

Payment for research participants

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Abstract

This paper looks at reasons that have been given in support of and against offering financial payment to participants in biomedical research. The objective is to question the reasons that lead a person to decide to participate in research, especially the notions of risks and benefits involved in participating, as well as the informed aspect of consent in these cases. The article draws a distinction between payment, reimbursement, and appreciation. Based on a historical review of the emergence of payment as an option for participation, the article proposes a series of procedures for the protection of the interests and rights of participants in biomedical research.

Keywords

payment; incentives; remuneration; reimbursement; human participants; biomedical research

Introduction

Must human subjects be paid for participating in biomedical research? What could be wrong, if any, with paying human subjects for taking part in biomedical research? Is it acceptable for biomedical research to be regarded as an opportunity for making money? What advantages can be gained by allowing human subjects to get paid? Does payment facilitate recruitment and ensure the continuation of ethically acceptable research on human diseases and their treatment? Would payment ensure just compensation for the contribution of human subjects to biomedical research? Could it possibly lead the way to professionalizing the relationship between in-

vestigators and human subjects? On the other hand, what disadvantages can result from payment? Does payment for human subjects promote undesirable consumerism in the field of medicine? Does it have the effect of discouraging volunteerism and altruism? Does it promote the exploitation of poor segments of the population?

All of these are important questions that have been asked, at one time or another, regarding the practice of paying human subjects for participation in biomedical research. It is therefore useful to come up with answers if one hopes to adopt a rational and consistent approach to the matter. For this purpose, one has to be clear about the objectives of giving payment and see if the outcomes ei-

ther conform or fail to confirm to the desired endpoints. Those who advocate payment apparently do not share identical objectives. Thus, it makes sense to examine the various justifications offered in support of the practice and analyze the corresponding objectives.

This paper looks at reasons that have been given in support of and against offering financial payment to participants in biomedical research. The objective is to question the reasons that lead a person to decide to participate in research, especially the notions of risks and benefits involved in participating, as well as the informed aspect of consent in these cases. The article draws a distinction between payment, reimbursement, and appreciation. Based on a historical review of the emergence of payment as an option for participation, the article proposes a series of procedures for the protection of the interests and rights of participants in biomedical research.

Why is payment considered necessary?

Biomedical research that is intended to have an impact on the medical treatment of human beings cannot be undertaken without the participation of human subjects. However, there are a number of factors that could pose obstacles in the way of human participation. For example, there is inevitably some cost involved when a subject has to travel to a site where research is to be conducted. There is also some cost involved when, in order to participate in a research project, a person could not report for work, for which one would otherwise get paid. Under such circumstances, it has been thought necessary to pay human subjects as a way of reimbursing them for expenses that they would not have otherwise incurred, or for costs that they should not have paid themselves.

Payment has also been justified as a way of providing incentives for participation. Some researches are considered to be so important that project sponsors should pay the cost necessary to ensure that they are carried out. If there are hindrances to the participation of human subjects, payment should be given to overcome those hindrances. In this way, providing payment can solve a lack of motivation on the part of possible recruits.

In some cases, incentives can be given to specific target populations that need to be adequately represented. For example, in a mixed ethnic population, there may be a need to give incentives especially to Asians in order to ensure that they have statistically sufficient numbers among the total subject population. Thus, financial incentives may be used to overcome barriers unique to certain subgroups in the research population, such as inconvenience, lack of awareness, or lack of trust. This means that money may be helpful not only in general recruitment, but also in achieving ethnic, gender, and social diversity of subjects participating in biomedical research. Viewed in this way, payment may be justified for the purpose of ensuring that conclusions can be validly generalized.

Even when motivation has not been an issue, payment has been justified in terms of providing compensa-

tion for time and inconvenience. Human subjects have to spend time and energy as part of the research project. They also have to put up with inconvenience, which can come in varying degrees. Time and energy have a cost for the human subject, and so does inconvenience. The view has been expressed that the subject should also be compensated for these costs.

Main concerns about payment

The case of Walter Reed, who paid volunteers to participate in yellow fever studies, is often cited as an example of payment being given to research subjects to participate in biomedical experimentation (The United States Army Yellow Fever Commission 2001). Participants in Reed's studies were each paid 100 American dollars in gold and an additional \$100 if they contracted yellow fever. The following was part of the informed consent form:

It is understood that at the completion of these experiments, within two months from this date, the undersigned will receive the sum of \$100 in American gold and that in case of his contracting yellow fever at any time during his residence in this camp, he will receive in addition to that sum a further sum of \$100 in American gold, upon his recovery and that in case of his death because of this disease, the Commission will transmit the said sum (two hundred American dollars) to the person whom the undersigned shall designate at his convenience. [...] The undersigned binds himself not to leave the bounds of this camp during the period of the experiments and will forfeit all right to the benefits named in this contract if he breaks this agreement. (English... 1900).

