Medicine and Society

Compensation guidelines for research-related injury in India could destroy investigator-initiated research

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INTRODUCTION

The Indian Council of Medical Research (ICMR) and the Central Drugs Standards Control Organization (CDSCO) of the Directorate General of Health Services (DGHS) in the Ministry of Health and Family Welfare (MoHFW) have uploaded the draft guidelines for compensation to participants for research-related injury in India and invited feedback and comments on these guidelines.[1,2] These guidelines were meant to elaborate on and provide operating details for the ICMR Ethical Guidelines for Biomedical Research on Human Participants (2006)[3] which specified 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'. The ICMR draft guidelines were prepared by the Indian Society of Clinical Research (ISCR) and Forum for Ethics Committees in India (FERCI). The scope of these guidelines is all-encompassing, including sponsored, industry-driven research and academic, institutional and investigator-initiated research. The ICMR and CDSCO have invited comments on these draft guidelines with a view to getting more opinions on this very controversial and contentious issue.

THE BASIC PRINCIPLES

The ICMR draft guidelines state in their Basic Principles (Section 3) that:

'3.1 Compensation be provided to the research participants *when temporary or permanent injury occurs due to participation in the clinical research*.

3.2 Compensation be paid *when injury is caused by a procedure which has been undertaken to manage an adverse reaction occurring during the research* (emphasis ours).

3.3 Compensation be paid to a child injured *in utero* through the participation of the parent in clinical research.'

If the above 'basic principles' are to be taken at face value, practically every serious adverse event (SAE) occurring during a research study should not only get free medical treatment, but also be compensated, regardless of causation. If so, the cost of conducting clinical research in the country would become prohibitive, especially in critical illnesses or diseases associated with high likelihood of serious events, which are precisely the clinical situations where the maximum research should be done! Conditions such as severe sepsis, life-threatening infections and cancer, which are currently responsible for a large proportion of morbidity and mortality in India, would have virtually no research conducted on them in the country. While these guidelines would probably only marginally deter industry-sponsored research in India, it would effectively stop investigator-initiated research completely. While for industry-sponsored research, compensation monies would still remain a fraction of their overall trial costs, this would be several times the total budgets of investigator-initiated research, thereby wiping out the possibility of the latter. While several organizations in science and technology such as ICMR, the Department of Biotechnology (DBT) and the Department of Science and Technology (DST) are doing everything possible to promote investigator-initiated research, the impact of these guidelines would be a reversal of all that has been achieved or aspired for in promoting academic research.

THE CIRCUMSTANCES FOR COMPENSATION

The next section of the draft guidelines states that:

'3.4 Compensation be paid irrespective of:

- Whether injury was foreseeable/predictable or not
- The fact that the research participant had freely consented in writing to participate in the research
- *The fact that the injury was caused by the comparator product(s) under investigation in the clinical research*
- *Irrespective of the cause of injury and individuals/agencies responsible* (excluding factors described in Section 4.4).' (emphasis ours)

INJURY CAUSED BY THE COMPARATOR PRODUCT(S)

The third point clearly states that injury resulting from the comparator product(s), i.e. the control arm of a study, should also be compensated. The control arm is most often either a placebo or the active treatment which is the standard treatment for the condition being researched. While the likelihood of a placebo causing serious injury is low, the active 'standard' treatment could. However, this is the treatment the patient would have received even outside the clinical trial. We fail to understand why this should be compensated. In a trial on advanced lung cancer testing a new chemotherapy drug, patients in the control arm would get platinum-based doublet chemotherapy as the standard treatment. This is associated with defined toxicity including the potential for temporary or permanent harm such as febrile neutropenia, nephrotoxicity, peripheral neuropathy, etc. Would these adverse events be entitled to compensation? If so, why? Would this not induce every patient with advanced lung cancer to participate in a clinical trial? Not only is the basic chemotherapy being provided free, but every single SAE would not only be treated free, but would also be compensated monetarily! While inducement is a real issue even now, compensation would multiply this problem manifold.

The guidelines of the Association of the British Pharmaceutical

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Industry (ABPI),[4] 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*' (emphasis ours). 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 seems a sensible approach. This also implies that when two standard forms of treatment are being compared (as is 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 informed consent form (ICF). We reiterate that if compensation is not to be paid in a research study, this should be made clear in the ICF, thereby giving patients full freedom of choice regarding whether to participate in the study or not.

