Compensation Guidelines for Research Related Injury in India

Jigeeshu V Divatia*, Abhidnya Desai**, CS Pramesh***, KM Mohandas****, Sudeep Gupta***** , Rajendra A Badwe******

Introduction

The Indian law for clinical trials i.e. the amended Schedule Y of 2005, has specified the need for provision of compensation of participants for research related injuries as an essential element of the Informed consent form (ICF). The Indian Council of Medical Research (ICMR) guidelines as well as Indian Good Clinical Practice (GCP) recommend 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. The Drug Controller General of India (DCGI) now mandates that all ICFs incorporate a clause stating that in case of study related injury or death, the sponsor will provide complete medical care as well as compensation. The Central Drugs Standards Control Organization (CDSCO) of the Directorate General of Health Services (DGHS) of the Ministry of Health and Family Welfare (MHFW) as well as the Indian Council of Medical Research (ICMR) have issued draft guidelines for compensation of research related injury on its website requesting feedback from all interested parties. These Guidelines apply to all clinical research, whether sponsored by the Pharmaceutical or Medical Device Industry, Government or Academia or individual investigators.

As an Academic Institute committed to highest clinical, ethical and moral standards and practices in Research, we too agree with the principle that patients who suffer injury due to their participation in a clinical trial must be provided with free treatment. We also agree that compensation over and above free treatment and rehabilitation costs may be payable to the patient, and in case of death the next of kin should receive compensation. However, we have serious concerns over some of the provisions, and believe that they may be detrimental to investigator initiated research. The net effect of the proposals, taken in their entirety will in fact only serve to make clinical research a monopoly of Academia or individual investigators.

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1. Mandatory compensation for the following is not rational:
   a. failure of an investigational product to provide intended therapeutic effect
   b. administration of placebo providing no therapeutic benefits
   c. adverse effects due to concomitant medications

The above clauses are included in the CDSCO draft guidelines as being grounds for compensating research participants. The basis for performing clinical trials and any form of research is because there is equipoise or lack of knowledge about the efficacy of new treatments. Therefore, compensating patients being treated with new investigational products because the product did not have its intended therapeutic effect does not make sense. In fact, lack of knowledge about this very fact is what mandates the research to be done in the first place. Similarly, placebos are frequently used in clinical research where no effective alternative treatment exists primarily to avoid bias in interpreting the effects of the investigational drug. The placebo is not expected to provide therapeutic benefit though on occasion it has shown to do so. Compensation being provided for patients because the placebo does not have a therapeutic effect again does not make sense.

Patients with disease are frequently prescribed multiple drugs and treatment, most of which are standard or routine treatment which they would take regardless of whether they are research participants or not. In addition, patients take the investigational drug as part of the research protocol. Adverse events occurring due to the other concomitant medications are common and are in no way related to the research itself. Having to compensate for injury resulting from these concomitant medications is again illogical.

Comparing the CDSCO draft guidelines with the ICMR guidelines as not being entitled to compensation while the CDSCO guidelines mandate it. While we hope that these clauses crept in inadvertently into the draft CDSCO guidelines (possibly a typographic error), we would like to make our opinion about these clauses clear.

2. Compensation need not be paid always for complications arising from the use of a standard therapy in the control arm of a clinical trial?

Several treatments that are offered to cancer patients in the course of routine day-to-day clinical practice (e.g. chemotherapy, radiotherapy, surgery, etc) have inherent toxic effects. Patients often experience serious side effects that necessitate other medications, hospitalization, intensive care unit admission, and can occasionally die from these complications. Clinical trials of new anticancer agents are often performed in the expectation that the new treatments would be more effective, or less toxic or both. We believe that for patients receiving standard therapy in the control...

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*Professor and Head, Department of Anaesthesiology, Critical Care and Pain, **Junior IRB Administrator, ***Associate Professor, Department of Surgical Oncology, ****Professor and Head, Department of Digestive Diseases and Clinical Nutrition and Director, Centre for Cancer Epidemiology, *****Professor, Department of Medical Oncology, ******Professor & Head Breast Service, Director, Tata Memorial Centre Research Administrative Council, Tata Memorial Centre, Mumbai, India.
arm of a trial, compensation should not be mandatory. This is justifiable as the subject would have received similar treatment and experienced similar adverse effects even if he was not a participant in the trial.