To this date, many human subjects are paid to participate in research. Offers of payment are indicated in advertisements on the internet and in print, published by researchers seeking to recruit participants. While there are people who consider the giving of payment necessary, the practice has given rise to a worrying tension between the need to recruit human subjects and the need to ensure their ability to decide freely and independently. The literature on paying research subjects tends to focus on the possible implications of the practice for the concept of voluntary consent. For the most part, the presumption is that payment constitutes a threat to one's ability to make a voluntary decision. Hence, the tension between payment and the protection of voluntary consent has provided the context for much discussion.

This tension has led to the observation "that a preoccupation with voluntary consent may have slowed the progress of the debate" (Hutt 2003: 16). Leah Hutt fears that the focus on this tension has been the reason for a continuing disagreement regarding the ethical aspects of the topic. According to this author (2003: 16), such focus has also been responsible for a lack of "practical and ethical guidance in evaluating the propriety of a given payment". Guidelines and regulations generally allow some type of remuneration to be given to research subjects. However, they fail to settle specific questions

that have been raised in the debate. Particularly interesting are questions that pertain to the distinction between reimbursement and compensation, or those related to the amount that could be considered acceptable. Questions arise regarding the acceptability of the amount given because it is thought that the magnitude of this amount could compromise the voluntary nature of consent, diminish the value of altruistic contributions to research, or promote the exploitation of research subjects.

One crucial issue concerns the types of inducement investigators may be allowed to use for the purpose of recruiting subjects. Human beings cannot be solicited for research in the same way that trial drugs can be synthesized in the laboratory or medical implements can be produced in the factory. Human subjects have to be allowed to make their own voluntary decisions to participate or not. The requirement is reflected in many international guidelines pertaining to the ethical practice of biomedical research, as initially exemplified in the Nuremberg Code (1949): "The voluntary consent of the human subject is absolutely essential. This means that the person involved should [...] be so situated as to be able to exercise free power of choice, without the intervention of any element of force, fraud, deceit, duress, over-reaching, or other ulterior form of constraint or coercion [...]"

If an offer of money is made in order to overcome a lack of motivation, is it not, therefore, being intended to inhibit one's ability to exercise free power of choice? Is it not the case that the incentive is intended to make the non-participation option incompatible with the considerations that are important for the human subject? If the objective is to make the option to participate the most agreeable one, is it not, therefore, going against the voluntary nature of consent?

If participation in a particular research project involves a significant amount of risk, the offer of money as an incentive could also inhibit the subject's appraisal of such risks. In other words, the offer of monetary incentives – or of incentives in general – could tilt the balance in favor of participation in the eyes of the subject. If so, the decision would be based on a factor that is irrelevant to the objectives and characteristics of the research itself. The decision would be irrational and arbitrary. Another concern raised about payment is the fear that compensation given to subjects may give rise to an uneven distribution of risks among various segments of the population. The poorer segments could be attracted more easily to participate in research when payment is made available. Hence, they will also be more likely to bear an unduly large share of the risks and burdens of participation.

Related closely to the first concern is the idea that giving payment to subjects might constitute inducement that is strong enough to jeopardize the capability of subjects to decide voluntarily, or with the level of understanding required to render a well-informed decision to participate or not. Regardless of the initial motivation for paying research subjects, money can function as a

convenient recruitment tool, resulting in subjects who generally lack understanding of the goals of the study or the risks involved, and are therefore unable to care about the outcome, or to provide support for the project in general. Consent given by a subject under these circumstances may easily be regarded as questionable, since the requirements for voluntary consent will have been put under pressure by the effects of incentives.

Are incentives necessarily coercive?

In itself, payment is not necessarily coercive. Payment is not always given as an incentive to try to motivate a person to participate, and may be offered for other reasons. It need not function as an incentive. Nevertheless, even payment not intended to serve as incentive may actually be interpreted as, or have the effect of being an incentive.

What would it mean if being paid does not undermine the voluntary character of a subject's decision? If payment does not deny the voluntary character of an individual's decision, it may then be given without compromising the validity of informed consent, provided there are no overriding considerations. One explanation lies in the fact that deciding freely does not always require having more than one available option. Conversely, having no more than a single option does not necessarily mean acting involuntarily. This explanation addresses the matter of offering significant amounts of payment as incentives to the poor.

Payment offered to a poor person in a desperate economic situation can be regarded as the only currently realistic option for dealing with that economic condition. Should the acceptance of the offer necessarily be seen as having been done involuntarily? The subject would have done what was consistent with his needs and interests at that particular point in time. There would have been no reduction in options available to the subject. On the contrary, the availability of payment would have presented an option that would otherwise not have been available. The desperate and poor subject already has nothing more than the limited options to begin with, regardless of payment being available or not. Given that kind of situation, one wants to ask why the availability of receiving payment as an option should be regarded as a constraint on the subject's choices. It seems more realistic to consider other ethical transgressions arising from the offer, such as exploitation.

