Review Article

Compensation in clinical research: The debate continues

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INTRODUCTION

Compensation for research subjects in clinical trials has been an old and established practice. There has been much documentation of investigators offering favor in the form of money to their research participants. One of the early examples is of Dr. William Beaumont, who, in the early 18th century while conducting trials on his patient, St. Martin Alexis, to study the gastric juice and physiology of digestion, paid him under an agreement that St. Martin Alexis would allow Dr. Beaumont to conduct research on him.[1] For over 200 years, compensation has been offered to research participants for various reasons like alluring them to participate, obliging them to stay till the completion, compensating them for their loss of daily wages, etc., But, unfortunately, for an over 200-year-old practice that we continue to follow till date, we still have not reached any consensus about the right way of doing it or whether it should be practiced in the first place! It still remains a contentious issue with endless debates at various platforms the world over.

WHY COMPENSATION?

Compensation in research is paid mainly for two objectives:[1] For participation in clinical trial and[2] for trial-related injuries. Compensation has often raised ethical issues regarding its influence on integrity in clinical research. So, why is compensation paid in research? The literature suggests that compensation is paid for reasons like relieving participants of financial sacrifice, as appreciation of participant's contribution to medical science, for achieving the sufficient number of recruitment in the required time frame or for accomplishing targeted recruitment where target population is difficult to reach or small in number (for instance individuals with rare conditions or certain races)[2-5] and also in cases of trial-related injuries.

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HOW IS A RESEARCH SUBJECT IN CLINICAL TRIALS COMPENSATED?

Research subjects in clinical trials are compensated by monetary and non-monetary means. Monetary benefits are provided for their time and effort for participating in the trial or money is offered as reimbursement for the expenses incurred by them, like travel, loss of daily wages, etc., Subjects are provided free medical management for the injury/harm encountered during their trial participation and, in case of serious trial-related injuries, the subjects are compensated financially in addition to free medical management of the injury.

The moot question is: How does one decide how much compensation to pay to the subject for trial participation? There are several proposed models of making payment to subjects for trial participation. Some of the ways are more ethically acceptable than the others.[2] The common models are:

The market model,[2,3]
The wage model,[2,3]
The reimbursement model,[2,3]
The appreciation model.[3]

The market model is based on the principle of supply and demand, which decides when and what is to be paid to the research subjects for a particular study in a particular location. This means that compensation is paid to the subjects for the studies that offer little or no benefits or the studies for which the target population is difficult to reach. Also, this implies that in case of studies that offer benefits or have a huge target population, little or no compensation is paid. This model has advantages like targeted number of subject recruitment achieved in the required time frame, decreased financial sacrifice by the subjects and high completion bonus ensures protocol compliance. However, on the flip side, this model leads to very high compensation in few of the hard-to-find-subject studies, which could serve as undue inducement and could unnecessarily commercialize the research participation. High payment can lead to subjects not paying attention to the risks involved in the study as well as leading them to hide important data that could deem them ineligible for the study. It could also create situations where the investigators are competing for subjects by paying higher amounts.[2,3]

The wage model is based on the concept that research participation requires little or no skill, but it does involve consideration of the time and effort of the subject and also discomfort that is faced by subjects. The model is in alignment with egalitarianism. This model suggests that the subjects engaged in similar activities be paid similarly. Thus, here, the subjects are paid on a scale parallel with that of the unskilled but essential jobs. The advantages of this model could include minimization of the issue of undue inducement, reduced inter-study competition as seen in the market model that would also encourage investigators to minimize the risks involved, decreased financial sacrifice by the subjects and prevention of discrimination between high-income and low-income groups (like the reimbursement model described below) as subjects of the same study receive equal compensation. However, it creates difficulty in achieving the targeted number of subject recruitment in the required time frame and it usually attracts the low-income population. It views subject's research participation as an unskilled job and many believe it to be inappropriate commercialization of the research participation.[2,3]

The reimbursement model is also in alignment with the egalitarianism principle. This model suggests that compensation should only recover the costs incurred by the subject for participating in the trial. Also, the time spent away from work can be reimbursed proportional to their earning capacity. This model helps in resolving the issue of undue inducement to a certain extent. Subjects are less likely to hide information or overlook the risks involved in the study. The model also decreases the financial sacrifice by the subjects. On the other hand, the issues with this model could be difficulty in achieving the targeted number of subject recruitment in the required time span. Also, different subjects have different earning capacities based on their qualifications, which leads to either preference for the low-income group or high cost of study if subjects from the high-income group are selected.[2,3]

The Appreciation model suggests compensation at the time of study completion as a token of gratitude or appreciation. This has no impact on the study recruitment as it is given at the end of the study.[3] However, this model could have an impact on subject retention and may act as an inducement to prevent a patient from discontinuing. It needs to be used along with one of the above-mentioned models. The researcher needs to carefully weigh the pros and cons of each of the above models and decide which one is best suited for the study on hand. It is also best to decide and document the mode of compensation before the trial is initiated, taking the stake holders and the Ethics Committee in confidence and with the mandatory approval obtained from these.