The guidelines of the Association of the British Pharmaceutical Industry (ABPI), mentioned in the Preamble to the draft guidelines, state that “Compensation should, be paid when, on the balance of probabilities, the injury was attributable to the administration of a medicinal product under trial or any clinical intervention or procedure provided for by the protocol that would not have occurred but for the inclusion of the patient in the trial”. The ABPI guidelines also recommend that while subjects suffering from research related injuries be compensated, no compensation should be paid for injury caused by other licensed medicinal products administered to the patient for the purpose of comparison (i.e. standard treatment arm or control arm) with the product under the trial. This would also mean that when two standard forms of treatment are being compared (as is usually done in many investigator initiated studies), any injury or death while participating in the study need not necessarily be compensated, provided this is made clear in the ICF.

Thus we believe that compensation should not be given in a blanket fashion to any participant in a trial who experiences an SAE, but to those in whom it can be reasonably attributed to having a complication that would not have occurred in the course of routine treatment outside of the trial. This should be the guiding principle for investigators, institutions and Ethics Committees in determining whether or not compensation should be paid.

3. Promise of mandatory compensation can impair rational decision-making by the patient or his /her surrogate?

We would also like to point out that insisting on compensation for patients who suffer from injuries while participating in a clinical trial may actually influence patients’ decisions (or decisions taken by surrogates) and infringe on the ability of patients to make rational choices of whether to participate in a clinical trial. Several patients (or their surrogates), especially those with severe life threatening illness (e.g. advanced cancer, myocardial infarction, stroke, septic shock), may consent to participate in a trial with high risk of complications knowing that compensation will always be available. This can be also be viewed as inducement. Keeping the compensation optional as part of the investigators’ or Ethics Committees’ responsibilities would be a better option. We agree that if compensation will not be paid in a research study, this should be made clear in the ICF thereby giving patients full freedom of choice regarding whether or not to participate in the study.

4. Compensation must be considered in the background of underlying risk of the condition being treated

The ABPI guidelines further provide for the situation where compensation may be abated, or in certain circumstances excluded, in the light of the following factors (on which will depend the level of risk the patient can reasonably be expected to accept):

1. The seriousness of the disease being treated, the degree of probability that adverse reactions will occur and any warnings given;

2. The risks and benefits of established treatments relative to those known or suspected of the trial medicine.

This reflects the fact that flexibility is required given the particular patient’s circumstances. To give an example, febrile neutropenia is a serious complication after chemotherapy for cancer, and has a definite mortality, especially if severe. Let us consider a clinical trial comparing a new antibiotic for the treatment of febrile neutropenia after chemotherapy. It is inevitable that some of these patients would develop infectious complications due to the neutropenia, or even die in an extreme case, despite the use of an effective experimental antibiotic. This would happen even with the best available comparator antibiotic for febrile neutropenia. Thus, in situations where severe morbidity or death is a common outcome of the disease process, it would be unreasonable to mandate compensation for such events in a clinical trial. There are several other examples of such situations such as patients with metastatic melanoma, glioblastoma, metastatic pancreatic cancer, cardiogenic shock due to myocardial infarction, severe sepsis and septic shock, acute respiratory distress syndrome, advanced interstitial lung disease, etc. in which a large number of patients routinely experience serious complications or die. Trials in such high risk diseases will stop if compensation is mandated through the proposed guidelines.

We believe that it is reasonable that compensation need not be paid in such high-risk trials as the patient had accepted the high risk and should not expect compensation for the occurrence of the adverse reaction of which he or she was told. Thus, we again wish to point out that compensation should be decided on a case-to-case basis by the Ethics Committee, after considering all incriminating and extenuating circumstances.

5. Compensation can be claimed under existing provisions in Indian Law

In USA, it is not mandatory by law for Sponsors and Institutions to provide either free medical care or compensation for research related injuries to trial participants. Affected patients can apply to the courts under the Law of torts to avail of relief for persons who have suffered harm in course of a clinical trial. Similarly in India, patients can claim compensation under civil laws or perhaps under Consumer Protection Act. Insisting on compensation guidelines such as these on the grounds that the legal system in India is inaccessible to the general public is only casting aspersions on the judiciary and is detrimental in the long run.

