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Consideration in Return for Consent: Ethics of Payments made to and by Clinical Trial Subjects

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Abstract

Clinical trials are less known about in India, especially by our rural population. There seems to be a dire need for creating public awareness and understanding of clinical trials/research and consequently the importance of informed consent, and other pre-requisites of conducting a clinical trial in India. This being the case, this paper shall specifically deal with the ethical and legal concerns that may arise out of paying clinical trial patients. This paper shall deal with the problems with informed consent in paediatric trials, trials relating to substance users and trials relating to other people incapable of giving consent. This paper shall also deal with the question as to whether money or other considerations in the form of incentives can be said to cloud the judgement of trial subjects while giving consent, thereby making it an uninformed consent. This paper shall also deal with the ethical aspect of accepting donations, etc. as criteria for accepting clinical trial subjects.

Keywords: Ethics, clinical trials, payment, informed consent, consideration

INTRODUCTION

Clinical trials are the gateway to medical discovery and invention. If not for this, we could never have been free from several of the deadliest of plagues that haunted mankind since our evolution. We, being who we are, have tried to regulate this process, especially after the horrors that happened during the Third Reich in Nazi Germany. The Nuremberg Code stipulated by the Military Court was among the first guidelines towards clinical trials. This was the consequence of the inhuman practices such as using prisoners-of-war and other persons considered as "undesirable" including Jews in concentration camps as subjects of clinical trials, without obtaining their consent. The Nuremberg Code followed by the Helsinki Declaration pressed on the need for informed consent as *sine qua non* of clinical trials. There has been a practice of paying the subjects of clinical trials even before these guidelines were introduced. This paper deals with the interplay between payment of clinical trial subjects and its effect on informed consent.

This paper begins trying to answer the question whether payments made to clinical trial subjects would compromise informed consent – a major requirement in clinical trials. For this, the definition of informed consent and its components is discussed. Following that, this chapter discussed the various types of payments that may be made to clinical trial patients. Further, the question posed in the beginning of this chapter is answered with the help of various studies and also going through the power of money in the Indian context.

The following chapter deals with the question of whether payment received by medical proxies for the participation of their wards in clinical trials is ethical. For this, this chapter discusses who a medical proxy is and tries to know if there is sufficient research in this regard.

Finally, this paper deals with the reverse of the question posed in the beginning of the paper. That

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is, whether it would be ethical for the researcher or a research facility to accept money as a criterion for deciding whether a patient is eligible to participate in a clinical trial. For this, an illustration is made, solved with the help of an existing method of clinical trials and study is made as to whether the existing method is limitation free.

STATEMENT OF PROBLEM

On the one hand, clinical trials are quintessential to the development of medical sciences. The society benefits from these trials as the outcome of these trials are usually new treatment methods, vaccines, cure or medications for diseases hitherto considered incurable/untreatable. On the other hand, there are several cases of abuse of clinical trial subjects including lack of informed consent. In the light of this, I felt that it was necessary to study this subject. However, due to the limitation of time and other resources, I have restricted myself to the area of informed consent as far as it is concerned with money.

Several clinical trials which have shown promise are in demand. There are cases where patients bribe their way into these studies despite them not being qualified enough to be in the study. It becomes necessary to study whether such practice is ethical given the possibility that such instances could compromise the outcome of the clinical trial. The reasons behind the study are these two problems facing the clinical trial studies.

HYPOTHESES

1. The payment of trial subjects would completely undermine the concept of informed consent in India.
2. Parents, Guardians and care takers do not have the right to consent to the participation of their child/ward/care-receiver, as the case may be, in clinical trials, especially after receipt of payment.
3. It is unethical to receive donations, etc. in exchange for spots in clinical trials.

PAYMENT OF TRIAL SUBJECTS VIS-À-VIS INFORMED CONSENT

This chapter would discuss the consequences of payment of clinical trial subjects (subjects) with regard to informed consent. For this, this chapter would begin with the explanation of the term ‘informed consent’ and its components. Following that, various types of payment made to subjects would be discussed. Further, this chapter would go on to discuss the effect that payment made to subjects would have on the voluntariness requirement in informed consent.