Exploitation as an issue arising from payments

It is easy to accuse investigators of exploiting a situation of dire need among a target population, for an offer of payment to the poor in order to entice them is regarded as exploiting their vulnerability. However, it would be a mistake to hold such investigators responsible for the general conditions surrounding the lives of their subjects. The researchers cannot be blamed for pre-existing unemployment or destitution. In this sense, should they

be held responsible for the decision of poor individuals to accept an offer to serve as research subjects mainly because of the presence of monetary incentives?

It seems that the answer should depend on the amount of harm that the subjects have to risk by their participation in research. For procedures that involve little risk, it would be difficult to say that the subjects are being exploited, because exploitation has to involve the element of significant harm. As the level of harm that is risked increases, it becomes more appropriate to consider the relationship exploitative. Some will say that it will be wrong or cruel to withhold from the subjects the payment that could be very useful for them under those circumstances, especially if the original intention was to make the payment available anyway to the research participants without regard for their economic situation. Withholding such payment would be unduly harsh and restrictive of their deserved options.

Do payments actually serve as incentives?

Although it is easy to presume that payment is useful or effective for the recruitment of clinical research subjects, the validity of this claim has to be established in specific situations. In some cases, altruism has been enough to motivate some people. The idea of being able to contribute to scientific advancement could be a motivation in itself, regardless of the benefits that people may actually derive from the outcome of the research.

There are also cases of unhealthy volunteers who believe in the possibility of benefiting directly through their participation in drug trials. Halpern et al. (2004) have shown that, in Phase III clinical trials, subjects are often motivated to participate by the hope of personal therapeutic benefit. In addition, curiosity could be a significant factor in itself. Curiosity tends to motivate people to do a lot of things, and that includes participating in medical research. For some, the mere possibility of attracting public attention could be an effective motivation. Hence, there are varying motives other than those that are anchored on monetary considerations. It is important to consider this broader context when viewing the possibility of payment serving as incentive for research participation, which allows for assessing the weight of financial reward in decision-making.

Investigators have paid subjects for participating in research studies for a long time. Nevertheless, this practice has remained controversial, especially when the primary purpose is to attract recruits. The ethical questions have continued to bother the research community, even as the importance of inducements as a motivating factor has been acknowledged.

Payment as benefit to subjects

Should payment be classified as a kind of benefit to research subjects? There is a sense in which this question can be answered simply by referring to the actual consequences felt by the subjects. If subjects are paid a

sum of money whose personal use outweighs any harm, then that amount of money can be regarded as a benefit. In this sense, to be a benefit means nothing more than to be a positive outcome for a particular person. However, a benefit in biomedical research represents more than a positive consequence for the subject.

In biomedical research, the term “benefit” is usually reserved for a positive outcome that could be attributed to a specific component of the research. The fact that a benefit could be attributed to a specific component of the research is important because the evaluation of a study requires that benefits be weighed against possible harm arising from the investigation. If payments were to be regarded as benefits, they could be used in the evaluation as a counterbalance to possible harm. But they could also be improperly used to justify proceeding with research that is otherwise too risky to undertake. In other words, payment could become a very handy instrument to compensate for a subject’s willingness to undertake the risks inherent in a particular research project.

Should altruism be the sole motivation for research participation?

Notwithstanding ongoing practice that has seen broad tolerance of payment being given to research subjects, some commentators have maintained that compensation should at least be limited. Some have even held that compensation for out-of-pocket expenses should not be exempt from this limitation. This position is anchored on the belief that altruism should be the subject’s exclusive motivation for participation.

But it seems that the only way this position can be logically maintained is to uphold the premise that people have an obligation to serve as subjects of biomedical research. The idea is that people who benefit from the outcome of biomedical research have an obligation to repay the contributions that others have made to bring about that outcome. Everyone has to acknowledge the advances in biomedical research by contributing their own voluntary participation as research subjects. In this extreme interpretation, there appears to be no justification for payments of any kind.

Given current realities, however, it appears that payments are inevitable. Even those who agree that people must be motivated altruistically cannot deny that there is an actual cost involved in participation and this cost cannot be imposed on those who take the time and energy to participate. It is admirable for people to participate in beneficial research without payment. However, it is not necessarily wrong to participate and to recover the expenses involved in one’s participation.

Paradoxically, this is particularly true for those who are poor and cannot afford to bear the cost of participation by themselves. If these individuals could not be included because they could not bear such costs, the statistical requirements for the demographic characteristics of the subjects may have to be sacrificed, and the validity of the results could be compromised. Thus, instead of paying attention to the payment versus no payment

debate, perhaps one should focus on the terms under which payment may be given.

Models for conceptualizing payment

Dickert and Grady (1999) have offered three models of payment: a market model, a wage-payment model, and a reimbursement model. Here is how they describe the market model, which is grounded in traditional libertarian theory:

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. (Dickert & Grady 1999: 200).

The market is the place to use money to encourage people to exchange goods that they own or to provide services that are in demand. If there is strong demand for a service that is in scarce supply, the cost of that service tends to rise. If the demand is weak and the supply is abundant, the cost tends to go down. Hence, a researcher who is in great need of a particular type of subjects will have to provide attractive incentives to recruit them. If the need for subjects is urgent, the cost will rise even higher. The idea is to be sensitive to market trends.