CAUSALITY OF INJURY

The fourth point in this section clearly states that compensation should be paid 'irrespective of the cause of injury and individuals/ agencies responsible'. This implies that every research related injury (or SAE), regardless of causation, requires compensation. This statement could be interpreted to mean that every injury occurring while the patient was a clinical research participant should be compensated. This is contradictory to the Council for International Organisations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects. The CIOMS guidelines state that 'Compensation and free medical treatment are generally not owed to research subjects who suffer expected or foreseen 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*' (emphasis ours). Compensation irrespective of causality is an extremely contentious point and could have two major repercussions: First, the cost of clinical research would skyrocket, thereby further increasing the cost of new medical products and overall medical care; second, participation in clinical research would become a vocation for the poor, by giving undue inducement to participate. Again, with one stroke, it will wipe out academic research in India at a time when there is a clarion call for increasing it exponentially.

DETERMINING THE QUANTUM OF COMPENSATION

The guidelines are silent on who will decide the quantum of compensation (and how) for research-related injury. Varying degrees of temporary and permanent injury (including death) are possible while participating in clinical research (and routine medical care!). How would the quantum of compensation be decided? Would it depend upon the earning capacity of an individual, the remaining productive years of life, or the extent of dependence of the family on the patient's earning in addition to the extent of injury? Who would decide the quantum of compensation—the investigator, the sponsor or the ethics committee? And whoever it was, would it be mandatory for them to be trained in deciding this? With this subjectivity involved, would it not mean that differing compensations would be paid for similar situations? There are too many unanswered questions, with not enough answers.

THE DELIVERY OF COMPENSATION

The draft guidelines state that 'compensation (be paid) to legal heir/lawful guardian in case of death'. In the absence of a will or clear legal-heir documentation (which could at best be expected in a miniscule proportion of India's citizens), how would the investigator/sponsor/ethics committee decide on the beneficiary? This is not a hypothetical argument—this situation came up at our institute when compensation was paid for the death of a patient in an advanced cancer trial. With the guidelines setting a 90-day deadline for settling claims, how can this ever be ensured, especially if the other relatives of the patient resort to litigation? Would this then mean that every patient participating in clinical research would have to specify a beneficiary for compensation prior to participating in the study? It would be ludicrous for an investigator to insist on specifying a potential beneficiary if the patient died while participating in a clinical trial for an innocuous intervention testing for example, a new skin product!

THE DEFINITIONS

The glossary provided as Appendix 2 of the draft guidelines have several terms defined ambiguously, the most important one being 'research-related injury' which has been defined as 'injury occurring as a result of participation in clinical research'. Does this imply effectively that all SAE occurring during a clinical trial is research-related injury which should be compensated? Or do the authors really mean 'injury occurring as a result of participation in clinical research which would not have happened if the patient was treated outside the clinical trial'? This distinction has important implications on subsequent compensation. Similarly, the draft guidelines define 'risk' as 'probability that harm will be caused by participation in research'. Again, does risk here include the risk the patient participating in a clinical research study would have from some component of the treatment which he/she would have received regardless of whether or not he/she was part of clinical research?

PROBLEMS WITH THE OVERALL GUIDELINES

Clearly, there are several major problems with the proposed compensation guidelines. These guidelines seem tailored for industry-sponsored research and ignore the large quantum of investigator-initiated research in India. Pharmaceutical companies and contract research organizations (CROs) are unlikely to be greatly affected by these guidelines and will be happy so long as there were guidelines on who would decide on the need and quantum of compensation. The compensation monies would be a small fraction of the entire cost of running a sponsored clinical trial and would not affect their budgets much. However, the main impact that these guidelines will have is on investigator-initiated research, which will be crippled if they came into force. Investigator-initiated research is generally done by clinicians to answer day-to-day problems encountered in clinical practice and are of immense value to progress in medical science. Typically, these run on shoestring budgets, as funding for investigator-initiated research is difficult to obtain. All government scientific organizations including the ICMR, DST and DBT encourage such research in the hope of being able to find cost-effective treatment options for common diseases in India. The consequences of adopting these guidelines will be a drastic slowdown and eventually a shutdown of investigator-initiated research, which will leave medical research purely in the hands of the industry. Medical costs, already beyond the reach of the common man, will skyrocket manifold and effectively make optimum healthcare available only to the elite of society.