Informed Consent

Informed consent is *sine qua non* for any treatment. This becomes inevitable in the case of clinical trials. The National Ethical Guidelines for Biomedical and Health Research, 2017 (the 2017 ICMR guidelines) involving Human participants requires a voluntary written informed consent from clinical trial subjects before admission into the trial [1]. The 2017 ICMR guidelines states that informed consent has three main components – (i) Providing relevant information to the clinical trial subject (information, in short); (ii) ensuring that the subject is competent to consent to the trial (competence, in short); (iii) ensuring that the information given on the trial is comprehended by the potential subject clearly and the assuring that voluntariness to give consent (voluntariness, in short).

Information

For the clinical trial subject to make an informed decision, the researcher should give the certain minimum information regarding the trial. The researcher should disclose the nature of the disorder that is being researched; the prognosis of the disorder with and without the treatment given in the relevant trial; alternative treatment options available to the prospective subject; the reason for conduct of the clinical trial and the drawbacks of the trial; the potential side effects from the trial [2].

Competence

Competence of a person is a complex issue to deal especially when it involves medicine and health. Indian law considers any person above the age of eighteen; of sound mind; and not disqualified as a competent person by any law for the time being in force to be a competent person [3]. In the absence of competence, consent shall be given by a Legal Representative (for the purposes of this paper, such person shall be referred to as medical proxy).

Voluntariness

The 2017 ICMR guidelines provides that the consent that is given by a person or their medical proxy should be in the absence of coercion, undue influence, mistake, misrepresentation or fraud [4]. Section 2(1)(i) of the Mental Healthcare Act, 2017 defines informed consent as follows –"(i) "informed consent" means consent given for a specific intervention, without any force, undue influence, fraud, threat, mistake or misrepresentation, and obtained after disclosing to a person adequate information including risks and benefits of, and alternatives to, the specific intervention in a language and manner understood by the person" [5].

Therefore, we may conclude that anything that would lead a contract to become void or voidable would also make a consent given invalid for the want of voluntariness.

Payment of Money to Clinical Trial Subjects

Scholars have identified three types of payments that may be paid to clinical trial subjects:

i. Reimbursement of out-of-pocket expenses
ii. Compensation for time and effort of the subject
iii. Incentive for participation [6].

Reimbursement

The first type of payment that may be made to the subjects is the reimbursement of the actual out of pocket expenses that they may have incurred due to the trial. This is the basic requirement of every trial and every subject should be entitled to receive reimbursement of actual expenses. In fact, the 2017 ICMR guidelines provide that the subjects may be reimbursed [7]. Payment under this head would include travel expenses, expenses incurred due to some requirement of specific equipment or otherwise to be purchased for the purpose of the trial by the subject, food expenses, etc. This reimbursement is to not put the trial subject at a financially worse position than they actually were at the beginning of the trial.

What is necessary to be observed in this regard is that the reimbursement made to the clinical trial subject must only reflect the actual amount expended by the subject in relation to the trial. Otherwise, a net benefit conferred by the difference between the actual expense and the reimbursement could become an undue influence, thereby affecting the voluntariness criteria of informed consent [8].

Compensation

Subjects of the clinical trial may be paid to compensate their time and effort at fair value. This payment is made to indemnify any loss that the subjects may incur due to their participation in the clinical trial. Participants may be allowed to take paid leave from their place of employment and the research centre may pay the leave compensation to the employer directly or alternatively, the leave compensation may be paid to the subject directly [9].

The payment of wage compensation may justify why differential compensation may be paid to different class of people. For example, a person earning Rs. 50,000/- a month loses more than a person who loses Rs. 30,000/- a month when they take one day's leave in the month. Therefore, the compensation would be calculated on proportional basis. This will automatically lead to the differential payment of compensation that is justified.

Any damage incurred by the subject during the pendency of the trial that happened due to the trial can also be compensated [10]. This would follow the same process as claiming damages for injury that occurred during a normal course of treatment.

Incentive

Unlike reimbursement and compensation, incentive is quite complicated and delicate to handle in relation to ethics. While the former two are driven by the concept of fairness, where the objective is to not make the subjects pay out of their pockets to participate in the trial, incentives are usually paid with the objective of better recruitment and retention of clinical trial subjects [11]. Incentive means any amount paid to the subjects over and above what is to be fairly reimbursed to them or compensated.