The wage-payment model puts research participation at par with wage paid unskilled labor:

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". 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. (Dickert & Grady 1999: 200).

The market model and the wage-payment model can easily overlap, especially because wages are usually set in recognition of the market and the law of supply and demand. Moreover, the idea of paying the subjects bonuses upon the completion of the study – something that is widely practiced – is compatible with both models, since the market is also prone to determine most of the acceptable practices and policies for giving bonuses. Bonuses make a difference for the wage-payment model only when they are too large and therefore deviate significantly from scales consistent with wage payment. Unusually large bonuses do not reflect the amount of time and effort contributed by subjects, thereby tending to constitute a form of questionable incentive.

The reimbursement model focuses on expenses incurred as part of the subject's participation:

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. (Dickert & Grady 1999: 201).

According to Dickert and Grady's account, the reimbursement model is different from the first two models in the following 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. (Dickert & Grady 1999: 201).

At a theoretical level this account of the differences among the models could be useful. For one thing, there are important symbolic representations in precluding profit and compensation for non-financial expenses. Also, the idea of payment that is independent of a commercial market also evokes positive connotations. However, practice is not easy to reconcile with theory.

The market is not something that can be readily switched on or off at anyone's discretion. One cannot just overlook market forces and say that the laws of supply and demand should not, and cannot be taken into account if the subject is merely being reimbursed for expenses. Also, it is not possible to simply ignore the market in determining how to compute the equivalent of wages commensurate to the contribution of the subject to the research activity. As far as reimbursement is concerned, it makes a lot of difference what sort of costs this payment model seeks to reimburse. As pointed out, there is a substantial difference between reimbursing a subject for the cost of transportation and even missed wages, on the one hand, and reimbursing a subject for the cost of time and inconvenience, on the other. The latter poses complex problems of interpretation, rendering the three models almost indistinguishable from one another.

When human subjects are offered an amount of money in exchange for their participation in research, it is not easy to ascertain what their actual reasons are for accepting or refusing the offer. Their reasons can remain private and they cannot be forced to adopt one or another motivation for their decision. Moreover, regardless of the payment model that investigators have in mind, there is no assurance that the research subjects will view what they receive, or expect to receive, in the same way.

Grady has added a fourth model to the three described above – the appreciation model:

An appreciation model conceives of money as a reward or token of appreciation for a subject's contribution to research. Appreciation can be shown by awarding a wide range of amounts of money as well as nonmonetary gifts. Unlike the other 3 models, appreciation payments may have little impact on study recruitment, as appreciation is often reserved until the study ends. (Grady 2005: 1685).

Again, the fourth model described by Grady offers an alternative that is useful at a theoretical level. In practice, one is at a loss to explain how it could make a difference if subjects get to know that they could be given money in appreciation for their participation in medical research, especially because such information ought to be disclosed in the interest of transparency and honesty.

These comments do not diminish the relevance of the four models. The list of potential advantages given by Grady (2005) provides very important guidelines for achieving the outcomes that may correspond to the researchers' specific objectives. In this sense, it is beneficial to recount here the advantages related to the models as enumerated by Grady:

1. a researcher can take advantage of the rates of payment under the market-responsive model to achieve more rapid recruitment because of the possibility of profit for participants, the absence (or minimization) of financial sacrifice on their part, and the encouragement to remain in the research that comes from the expectation of receiving completion bonuses;

2. the wage-payment model enables the researcher to recognize the subjects' contributions, provide payment corresponding to a scale that applies broadly across studies (equal pay for equal work), and minimize the risk of undue inducement;

3. with the reimbursement model, the researcher has a means to make the proposition revenue-neutral for the subjects, minimize the risk of undue inducement, and provide an option that has little or no financial sacrifice if lost wages are also reimbursed;

4. under the appreciation model, the researcher can express gratitude through payment in a way that is not market dependent and avoids undue inducement.

There appears to be an assumption that if the boundaries separating these models were clear enough, not only the researchers, but also the subjects could be equally clear about the reasons for payment and the calculations that should be made in order to determine the appropriate amount to be given. However, things do not seem to work out that well in practice. In addition, there are other forms of payment that do not fall neatly into any of these models. These include compensation for harm or injuries sustained by subjects during research and payment given to investigators. In any case, it is worthwhile for researchers to be aware of the characteristics of each model, to be so guided in determining amounts to be paid to subjects, and to achieve a measure of consistency.

Such consistency is necessary for policy-making. It could be also useful for members of research ethics com-

mittees to be similarly aware and to take such matters into account in conducting the ethical review of research protocols. Having this in mind, one needs to identify specific recommendations that may be drawn, irrespective of the particular model of payment that researchers may adopt – if they feel that they need to adopt one model at all in order to provide unity and consistency to their approach.