COMPENSATION POSES CRITICAL ETHICAL CONCERNS IN CERTAIN POPULATIONS

Compensation raises ethical concerns, which mainly include undue inducements, disproportionate burden on the poor and commodification.[2-4] However, it can have more detrimental effects on some of the vulnerable populations, which include children, the mentally challenged population, population with poor economic background and illiterates. The vulnerable population includes a large segment of other populations also, but compensation specifically affects the above-mentioned groups. Vulnerability is characterized as limited autonomy of the individual in making a decision, and all of the above-mentioned groups have limited autonomy. Furthermore, the condition worsens when money is introduced as an inducement.

The issue of compensation has special concerns in vulnerable populations and requires a deep understanding of the science coupled with genuine social concerns. For children and the mentally challenged, determination of compensation is crucial as they do not make their own decisions but their parents/legal guardians do it for them. Here, the children and mentally challenged bear the risks of clinical research (although they may benefit too) whereas

the compensation is received by their parents/legal guardians who are not exposed to any risk themselves. Although one may like to believe that parents/legal guardians would always make the decision that is in the best interest of their children/relative, the possibility of compensation distorting their decision cannot be ruled out. However, many debate that parents/legal guardians incur costs for making it possible for the subjects to participate and therefore they should be rewarded and supported financially.[3] Efforts could be made in offering options that will make the task of such patients' care takers–parents/legal guardians easier and relieve their burden of caring for these patients.

For the poor, illiterate and the unaware, monetary inducements can easily be enticing. Poverty and illiteracy are known to coexist.[6] In this situation, they are unable to comprehend the research information provided in the informed consent document but they do clearly understand the importance of monetary benefits and their utility in their lives. They may pay less attention to the risks involved and participate in the study only for the monetary benefits. Although they cannot be excluded from trial population as they represent a certain group of the society and contribute to generalizability of the research findings,[6] their inclusion should be carefully evaluated and also, whenever their inclusion is necessary, a cap could be placed on the number of subjects that can be included from these populations so that they do not constitute the entire target subject population.

COMPENSATION IN DISCUSSIONS IN THE MEDIA

Compensation is one of the most talked about topic in the media in recent times. In the recent past, the parliamentary standing committee was appointed by the Ministry of Health and Family Welfare to evaluate the functioning of the Central Drug Standard Control Organization (CDSCO). The reports suggested that in 2010, 668 cases of serious adverse events (SAEs) were reported, of which 22 were related to clinical trials; in 2011, 16 cases of the 438 reported SAEs were research related.[7,8] The committee observed that no compensation was paid for these cases. The respective sponsors were asked to pay the compensation for all of the study-related death cases.[7,8] Following this, there have been many discussions over the regulations regarding compensation to research participants. The CDSCO has issued draft guidelines for compensation in case of injury or death during the clinical trial[9] and guidelines for determining the quantum of financial compensation to be paid in case of clinical trial-related injury or death.[10] There have been certain criticisms regarding these draft guidelines.[11-13] Expert groups of all stake holders have been formed to deliberate and provide suggestions to the ministry on these guidelines.

COMPENSATION FOR TRIAL-RELATED INJURIES: GUIDELINES AROUND THE WORLD

Compensation for trial participation has been discussed above with four proposed models. But, for the compensation for trial-related injuries, there are various guidelines in place in different parts of the world.

INDIAN GUIDELINES

Starting with the Indian guidelines, compensation has been mentioned in both the Indian Council of Medical Research (ICMR) Ethical Guidelines for Biomedical Research on Human Participants[14] and the Indian Good Clinical Practice (GCP) guidelines.[15] Both these guidelines suggest that research participants who suffer physical injury as a result of their participation are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability; in case of death, their dependents are entitled to material compensation. Participants may be paid for the inconvenience and time spent, and should be reimbursed for expenses incurred, in connection with their participation in research. They could be provided free medical services. The guidelines also state that the protocol and informed consent document should have clear information regarding the proposed compensation in case of accidental injury.[14,15]