It is not unknown that incentives would be paid to attract people to join clinical trials where there is less number than expected or where there is a lot of attrition. There is a school of thought that says that every individual owes to the society a moral duty of participating in clinical trials in the light of technical and medical advancements enjoyed by us which are there due to trials conducted in the past [12]. It becomes necessary to balance the interests of the world at large which would benefit out of the clinical trial and the right of an individual to not participate in clinical trials. In these cases, perhaps, incentivising the participation in clinical trials would help. Studies show that incentives draw more participation to clinical trials [13]. However, these incentives should not exceed certain amounts that would make it the sole reason for participation [14].

When Payment Compromises Consent

There are different points of view as to whether payment of money, especially in the nature of incentive would compromise the voluntariness to consent by the subject. *Grady* argues that paying incentives/ compensation/ reimbursement to trial subjects is not inherently unethical [15]. He also states that worries about undue inducement may be contained by careful assessment of risks and taking into consideration eligible criteria of research subjects and selecting them based on those alone [16].

Horn argues that the payment of money to clinical trial subjects cannot be dealt with in a "one-size fits all" manner [17]. He states that the nature of study; degree of risk to the subjects; profile of the subjects; source of funding; among other things are factors that need to be considered before arriving at a conclusion with regard to the ethical nature of payment made to the subjects [18]. A similar view is taken by *Koen, Slack and Essack [19]*. *Emily Largent et. al.,* in a survey found that test subjects and the general public think that the ethical concern that payment could constitute coercion or undue influence was a considerable ethical concern and cannot be brushed aside lightly [20].

One may notice that these studies are all from outside the country and may not truly reflect the position in India. Therefore, it is pertinent to note the attitude of Indian Jurisprudence in matters concerning coercion and money in the form of compensation. In India, there is a lack of knowledge on clinical trials among the general public and there is necessity of educating them on the said issues [21]. Therefore it becomes necessary to study this issue in the light of the situation in India.

PUDR v. Union of India

Though not directly related to the matter at hand, the judgement of the Supreme Court in *Peoples' Union for Democratic Rights v Union of India and others [22]* is of great significance to explain the nature of potential coercion or undue inducement that money may be to the ones that do not have it. During the IX Asian Games that were held in the year 1982 in New Delhi, workers from Haryana were employed for construction work. These construction workers were paid less than minimum wages. A Public Interest Litigation was filed asking the Court to direct the government to ensure that the said construction workers were paid minimum wages as stipulated by law stating that paying less

than minimum wages would amount to forced labour. The Respondent took the view that the workers were ready to work for less than minimum wages on their own accord and no one forced them to work for such wages. The Court disagreed with the Respondent and held that the very fact that the construction workers are ready to work for less than minimum wages means that they could not find any job that paid them minimum wages. Therefore, the Court held that exploiting their work for less than minimum wages would amount to forcing them to work for less than minimum wages.

Analogy

In the matter at hand, a study shows that 5 per cent of the clinical trial subjects that were interviewed entered the clinical trial for the money incentive that the trial provides [23]. We also see that a small payment made as an incentive improves the patient response to clinical trial invitations and also consent given by said prospective subjects [24]. Certain studies have published testimonials of respondents who state that they would not have participated in the clinical trial if not for the monetary incentive or the free medical care that comes along with said trial [25].

In light of the discussion above, it may be inferred that there are certain class of subjects that participate in clinical trials only because of the incentives offered by the trials. In the absence of any other factor, they would not participate in the clinical trial. Therefore, the incentive paid in such cases acts as an undue influence or even as a coercive factor for the subject to join the clinical trial. Once there is an undue influence or a coercive factor, the consent given by the subject cannot be treated as being informed. Therefore, we may conclude that if money is the only reason behind one joining a clinical trial, in such cases, payment of incentives would lead to non-voluntary consent and consequently, lack of informed consent on the part of the subject.