Reimbursement and compensation for harm

It is only proper that subjects be reimbursed for transportation expenses to and from the place of research, or for salaries foregone when they skip work in order to participate. It is also a matter of justice that compensation be given to subjects who suffered harm or injury as a result of their participation to enable them to cope with the cost of treatment. However, the idea of providing subjects remuneration for "time and inconvenience" could have controversial consequences. One reason is that time and inconvenience are very fluid concepts. The terms are open to a wide variety of interpretations, including those that could have the effect of unduly inducing consent. This opens the door to a broad range of circumstances when payment could be given, including those in which it could serve as improper inducement.

Moreover, the cost of time and inconvenience is not easy to measure. Remuneration for time and inconvenience is unlike reimbursements for expenses incurred in participation, which would not be very difficult to quantify. Expenses actually incurred can be measured exactly. The cost of transportation and the equivalent of a day's wage can simply be added up, and one can perhaps expect computational rather than conceptual issues.

Payment corresponding to injury cannot be construed as providing an improper incentive to participate, since the injury itself – or the likelihood of its being suffered – constitutes a huge disincentive. This is especially true when the injury is of such magnitude that the participant needs to be given significant compensation for it. Although compensation for injury might not be quantified as easily as reimbursements for actual expenses incurred in participation, there is a limit on one's willingness to participate that is naturally determined by the reality of the harm or the likelihood that it is going to be suffered. Perhaps, one need only sound a warning that injury can be other than physical. Injury can also entail civil liabilities, such as those that may have to do with legally defined forms of negligence or misdemeanor. Additionally, it can involve moral damages.

These are complications that may provide reasons for giving unusually large payments. Nonetheless, in this case payment does not present a problematic threat to the validity of the subject's consent, provided that it is given as a result of actual injury rather than in anticipation of its possibility. In other words, if compensation were to be given for injury, it would not seem to be problematic if injury has already been actually experi-

enced. But it would tend to be problematic if subjects were to be given compensation for the mere likelihood or risk of injury.

Among the models of payment considered, remuneration for time and inconvenience is uniquely problematic. By being amenable to various interpretations, it provides an opportunity to introduce material payment that can become or that can be understood as an unacceptable incentive to participate. This appears to be true of any amount that is given to research subjects over and above that which can be interpreted as reimbursement of actual expenses or compensation for injury.

Incentives, coercion, and undue inducement

“Undue inducement” has been a common slogan for commentators critical of the role that monetary incentives could play in getting the consent of human subjects to participate in research. For example, McGregor has said (2005: 25):

Undue inducements might be referred to as “coercive offers”. They are *offers* because they propose to make the person “better off” relative to his or her baseline, they hold out a good or option for the recipient that wasn’t there before, but they are *coercive* since, because of the recipient’s lack of options, the proposal is likely to present the only eligible choice (all victims of coercion have a choice, nevertheless, the consequences of not going along with the proposal is the greater evil). For extremely impoverished people with no medical alternatives, the offer of any medical treatment, even in trials where they have a 50% chance of getting no treatment, is better than their current alternative of no medical treatment – making going along with the trial their only choice. They are coerced to accept the offer given their miserable circumstances. Offers of money or other resources for impoverished people with little or no alternatives may have them seeing only the promised reward – without regard to conditions on getting it.

For Wilkinson and Moore (1997), inducement is a good thing in that it attracts enough subjects for research. They point out that those who accept an inducement would not do so unless they considered it valuable. Hence, researchers are able to attract the subjects they need, and subjects receive a reward they consider valuable. The transaction satisfies both parties and they end up being better off. Neither party is left worse off. Wilkinson and Moore find this explanation similar to arguments justifying wages for work or other market transactions. Many people would not work if they were not paid. Wages are obviously inducements. For these people, it is not wrong to offer wages.

McNeill (1997) expresses a different view of inducements as he rejects the wage-payment model, saying that human subjects are not being paid to do regular work. His view is that wage labor is not normally a risky practice, while experiments with human subjects usually involve an inherent risk. According to him, Moore and Wilkinson are mistaken in their use of the analogy, since

activities that involved no risks and had outcomes that were known to be safe from the beginning would not truly be recognized as experimental.

Undue inducement may be seen as an antithesis to autonomy in the sense that informed consent rests on the principle of self-determination. For the purposes of this paper, three important conditions may be pointed out that need to be met in order that a person’s decisions and actions could be considered autonomous or self-determined: a) a capacity to assess and make value choices; b) a capacity to select and understand relevant information; and c) a capacity to evaluate rationally.

The first has to do with the ideal of autonomy. Day-to-day decisions should be rational in that these are consistent with the person’s life plans. For an evaluation to be autonomous, it must be based on a correct understanding of the relevant facts and made without a relevant error of logic. The decision-maker should also have the ability to anticipate what the states of affairs will be like as a result of the various options. Philosophers offer different definitions of autonomy, and philosophical views concerning the requirements for autonomous decision-making tend to vary. But many people agree that the three conditions mentioned are important for human decision-making, whatever exactly we mean by autonomy.

The capacity to assess and make value choices is something that develops throughout a person’s life. It is something that is difficult for anyone to lose even in the face of a monetary inducement to participate in research. Making value choices takes place over a long period of time, rather than in the instant it often takes to give one’s informed consent for research.

