Compensation conundrum

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Abstract

Pressured by questions tabled in parliament that point to a lack of adequate enforcement of regulations, the DCG(I) has abruptly initiated action to ensure payment of compensation for trial-related injuries. While it is astounding that non-compliance to the existing regulations could have gone unnoticed by quality assurance staff as well as by the ethics committees and the regulator, for over six years, sudden enforcement of the regulation has thrown up issues and challenges that are difficult to resolve in the absence of an adequately debated and thought-through guidance. In implementing regulations for *suo moto* compensation, India is seeking to establish a practice not previously tested elsewhere in the world. There is no doubt that industry must support the idea of putting patients first, but procedural considerations in fixing causality and determining the quantum of compensation promise to raise questions of morality, ethics, and jurisprudence that will not be easy to answer.

Key words: Accidental injury, compensation, insurance, trial-related injury

INTRODUCTION

By the year 2000, India had begun to gain reputation for quality and efficiency in clinical research.[1] Yet local regulations at the time made no mention of Good Clinical Practice (GCP). Thus, compliance to GCP was not a local regulatory requirement 10 years ago. In an effort to plug this gap the Central Drugs Standard Control Organization (CDSCO) commissioned the writing of GCP guidelines that would be applicable in the country and, in December 2001, published *Good Clinical Practices: Guidelines for Clinical Trials on Pharmaceutical Products in India.*[2] A lot has been said and written about the need, quality and format of this document. Till 2004, all that did not matter, as the rules that governed clinical research, namely, Schedule Y of the Drugs and Cosmetics Rules, still did not refer to this or any other GCP guideline as a necessary requirement. That changed in January 2005, when Schedule Y was revised to include, among other things, several references to GCP, and specifically to the GCP guidelines issued by the CDSCO.[3]

Now that this guideline had become a necessary requirement, Quality Assurance (QA) staff in clinical research organizations began to pay more attention to its minutiae. Differences between this document and the standard ICH E6 guidelines were difficult to spot because of divergent formats that made comparisons a very daunting task. However, references to compensation for accidental injury were unambiguous. Item 2.4.7 titled *Compensation for Accidental Injury* stated: 'Research subjects who suffer from physical injury as a result of their participation in the clinical trial are entitled to financial or other assistance to compensate them equitably for any temporary or permanent impairment or disability, subject to confirmation from the Independent Ethics Committee (IEC). In case of death, their dependents are entitled to material compensation.' Item 2.4.7.1 titled *Obligation of Sponsor to Pay* went on to

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say: 'The sponsor whether a pharmaceutical company, a government, or an institution, should agree, before the research begins, to provide compensation for any serious physical or mental injury for which subjects are entitled to compensation or agree to provide insurance coverage for an unforeseen injury whenever possible.' It is astounding that these provisions in the Indian guidelines did not lead to changes in operating procedures of clinical research groups operating in the country. Perhaps this has something to do with the fact that these provisions appear under Section 2.4 of the document titled *Ethical and Safety Considerations* rather than under Chapter 3.1, *Responsibilities of the Sponsor*. Moreover, in Appendix V *Essential Documents for the Conduct of a Clinical Trial,* the words 'where required' and 'if any' appear in parenthesis next to item 7, *Insurance Statement,* and item 8, *Subject Compensation,* giving the impression that these requirements may be optional.

The fact that neither the regulator nor ethics committees raised any issues regarding compensation, even though a myriad clinical trials were approved in all these years, as also the fact that Indian clinical trial sites and units fared very well in numerous inspections conducted by the US Food and Drug Administration (FDA) and other overseas regulatory authorities, must have lulled QA staff and senior management in clinical research units into a state of complacency. Sponsors were already routinely covering patients for expenses incurred on management of serious adverse events, often regardless of whether they were study-related or not. It was assumed that the process for payment of any compensation over and above this would be the same as elsewhere in the world – a claim, followed by adjudication, and payment or denial of payment, depending on the merits of the case, with the claimant having the right to seek a review of the decision by an appellate or court.[4] Few claims for compensation were ever received, and cases where compensation was claimed and paid out were few and far between. Compensation was never known to have been paid *suo moto*, and this matter did not trigger any observations of non-compliance by QA staff. Phase 1 units that employed healthy volunteers for bioequivalence trials were known to make no-fault compassionate payments in some cases where a volunteer died of unrelated causes that had nothing to do with his or her participation in the trial. However, companies preferred to keep these payouts confidential for fear of unwanted publicity.