CONSENT FOR CHILDREN AND INCAPABLE PERSONS

The 2017 ICMR guidelines treats children, mentally challenged persons, and other incapable persons as a single class – persons without competence [26]. The Mental Healthcare Act, 2017 requires that consent be given by medical proxies (guardians/ legal representatives) instead of these "incompetent" persons. From the discussion in the previous chapter, it may be clear that there may be nothing wrong in the medical proxies receiving reimbursement/ compensation from the clinical trial. However, receipt of incentive by the medical proxies begs the question as to whether such payment of incentive would dilute the voluntary nature of consent by the medical proxy.

The principles of contract are clear that a guardian cannot enter into an onerous contract on behalf of a minor. That principle is squarely applicable in our case also. However, the stakes in consent to clinical trials is higher because the consequences of the said consent are irreversible in most cases here. Since the medical proxies have no chance of personal injury in this case, it is possible that the incentive paid may sway the proxy towards making the incompetent person participate in the trial [27].

The 2017 ICMR guidelines states that –

"When the LAR is giving consent on behalf of a participant, payment should not become an undue inducement and to be reviewed carefully by the EC. Reimbursement may be offered for travel and other incidental expenses incurred due to participation of the child/ward in the research."

The 2017 ICMR guidelines clearly understands that payment could be an undue inducement in the case of incompetent persons more than it does in normal cases of consent. Therefore, it makes it mandatory for the ethics committee to review the amount that is being paid to a medical proxy for the participation of their ward in the trial. A better option would be giving the children gifts that they will be able to use instead of paying the medical proxies [28]. However, this too has its limitations because children of different ages treat gifts differently. One more suggestion that could be made is the direct deposit of the amount to the bank account of the child which the child may use after attaining

majority. It may be noted that this cannot be made applicable to other incompetent persons such as persons of unsound mind. Therefore, with regard to payment of incentives to incompetent persons, there is a need for empirical research and discussion in this regard [29].

RECEIPT OF MONEY BY LAB/ RESEARCHER

Clinical trials are done in four stages. In India, drugs need to undergo all the four stages of clinical trial [30]. The first stage of the trial or the clinical pharmacology trials is where the drug is tested on a very limited number of informed and healthy volunteers [31]. This would be the first time the said drug is tested on the human beings. In the second phase, also called the therapeutic exploratory trials [32], a slightly larger number of volunteers are tested with the drug at three or four centres [33]. In the third phase, the drug is administered to around 3000-4000 subjects, where in certain cases, placebo groups are also made to enhance the reliability of the trial [34]. The final stage is where the drug is marketed and is surveillance is made for any hitherto unregistered side effects [35]. Before the end of these phases of trial, it will not be possible to know the efficacy of a drug. However, by the end of phases one and two, when the results are made public, a perception of the efficacy of drugs is created. Therefore, in these cases, demand to enter into the trial and have access to the said drug at an early stage can be more [36]. A study has noted that around 13% of the clinical trial subjects join a clinical trial on a perception of the efficacy of the drug [37]. Therefore, the criteria to enter into the trial would be followed to the letter in these trials. However, a question arises as to whether money in the nature of a bribe/ donation can be used as a criterion to admit a subject to the trial. This question shall be answered in this chapter.

Ethical Dilemma

Let us assume a situation with a disease X, for which there is a serious necessity to start Phase III clinical trial as there is a potential drug, showing promise after Phase II. Now, there is a person affected with disease X, who is ready to fund the trial on the condition that they would be admitted to the trial. Applications are called for the trial with 3000 subjects. Perceiving the efficacy of the potential drug, several applications come in and there are 3000 subjects that completely fall in the criteria for selection. The person funding the trial unfortunately does not come in the top 3000 candidates. Let us say that disease has not progressed so much in the person funding the trial or has progressed too much that the drug, even if administered may not be effective. Question arises as to whether it would be ethical to admit the said person even though we know that the study could be disrupted by this entry. On the other hand, if he is not admitted, there is a threat of lack of funds to continue the trial. This would completely put off the purpose of the trial.

Randomised Double Blind Trials

The answer to the ethical dilemma posed in the previous paragraph is randomised double blind placebo-controlled trials. This is considered to be the golden standard of intervention based studies [38]. This involves the following steps:

i. Randomisation
ii. Placebo control
iii. Blinding.