The capacity to select and understand relevant information could be jeopardized by a monetary inducement. In fact, the value of the money for the individual being recruited could be so significant that one considers it a relevant factor in what should ordinarily be a balancing of the inherent benefits and risks of participation in a particular research project. The attractiveness of the incentive draws the recruit’s attention to factors external to the research. The capacity to evaluate rationally is put under pressure because the expectation of monetary gain could outweigh the possibility of experiencing harm in a way that would not normally be done by a person acting rationally. At the very least, inducements for participating in research could make it very difficult for subjects, especially those who are poor, to make a decision purely on the basis of the possible benefits from study outcomes and the risk that the procedures entail.

On this account then, monetary inducement compromises two components of autonomy – the capacity to evaluate rationally and the capacity to select and understand relevant information. However, this is only one side of this issue. As mentioned earlier, the monetary inducement could be viewed as an additional option that is beneficial for the subject as well as for the investigator. It is potentially beneficial for the subject for as long as safety measures are in place to guard against unacceptable levels of harm or risks.

The offering of inducements can reach unacceptable levels by appealing to the subjects' irrational preferences or desires in such a way that they are enticed to act inconsistently with their assessment of the information. Human subjects can also be misled into thinking that some factors are relevant when they are not. Higher desires in their hierarchy may be suspended as less rational preferences become momentarily more attractive. The research subjects may prefer paid risk-taking to their more secure longer term well-being, which they would ordinarily consider to be of a higher order of values. The offered payment could be so large or the medical services so extensive that they are encouraged to consent to participate in research against their better judgment.

Compensation may appear to be a tool for self-determination in such circumstances. In reality, it could be nothing more than a transient response to one's inner compulsions, driven by a lingering need that could not be satisfied because of the conditions related to poverty. In the face of compensation, individuals could think they are exercising their freedom. However, from the perspective of their own higher values, their self-determination is being actually frustrated. Thus, when desperately poor people choose to accept compensation in exchange for their participation in research, they could be doing so out of a false sense of what they truly want or what they want in the longer term.

One factor that contributes to poor persons accepting inducements is that, to begin with, they do not have good options for advancing their economic situation. This situation has nothing to do with the investigators prior to the research or the offer of research money. Even before they accept an offered inducement and agree to participate, desperate and poor subjects already have severely limited options. When the compensation option is presented to them, their original options are retained, but these remain unacceptable. The inducement does not contribute to the subject's lack of self-determination, although it could highlight that pre-existing lack.

If a prospective recruit perceives research participation as a viable means to provide for part of his family's needs, does that person act rationally? It may be said that he does act rationally if he is fully aware of the options and the logical outcomes. If at all, the decision could be challenged for being inconsistent with his hierarchy of values. One could point out, for example, that his long-term safety is more important than the short-term gain that compensation for his participation could provide. But, even if that were so, what ought to be the proper response? Should the prospective subject be barred from participation?

From the point of view of autonomy, the best option seems to be that of providing all the relevant information and giving advice to enable the person to see the decision in relation to his hierarchy of values. Once it could be ascertained that the person has considered his options rationally, it would be wrong to prevent him from implementing his decision. Even when he does not seem to others to have made the best decision, his right to

self-determination ought to be respected; this can still be consistent with the person's self-perceived life plans. Even in situations when he chooses an option that is relatively lower in his own hierarchy, his choosing it may be seen as a good enough reason for its implementation.

Coercion and undue influence arising from the giving of payment to research subjects are two issues that were highlighted in the Belmont Report, published by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. In its discussion of respect for persons, the report stresses the importance of ensuring that consent is given by the subject without coercion or undue influence (The National Commission 1979). Coercion is said to take place "when an overt threat of harm is intentionally presented by one person to another in order to obtain compliance" (The National Commission 1979: 6). As for undue influence, it arises when there is "an offer of an excessive, unwarranted, inappropriate or improper reward or other overture in order to obtain compliance" (The National Commission 1979: 6). Depending on the amount involved, money or some other material reward can be interpreted as excessive, unwarranted, inappropriate or improper. Moreover, when subjects are rendered vulnerable by their poverty or by being imprisoned, inducements can have an irresistible appeal that would not usually be applicable to subjects who are free and are not in an economically compromised position.

In elaborating the concept of justice, the report mentions the requirement for fairness in subject selection (The National Commission 1979). Apart from the views expressed in the commission's report, the question of fairness may arise in connection with: 1) distributing the burdens and risks of research among different segments of the population; 2) establishing safeguards for the protection of the vulnerable; and 3) providing compensation for injury. The commission identified the involvement of vulnerable subjects, including the economically disadvantaged, as a "special instance of injustice". It warned that:

Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their [...] socioeconomic condition. (The National Commission 1979: 8).