INTERNATIONAL GUIDELINES

Some of the International guidelines like the Association of the British Pharmaceutical Industry (ABPI) and the Council for International Organizations of Medical Sciences (CIOMS) guidelines have laid down the approaches for compensation in a very descriptive manner taking into account the situations encountered routinely in the practical scenario, whereas there are other earlier guidelines like the International Conference on Harmonization-GCP (ICH-GCP) and Declaration of Helsinki that briefly mention compensation. Also, there are guidelines like the code of federal regulations, which provide ambiguous information regarding compensation.[2]

The ICH-GCP guidelines state that compensation should be paid and/or treatment be made available to the subject in the event of trial-related injury. If required by the applicable regulatory, the sponsor should provide insurance or should

indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence on their part.[16] The World Medical Association-Declaration of Helsinki suggests that the design and performance of each research study involving human subjects must be clearly described in research protocol provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.[17]

The US-food and drug administration (FDA) does not have detailed instructions on compensation. The code of federal regulations suggests that the institutional policy, not FDA regulation, shall decide whether compensation and medical treatment(s) will be offered and the conditions in which the compensation will be offered. The FDA informed consent regulation on compensation requires that, for research involving more than minimal risk, the subject must be told whether any compensation and any medical treatment(s) are available if injury occurs and, if so, what they are, or from where further information can be obtained. The guidelines strictly instruct that any statement of no compensation mentioned in the consent document or protocol must not waive or seem to waive the investigator, sponsor or institution from their liability in case of misconduct or negligence on their part.[18,19]

The CIOMS guidelines prepared in collaboration with the World Health Organization (WHO) suggest that during informed consent, the investigator must provide information regarding how and from whom the subject, subject's family or dependents can be compensated in case of injury or death. Also, subjects should be informed about their legal rights to compensation depending on the country they are participating in. Investigators should ensure free medical treatment and financial or other assistance for research subjects who suffer injury as a result of their participation, in order to compensate them equitably for any resultant impairment. In the case of death as a result of their participation, their dependents are entitled to compensation. Subjects must not be asked to waive their rights to compensation or required to show negligence or lack of a reasonable degree of skill on the part of the investigator in order to claim free medical treatment or compensation. Compensation is owed to subjects harmed as a consequence of injury from procedures performed solely for the purpose of research and not for expected adverse reactions to investigational therapeutic, diagnostic or preventive interventions when such reactions are not different in kind from those known to be associated with established interventions in standard medical practice.[20]

These guidelines also reflect the issue of compensation in various trial phases. It explains that in the early stages of drug testing (Phase I and early Phase II), the subjects generally have no direct benefit from the investigational drug and hence compensation is owed to the subjects injured due to participation in such studies. The guidelines recommend the Ethics Committees to review and determine the injuries for which the subjects should or should not be compensated. However, in case of unexpected adverse reactions, such determination is not possible. Hence, any unexpected adverse reactions must be considered compensable and forthwith reported to the Ethics Committee for its review.[20] The ABPI has issued very detailed guidelines on compensation. They have promulgated separate compensation guidelines for injury caused to patients involved in Phase II and Phase III trials, studies involving non-patient volunteers and studies on marketed products. The guidelines cover in detail the basic principles for providing compensation, type of clinical research covered, limitations, assessment of compensation and miscellaneous issues related to compensation,[21] and serve as a good reference for future compensation guidelines.

CONCLUSION

There is need for explicit guidelines regarding compensation to research subjects – for both trial participation as well as for research-related injuries, to be in place. The compensation guidelines for research-related injuries is already underway, with the government being committed to bringing about the much-needed change in the clinical research industry and its functioning. It would be helpful if it is not limited to guidelines and becomes a law to ensure compliance by the parties concerned. It would also help to have written guidance regarding compensation for trial participation as well. Also, certain innovative ways of offering health benefits to research participants and motivating them for participation rather than simply offering monetary benefits may also be evolved; however, it would be like lending a different perspective to the same issue. The intent behind the compensation is more important than the means. The dictum of "do no harm" that guide a clinical researcher should not be overridden by the forces of compensation. In a scenario laden with competition, time constrains and paucity of eligible subjects for clinical research, it is easy to use compensation as a bait to lure potential subjects. One needs to understand that clinical research is the process for transforming the biomedical research done by today's generation for the improved medical practice of the generation of tomorrow. Spreading awareness that the basic objectives of clinical research are improvement of disease outcome and improvement of quality and efficiency of the healthcare system could help in changing the perception of research participants as guinea pigs and could help mitigate

the researcher's problems to a certain degree. The ideal situation would be when subjects volunteer for the altruistic reasons rather than for the material gains. Until then, let us learn from the debates and experience and remember the ethical concerns that guide clinical research.

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