SURGICAL AND PROCEDURE-BASED TRIALS

The guidelines seem oblivious of their impact on surgical and procedure-based trials. One of the common criticisms against surgical specialties is that 'new' and 'improved' surgical procedures are not tested in well-conducted clinical trials before they are widely adopted by the surgical community. There are clarion calls for increasing the quantum of clinical research in all surgical specialties. Surgical trials are almost exclusively investigator-initiated and typically compare two techniques of surgery. These types of trials are almost never industry driven, as there is no commercial interest. However, these are the trials which have drastically changed the way we practise surgery. Examples of such research include landmark trials which proved that breast-conservation therapy is equivalent to mastectomy, laparoscopic cancer resections are equivalent to open procedures, organ-preserving concurrent chemoradiation is equivalent to laryngectomy, and several others. None of these trials would have been conceivable if the suggested compensation guidelines had been operative. All these trials compared two 'standard' treatments for these diseases. All these procedures are associated with complications, some of them major, or even fatal. All these postoperative complications of 'standard' surgery would need to be compensated by the investigators if these draft guidelines became law. Why would any researcher want to do any of these studies if he/she had to look for funding to enable compensating all patients who had postoperative complications, which can reach 40%–50% with major cancer surgery? And how much poorer would surgical science be if such studies were not done?

INDUCEMENT FOR PATIENTS IN CLINICAL RESEARCH

An important consequence of offering blanket compensation for all research-related injury would be the potential for inducement to patients participating in clinical research. It is considered by many that even by providing free treatment as part of clinical research, there is potential for poor patients to be induced to take part in clinical trials. This problem would get multiplied if in addition to free treatment and management of SAEs, compensation was also provided. Patients would flock to participate in clinical research because not only would they be assured of free treatment, free management of complications arising from even standard treatment in a clinical trial, but would also get monetary compensation for injury or death. This could be a serious problem where the basic principles of clinical research ethics would be compromised.

FUNDAMENTAL RIGHT OF CHOICE: RESPECT FOR AUTONOMY

Finally, the policy of making compensation mandatory infringes on an individual's basic human right—the right of a patient to make a conscious decision whether to participate in a clinical trial which does not offer compensation. In our view, as fundamental as the right of a researcher to design a study which does not offer compensation for research-related injury is the right of the patient to decide whether to participate in such a trial. Respect for autonomy (defined as 'which requires that those who are capable of deliberation about their personal choices should be treated with respect for their capacity for self-determination'), one of the three basic tenets on which biomedical ethics are based, would no longer exist if patients were deprived of an opportunity to participate in all forms of scientifically- and ethically-sound research. The argument that poor patients from developing countries are incapable of making this choice of their own free will is not only patronizing but also intrinsically a weak argument. This would probably be the easiest point for a patient to understand of the entire informed consent process of a complicated clinical research protocol.

THE SOLUTIONS

We suggest that compensation in clinical research be optional for some studies and mandatory when new investigational drugs are tested. Though at first glance, this might seem radical, this is followed universally in the USA, where compensation is not mandatory in clinical research.[5] The ABPI compensation guidelines clearly differentiate phase 2 and phase 3 trials from other forms of research involving trials on marketed products, where the compensation guidelines do not apply. A similar policy of different compensation guidelines for registration trials for new investigational agents and other academic research could be adopted. Ethics committees could decide whether research-related injury needs to be compensated depending on the circumstances, as in any case, all SAEs are reported to them. We feel that research-related injury which would not have occurred as part of standard treatment (out of the research protocol) should certainly be compensated, provided causality is established. Compensation should not be mandatory for injuries which would have occurred even if the patient had standard treatment nor when two 'standard' treatments are compared. This would protect the rights of the patient, prevent undue inducement and continue to promote investigator-initiated research. We are at an extremely important fork in the road of clinical research in India, and the path we take today could either promote or destroy the future of medical progress in India. The choice is ours.

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