Then, earlier this year, senior clinical research executives in pharmaceutical companies and clinical research organizations (CROs) began to receive phone calls from the office of the DCG(I), enquiring whether compensation had been paid in cases of death among patients and volunteers participating in clinical trials. It was learnt that the queries were related to unstarred questions raised by individual members of parliament.[5] Companies responded guardedly, particularly the ones that had made any compensation payments, as there was fear that if the company admitted to paying money as compensation for study-related injuries this would be held against the safety record of the drug, or worse, as proof of guilt or wrong-doing on the part of scientists and the management staff of the unit.

In May 2011, the DCG(I) issued notices to all private sector clinical research entities that had reported deaths in clinical trials in 2010, where a contributory effect of the drug or study procedures was not ruled out by the investigator. In some of these instances it is understood that the patient had not received the study drug, but had in fact been randomized to the marketed reference product in a blinded randomized study. The notices required companies to pay compensation irrespective of a claim but did not specify the amount of compensation. There was no guidance on the procedure to be followed in case of dispute regarding causality, or disagreement regarding the amount of compensation.

There was considerable confusion in companies that received the notices. Study procedures require all adverse events occurring in clinical trials to be recorded, and it is never easy to determine for sure whether an adverse event, in a patient suffering from an illness and receiving many medicines, is the result of the administration of a particular drug.[6] Sometimes a patient participating in a clinical trial may suffer an unrelated injury from an accident, suffer from an intercurrent illness, fall prey to consumption of contaminated food or water, or catch an infection from other patients in the hospital. All these are treated as adverse events. More commonly, adverse events are related to the primary illness for which the patient sought treatment in the first place, and often to the other medicines the patient received in addition to the test drug. Whether the test drug is related to the event or not has to be determined on the basis of a complex body of information that includes elements such as the temporal association of the event with drug administration, the expected blood levels of the drug at the time of the event, the consistent appearance of the event with previous or later administrations of the drug and whether the event disappeared on withdrawing the drug, the known risks associated with the drug, the known risks of the underlying condition of the patient and the other medicines being administered, and other relevant information such as the age and sex of the patient and the results of laboratory tests.[7]

As with all complex problems, the opinion of experts can vary and depends heavily on the weight given to each factor.[8] In view of this, regulators and expert committees across the world, such as the Council for International Organizations of Medical Sciences (CIOMS), have never insisted on an all-or-none opinion on causality of adverse events, preferring to classify causality in grades of relatedness, such as not related, unlikely, possibly related, probably related, and definitely related.[9] Whether a particular type of adverse event is actually related to the study drug is finally determined through analysis of the clinical trial results at the end of the trial by comparing the frequency of events in the test group against the control group, often supplemented by results from other pre-marketing studies and post-marketing surveillance.[10] Here, the DCG(I) was insisting that the causality determination be based solely on the assessment made by the investigator, and that the assessment be all-or-none, disregarding the strength of the causal association between study interventions and the adverse event. It also meant that there would be no scope for the opinion of any other experts to be considered, that patients who received standard therapy would also be eligible for compensation even though they may have suffered from the same adverse effects had they not participated in the trial, and it is possible that sponsors would end up paying large aggregate sums in compensation even though statistical analysis at the end of the trial may later prove that the test drug was in fact less likely to cause the side effect than standard therapy.