6. No fault compensation does not necessarily imply no blame

In Europe, clinical trial insurance is mandatory, and participants are often covered regardless of fault. These guidelines apply to injury caused to patients involved in Phase II and Phase III trials, and only cover the medicinal product under trial for which a product license does not exist. Thus standard of care is not covered. As far as no-fault compensation is concerned, the fact that compensation has been paid may be seen by the general public, society and media as an admission of guilt or negligence, and can seriously hurt the reputation of the Investigator / Institution.

7. Impediment to undertaking research on cost-effective therapies for developing countries

In developing countries such as India, it is vital to carry out research to develop cost-effective treatments. There are
treatment regimes that are the standard of care in Western countries, but are available only to those patients in India who can afford the high costs of treatment. On the other hand, there may be treatment protocols involving cheaper and more easily available therapies that are affordable by most patients. It would be of great significance for Indian patients to undertake a trial comparing these two treatments, both of which are standard treatments depending on the patients’ circumstances. Providing for compensation for adverse events in such a trial would make it virtually impossible to carry out trials exploring cost-effective treatments suitable for patients in developing countries.

8. Detrimental for non-industry sponsored, academic research

We would also like to point out that provision of compensation for all patients, including those subjects receiving standard treatment would make research extremely expensive, and it would be beyond the means of individual investigators, academic groups of investigators and academic institutes to carry out interventional research studies. Such guidelines will kill academic initiative, and skew the entire process of clinical research in favour of industry, for it will only be possible for large corporate entities to make provisions for the huge amount of funding necessary for compensation to all participants in clinical trials. Industry would probably find it convenient and expedient to offer compensation for injuries while participating in a trial. Perhaps individual institutional investigators can procure insurance cover for all trials, but then investigators, patients and families of participants of research would be at the mercy of the insurance companies, both in terms of whether or not compensation will be paid as well as the quantum of compensation. Insurance premiums for high risk studies in critically ill patients (where the maximum research needs to be done) would be exorbitant and make these studies virtually impossible in an academic setting.

Consider a multicentre investigator initiated trial such as the HPV vaccine trial funded by the ICMR/DBT/DST/TMH. Several girls died and the study was temporarily stopped. Some died due to accidents, snake bites, and other illness like Japanese Encephalitis, etc. If any subject developed Guillain-Barre syndrome which an investigator attributed as possibly due to the vaccine, should the sponsor pay up? There is move to enhance (double) post graduate medical seats in India and all those students will have to do research. What will happen if the proposed guidelines are imposed on 350 medical colleges? It will create an entirely new problem for all Deans and MCI in the country.

9. Respecting the ability of the patient to exercise his rights

If provision of compensation is made on a study to study basis (and not mandatory, in all trials), the patient retains the right to consent or refuse to be part of a clinical trial which does not offer compensation. We would further like to state that any patient who understands and accepts to be part of a clinical trial, is capable of understanding that compensation is not automatic after injuries while participating in a trial. The assumption that patients would not be able to understand what is probably the most easily understandable part of the entire informed consent process in a clinical trial seems patronizing and an extreme viewpoint.

10. Who will determine the quantum of compensation?

Indian GCP states that compensation must be paid “subject to confirmation from IEC”. The DCGI has also stated in its correspondence with the Ethics Committee that it is the duty of the Ethics Committee to ensure that due compensation for the study related death in the clinical trial is paid to the dependents of the deceased by the sponsor in time. It would thus appear that this job would fall on the Institutional Ethics committee. However, given the composition of ethics committees, it is unlikely that ethics committee members will have the necessary expertise or experience to determine quantum of compensation or whether fair compensation was paid.

In summary, we the clinical investigators at Tata Memorial Centre, Mumbai do agree with the principle of compensation for trial related injury. We believe that there needs to be some more healthy debate on the issues we have stated above and due attention must be given to the concerns of academic investigators. This debate should involve all stakeholders in clinical research in the country – investigators, ethicists, patient representatives, and regulatory authorities.

**References**

3. Indian GCP http://cdsco.nic.in/html/GCP.htm