The vulnerability of subjects is a special concern when dealing with the possible consequences of giving payment. The compromised capacity for free consent has been evident among vulnerable populations in various circumstances, for example, in developing countries in Asia. In the Philippines, some street children are known to have been recruited to research by being given payment in the form of biscuits or breakfast buns. The experience clearly shows that even very small amounts can serve as inducements to severely vulnerable populations. In some cases, payment in the form of medical assistance that is totally irrelevant to the research being

conducted has served as inducement. In other cases, participants have not even been aware of their participation in research.

In general, the vulnerabilities may be of different kinds, but in many cases they entail a diminished capacity for free consent characterized by drastic limitations of realistic options or by offers that are too difficult to refuse, given the conditions surrounding the lives of the persons concerned. In other words, vulnerability makes one liable to exploitation and manipulation through offers of payment or some other material compensation.

“Administrative convenience” is an additional angle to such exploitation or manipulation. When potential subjects are characterized by vulnerability, one could speak of undue influence being exerted also upon investigators, and not only upon subjects. Undue influence gets to be felt by investigators in the form of pressure to bring a research project to successful completion. The fact that some subjects are vulnerable to manipulation constitutes an invitation for investigators to make their own task easier, possibly by using monetary incentives. This window of opportunity for “administrative convenience” is likely to be an enticement, which could also have negative repercussions regarding the safety of subjects or the validity of research outcomes.

Considering the available infrastructure for review of research protocols in various countries, perhaps the best way to deal with the concerns expressed above is to ensure that these are adequately considered in the deliberations of ethical review committees or institutional review boards. This will perhaps require more resources for capacity building, especially in economically developing countries.

Prison experiments

For a significant period of time, the debate concerning the clash between giving payment and the need for voluntary consent had to do with the recruitment of prisoners and the use of payment as incentives or rewards. Discussions arose during World War II, when researchers were widely known to have used prisoners for medical experimentation. Questions were asked about the ethics of the activities, but these did not pose a challenge serious enough to put an end to the practice, perhaps because authorities were convinced that it was justified by the urgency of the war. Many researchers merely explained that prisoner-subjects freely chose to participate. Indeed, before research was conducted, subjects were asked to indicate approval. How the approval was to have been interpreted has been the subject of criticism and debate.

Some critics argue that the rewards were excessive because of the conditions of imprisonment. Fears were raised that subjects could be withholding information about symptoms so they could qualify for the experiments and the money offered. This possibility increased in likelihood as the offered amounts became bigger, thus tending to put in question the validity of research results themselves. If subjects were lying about their symptoms,

the research would have been conducted on the basis of the wrong premises. Hence, the conclusions would have been questionable.

Moreover, because the recipients of the incentives were prisoners, the offer inevitably led to issues regarding the voluntary nature of the consent given. The idea was that, as long as prisoners were involved, the research dealt with people who were not completely free. The subjects were under the control of prison administrators, on whom they depended for many of their needs and wants. In order to satisfy those needs or wants, they had to comply with rules or regulations imposed and implemented by the authorities. Hence, the subjects were in a compromised position as regards the satisfaction of those needs and wants. To the extent that they depended on the authorities, the subjects did not have real freedom to make decisions within the context of their surroundings.

The situation was complicated by the fact that incentives were given. Options were limited to begin with, and incentives were dangled to encourage a type of behavior among the prisoners. The incentives constituted a further challenge to the autonomy of decision-making. It became more difficult to say that decisions were voluntary because, in addition to the fact that those faced with the decisions were imprisoned, they were subjected to the offer of incentives that they obviously found very difficult to resist.

Thus, the giving of payment to subjects was closely related to the issue of exploitation in research involving vulnerable subjects, such as prisoners. Among people in a population with severely limited options, the concept of exploitation appeared to be a natural issue already. Almost any payment could be regarded as being too much compared to any opportunity that arose in prison. On the other hand, the use of payment was also exploitative in that the amount would have been regarded as too small compared to opportunities that could have arisen had the subjects been outside prison. Thus, there is also the paradoxical situation of monetary incentives regarded as exploitative both for being too small and for being too large.

The undesirable consequences of using monetary incentives were partly responsible for bringing research among prisoners to disrepute, even if the use of material rewards was an issue distinct from the engagement of vulnerable populations such as prison inmates. In their case, it could not be ascertained whether, in a particular situation, the explanation for the lack of voluntariness laid in the heavy attraction of the incentives or in the imprisonment of the subjects. The question to be asked, therefore, was: was voluntariness compromised because of the giving of payment itself or because of the giving of payment to people who were imprisoned? In other words, was it the imprisonment that rendered the prisoners vulnerable to the incentives, or was it the incentives in themselves that had to be blamed?

In the United States, controversy erupted when prison-based malaria research conducted in Illinois during World War II gave rise to undesirable side effects.

The adverse events led to the creation of an investigating committee, which later determined that the research had not violated ethical rules (Mitford 1973). However, the committee found the need to call attention to the implications of giving rewards to prisoners. It took the occasion to highlight the importance of promoting an altruistic motivation for participating in research. It even went so far as to say that a subject prisoner should be motivated only by a desire to contribute to human welfare.