Randomisation

Randomisation is the process by which the test subjects are assigned into two groups in a completely chance based manner. The two groups are – (i) experimental group and (ii) control group. Experimental group is the group of clinical trial subjects that are given the investigative drug [39]. Control group is the group of clinical trial subjects that are given a placebo treatment in place of the investigative drug [40]. This process eliminates *selection bias [41]*. Selection bias is when the researcher is able to pick and choose which clinical trial subject is given the investigation drug and who is given the placebo treatment. In our illustration, it would mean that the researcher cannot allot the person funding the trial to the experimental group. This becomes a barrier to the objective of the person funding the trial – access to the investigation drug.

Placebo Control

As explained earlier, the control group is given a placebo drug in the place of the investigative drug. Placebo is a substitute to the investigative drug that has no significant effect on the treatment of the disease or condition that is sought to be treated [42]. This should not be confused with not treating the subject because the administration of the placebo drug gives the subject a psychosomatic effect induced by the calming of the fear, anxiety and/ or stress caused by the disease [43]. By this, we understand all the effects of the placebo treatment and separate it from the effect that the investigative treatment has on the experimental group over and above the placebo effects. That would be the objective of the trial [44].

Blinding

Blinding is the process by which the components of the treatment that is not necessary to be known by a certain group involved in the clinical trial. A single blind trial is when the trial subject does not know whether they are receiving the investigative treatment or placebo treatment [45]. Double blind trial is where the researcher as well as the subjects is blind to the treatment that is received by the subjects. Triple blind trial is where this information is blinded to the data-analyst along with the researcher and the patient [46].

The process of blinding eliminates both observers' bias and reporting bias [47]. Observers' bias is the when the researcher knows what group a particular subject belongs to and expects certain reaction. In the absence of the said knowledge of the group, the researcher would not know what to expect out of a particular trial subject. Reporting bias is the selective reporting of the observations made by the researcher due to the non-blinding which leads to the distortion or inflation of final results of the study.

Limitations of Double Blind Study

Though randomised, double blind, placebo controlled trials are the golden standard of intervention based treatments, they still have certain limitations such as non-compliance, attrition, enrolment of ineligible patients, among other things [48]. It is still possible for an ineligible patient to be enrolled to the trial by breaking the blind. More than the ethical aspect of breaking the blind, it would distort the outcome of the trial to a great extent and completely ruin the very reason the trial was conducted, all for the need of a single person as against the greater public good. Therefore, it is completely unethical to enrol an ineligible person to the trial merely because he is ready to pay for his place in the trial.

CONCLUSION

From the discussions in the paper, we have looked into three main questions, having arrived at three different hypotheses. This chapter shall try and answer them one by one. The first hypothesis posed was that it was unethical to pay money to clinical trial subjects as it would compromise informed consent. This hypothesis was tested and is partially accepted to the extent that when payment made is the only consideration for the subject to enter into a clinical trial, being blind to all other factors such as side effects, it would be unethical to pay incentives. This is because money has the power of compromising voluntariness and force people to do things that they would not otherwise do. It is fine to pay the subjects so long as it is in the nature of reimbursement, compensation or reasonable incentive to increase participation in a much needed trial.

The second hypothesis posed is that it is unethical for medical proxies to receive money for the participation of their wards. This hypothesis is also accepted partially with certain reservations. Like the first hypothesis, it is right to pay reasonable reimbursement, compensation or even incentive. However, since the medical proxies usually do not have any personal loss in the trials, there is a possibility of clouding of their judgement. Therefore there is a need for further empirical study in this regard as far as reasonable incentive is concerned. However, like in the first case, here too, it would be unethical to pay a disproportionate incentive just to ensure participation in the study especially when the payment is made to a vulnerable person.

The last hypothesis posed was that it would be ethical for researchers to receive payments to admit patients to a clinical trial. This hypothesis is also accepted partially. There is a reasonable barrier towards any possible biases that may arise out of the conflict of interest that may arise out of the receipt of money by the researcher from a subject. This is the randomised double blind placebo controlled clinical trial method. However, this method too has its limitations and there is a possibility of breach of this blind by the researcher owing to the conflict of interest. Therefore it becomes necessary for the ethics committee to strictly follow all protocol and makes sure there is no breach in the double blind trial process.

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