because altruism might motivate an insufficient number of people to participate. The organ transplantation system in the United States relies on altruism to motivate donors, and a limited number of eligible donors actually donate organs. For example, it is estimated that approximately half of families asked to donate the organs of a deceased relative consent to donation and about forty percent of decedents who are eligible to donate become organ donors (Sheehy et al., 2003). As a result, an IOM committee charged with identifying ways to increase organ donation recommended, among other things, that the pool of eligible donors be expanded by increasing donation after cardiac death (DCD) (IOM, 2006). Others have challenged the claim that we should continue to rely on altruism alone to motivate people to donate organs and have recommended use of incentives or markets (e.g., Veatch, 2003; Cherry, 2005; Taylor, 2005; Hippen, 2005), conscription of organs (e.g., Spital, 2003), or reciprocity plans in which persons who are willing to donate are given priority to organs (e.g., see www.lifeSharers.com). If altruism alone does not motivate sufficient levels of organ donation, there is no reason to believe that altruism alone will motivate a sufficient number of people to participate in phase 1 studies.⁴ As with other alternatives, a full evaluation of this option requires more empirical data than we currently have.

Mandatory Participation

A fourth possibility is to require participation in research through a lottery or another mechanism to distribute the burdens of participation in a way that is divorced from socioeconomic status or present access to money, food, shelter, or health care as well as from one's level of altruism or interest in research. Some proposals have been made regarding mandatory participation, but these typically have been for research that does not require participants to do anything they would not otherwise do or poses only minimal risk, for example, educational research involving assessment data (DuBois, 2002) or research involving standard medical treatments (Orentlicher, 2005). Others have suggested that some research participation be required but that individuals not be required to participate in any particular kind of research or study (Rhodes, 2005). To recommend forced participation of healthy individuals in phase 1 trials would require a radical change in the underlying ethical principles that govern research. To adopt this view would be to privilege justice in the distribution of the burdens of research participation over voluntariness, which is the basic requirement for the ethical conduct of research from which the obligation to avoid undue influence is derived. Such an approach would violate conditions this author and many others hold must be met for the ethical conduct of human research.

V. CONCLUSION

To evaluate payments to research participants with an eye only or primarily to minimizing undue influence without seriously taking into account the obligation of justice as outlined in the Belmont Report and CFR is an ethical failure. If one takes into account not only the obligation to minimize undue influence but to respect the principle of justice in the recruitment and selection of subjects, we must first make a concerted effort to determine who are the NHVs who participate in phase 1 studies and why they participate. If the less well-off are over-represented because the better off are not willing to participate for the low payments currently offered, to continue offering low, equal payments for all is to *de facto* target the less well-off. This would violate the principle of justice as described in the Belmont Report. Then, we must consider seriously the alternatives discussed here. There are important theoretical questions, such as whether it necessarily is unjust to pay participants differently, and empirical questions, such as what amount of money unduly influences particular persons and what value is necessary to motivate the better off, that are central to evaluating the permissibility of the status quo and the alternatives presented here. In light of the limited evidence we have that NHVs in phase 1 studies are more likely to be from among the less well-off, we must evaluate the status quo to determine whether the concerns raised here regarding justice are valid. If they are, we must seriously consider alternatives.

NOTES

1. The motivation of affected individuals/patients to enroll in phase 1 studies, when they are eligible, such as in phase 1 studies of potential oncology drugs or phase 1 gene transfer trials, raises different yet very important ethical concerns. There is evidence that some patients enroll in phase 1 studies at least in part because they hope for or expect therapeutic benefit even though such studies do not aim to offer benefits to participants and generally do not yield therapeutic benefit. For further discussion of the therapeutic misconception in phase 1 studies enrolling patients, see Daugherty et al. (1995), Miller (2000), Arkin et al. (2005), and Horng and Grady (2003).

2. Menikoff offers a separate reason for sometimes paying all subjects more for their participation. He argues that in studies where subject's contribution is not just time but a willingness to assume substantial risks for little or no prospect of direct benefit, then higher payments are justified. Subjects should be compensated for the risks they assume in such studies.

3. A broader question is how well any potential participant must understand and evaluate risk and benefit and how that capacity should be measured. For further discussion, see Wicclair (1991, 1999), Wilks (1997a, 1997b), Cale (1999), and Iltis (2006).

4. I would like to thank Lisa M. Rasmussen for pointing out this example.

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