As the practice of rewarding prisoners for research participation continued, there were interesting implications for the correct interpretation of the reduction of sentences for cooperative prisoners. In this context, a reduced sentence could no longer be easily seen as improper inducement. There was the option to view it as a reward for altruistic behavior. With the ensuing support provided by pharmaceutical companies, the practice became institutionalized (Hutt 2003). However, experimentation on prisoners generated controversy because of news about epidemics in prisons, thereby raising issues about the standard of care given to the subjects.

The controversy also highlighted questions about the magnitude of the payments given to the prisoners. It was thought that the prospect of monetary reward had a negative effect on the truthfulness of information provided by the subjects. Some of them deliberately gave false information about their condition or about past experiences in order to continue to qualify as experimental subjects. While the deception enabled subjects to retain eligibility for payments, it had the effect of misleading investigators. It also tended to put those subjects at risk for side effects that could have been avoided. The investigating committee in Alabama confirmed that money given for participation provided the motivation for the prisoners to serve as subjects. Money was also the reason why prisoners struggled to remain in the experiments even when they suffered serious side effects (Mitford 1973).

Thus, the voluntary nature of consent for participation was rendered questionable by the offer of payment. Prisoners obviously found it difficult to resist the monetary gain when they were being asked to participate. Even later on, when side effects proved to be harmful, prisoners considered the possible loss of money too much of a disincentive. Although the studies conducted eventually proved to be useful for drug development in general and for individual prisoners who badly needed the money, one had to balance these benefits against the harm that prisoners suffered and the integrity of some of the data, at least to the extent that subjects found it necessary to lie in order to remain in the studies.

Concluding remarks and recommendations

One would not normally consider it unusual for a person to get paid for taking risks in order to derive excitement, or even to provide entertainment to others. In fact, that is how some people earn a living – they provide entertainment by taking spectacular risks that others would not ordinarily dare to run. It would seem

that the more realistic and dangerous the risks are, the more spectacular they would be, and the more the providers would be in a position to create excitement, thus gaining money from those who are interested in the kind of entertainment being offered.

However, there are differences between taking risks to entertain and taking risks in biomedical research. Persons who take risks for entertainment usually realize that they enjoy taking a particular type of risk and then move on, given their courage, to try to make money in the process. In other words, the persons concerned make a decision regarding the level of risks that they want to get into before they make a decision regarding the use of their willingness to be subjected to risks to entertain others and make money. The sequence of events allows the persons to make a risk assessment independent of the money they could eventually earn.

But that is not usually the case with biomedical research, where the willingness to take risks is often tied down, from the beginning, to the possibility of making money. As pointed out earlier, however the investigators view the compensation that is offered to the subjects, that compensation is liable to be seen as an incentive, especially by those to whom the amount matters the most because of their economic situation. It is very important, therefore, to examine very thoroughly the risks that the subjects agree to take as a consequence of their participation. That level of risks has to be fully reviewed even before the subjects, vulnerable as they are to the attractions of the incentive, have the opportunity to balance its value against their long-term interests.

Having this in mind, a few considerations arise that ought to be among the menu of options for ethics reviewers and investigators in preparing to undertake research that provides compensation to subjects:

1. in the interest of transparency, it is necessary to have a written policy, specific guidelines and procedures;
2. ethical review committees must determine the allowable level of risks without regard for the amount of compensation that may be given to research subjects. Once a decision has been made to allow research, compensation may be determined in a way that takes into account the level of risks entailed;
3. investigators must present a clear statement of the purpose of payment;
4. investigators and research ethics committees must strive to develop a standardized way to determine acceptable amounts of compensation;
5. informed consent documents must indicate the amount of payment subjects can expect and the terms under which payment is due to be given;
6. ethical review committees should take into account the specific vulnerabilities of the study population and the corresponding inclusion criteria, the recruitment and screening procedures, as well as the steps to be taken in evaluating the subjects' capability to process information and make decisions freely.

In addition, it is worth considering whether the following guidelines could be acceptable in particular contexts:

1. prohibiting mentions of payment in advertisements to minimize the possibility of undue inducement;
2. prohibiting completion bonuses to limit the possibility that subjects would continue participation against their better judgment just to be eligible for payment;
3. prorating payment given to subjects who do not complete a study in order to minimize the effects of unreasonable factors on decisions of human subjects to continue participation;
4. limiting monetary payment to reimbursement of actual expenses;
5. allowing only non-monetary gifts as a sign of appreciation (announced and given post-trial);
6. in the case of children and persons lacking the capacity to give informed consent, prohibiting payment to those giving proxy consent, but allowing gifts in kind provided these are given directly to the subjects and are not directly beneficial to the proxies.

Finally, it is necessary to conduct further research to understand better the effects of payments on decision-making, and to determine the point at which reasonable compensation becomes an undue inducement. Even as commentators continue to discuss theoretical approaches to the understanding of giving payment to research subjects, there is no reason why investigators and ethical review committees could not come to an agreement regarding the adoption and implementation of guidelines that can ensure a systematic and consistent perspective on paying human subjects.

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