Even if companies were to go along with this, the amount of compensation to be paid still remained unclear. Who would determine this? On what basis would it be determined? What if there was lack of consensus among investigator, ethics committee, and sponsor? What if, based on ethics committee recommendations at different institutions, disparate amounts of compensation were paid out for the same type of event in the same trial — would that lead to accusations of unfairness? Sponsors worried about the long-term consequences of all this and the practicalities of sustaining a system of compensation payments on a continual basis. In the short term they struggled to get ethics committees to meet and provide an opinion.

In the mean time, the office of the DCG(I) was under pressure from the weight of questions from interested parliamentarians that hinted toward a dereliction of duty on the part of the office of the DCG(I) in not ensuring compliance to a regulation that had seemingly come into effect as far back as 2005. Letters were forwarded to the involved companies to attend a meeting on June 6, 2011, and attendees were asked to report on the status of compensation payments. Companies were directed to ensure that all payments were completed by June 20, 2011, and it was made clear to the industry that unilateral payment decisions would be acceptable in the event of lack of consensus between investigator, ethics committee, and sponsor regarding the amount of compensation. With the threat of disciplinary action hanging over their heads, companies complied, and by June 20 the DCG(I) received confirmations of compensation payment for all 22 cases, including one, on the insistence of the regulator, in which the investigator had later concluded that the event was unrelated to the study.

With the immediate crisis having passed, the industry is now waking up to the new challenge of sustaining a system of smooth payment of compensation to all study participants who suffer from a serious adverse event in the course of a clinical trial, that, in the opinion of the investigator, is study-related. Contract research organizations are in the most difficult position of having to comply up-front with the regulation on the one hand, while having to get sponsors to agree to an open-ended commitment to pay for it on the other. It calls for companies to put in place clear internal procedures for the identification of cases possibly eligible for compensation, getting sponsor concurrence on causality, agreeing on a formula to arrive at the quantum of compensation, getting ethics committee confirmation for the payment to be made in each case, documenting payment, and keeping the regulator informed. Hidden in this seemingly straight-forward process flow is a sea of unanswered questions that may take months if not years to answer, and issues that may never be satisfactorily resolved. How do you get investigators to make a scientific assessment of causality when there are acts of commission or omission on his part, or that of his team, that may color his judgment? How do you get uniformity and fairness in compensation payments in a trial that involves a multiplicity of investigators and ethics committees across disparate public and private institutions? How do you resolve disputes between the investigator, ethics committee, and sponsor? How do you discourage ethics committees from making unreasonable compensation demands, on behalf of patients, that would drive the cost of doing research so high as to drive sponsors away? How do you calibrate compensation payments to different grades of injury so that a sense of logic is maintained and the overall cost of compensation payments does to reverse the cost advantages that India has as a location for clinical trials? In compensation payments for death, how do you strike a balance between the contradictory implications of linking payout to wages and earning capacity of the deceased versus the real needs of the family? Is it

ethical to value the life of the wealthy differently from that of the poor?

In grappling with the need, now, to put internal procedures in place for a system of regular compensation payments for all serious adverse events, where a relation to the study cannot be ruled out, clinical research organizations must take cognizance of item 2.4.7.1 of the Indian GCP guideline. It requires sponsors to agree to provide compensation for any serious physical or mental injury *before the research begins*. By implication, the sponsor's obligation to pay compensation must be documented either in the protocol signed by a representative of the sponsor, or in the separate agreements that exist between the sponsor and the CRO / investigators. CROs would do well to make these obligations known to sponsors as part of the contract for each study or as part of the local addendum to a global contract. It would be best if the process for adjudication of causality and the method for calculating the quantum of compensation were determined up-front and ethics committee confirmation taken before the start of the study. It is conceivable that these will not differ too much from one study to another and it may be possible to develop a common algorithm that can be applied to all studies.

The clinical research industry in India is resilient and resourceful, and one can be confident that it will find for itself a way out of the conundrum. Watch this space.

This article was written prior to publication of GSR 821(E) Draft Rules and hence does not address implications of the provisions outlined in that document. Views and opinions presented in this article are solely those of the author and do not necessarily represent those of the author's present or past employers.

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