

The issue of regulation of the private sector in India has been the focus of much discussion and debate over the last few decades. Whilst, on one hand, health activists have struggled for greater regulation, the state has been half-hearted in implementation of its own legislations (2). Often, powerful lobbies of medical professionals have scuttled any substantial attempts to implement regulatory laws. Whilst individual cases of medical negligence continue to hit the headlines, litigation has increased and 'accreditation' is the new buzzword, serious regulation is still elusive. In the context of this tragedy, this issue could, once again, have become the focal point of the public debate. Alas, but not surprisingly, the mainstream media chose to ignore this and focus only on symbolic arrests and a blame game. On the other hand, political formulations traded charges with each other.

Some other questions that emerge out of this churning are equally disturbing and befuddling. Why is the safety quotient so low in our society both in general, and in healthcare? Should our natural instinct for self preservation not make us sensitive to basic safety issues? Are there some socioeconomic and cultural factors at work here which numb us to safety? And shouldn't an industry like healthcare which is critically dependent on outcomes and results for its growth in a fairly competitive environment be intrinsically sensitive to safety concerns? To phrase it differently, won't hospitals which show a record of safety actually do well in their business, and therefore naturally adopt these practices? This idea which seems so obvious doesn't seem to have support even amongst other industries. For example, car manufacturers have always projected the look of their product rather than its safety features. The construction industry almost never talks about the earthquake-resistant capability of its projects. No airline ever projects its safety record as a way to attract passengers. It seems that safety doesn't necessarily sell and is thus given short shrift by industry. Perhaps, even the elite consumer is ambivalent to safety concerns.

It doesn't need deep philosophical study to appreciate that we live in an age where the illusory look and image is what sells and can substitute for standards and performance. And in that narrow sense, the healthcare industry is playing a game that works. It is another matter that in the context of healthcare this compounds one tragedy with another. The hapless victims at AMRI and their families have faced an unprecedented triple whammy of tragedies: first being pushed into private healthcare by a public health system that has been systematically dismantled; second, their severe illness needing hospitalisation, and third, a sudden manmade disaster that took away their lives whilst they were battling the first two afflictions.

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## Putting patients first: draft guidelines for compensation for research-related injury in clinical trials in India

**GAGANDEEP KANG**

Professor and Head, The Wellcome Trust Research Laboratory, Department of Gastrointestinal Sciences, Christian Medical College, Vellore, Tamil Nadu 632 004 INDIA  
e-mail: gkang@cmcvellore.ac.in

With the recent highlighting of ethical issues in several clinical trials, and the increase in awareness among parliamentarians, there has been some concern about the conduct of trials in India. The areas of concern include ensuring that consent is truly informed, and monitoring participant safety, the occurrence of deaths, and the payment of compensation. On November 18, 2011, the draft of the Drugs and Cosmetics (3<sup>rd</sup> Amendment) rule, 2011, was published (1) in the Gazette of India, with a plan for implementation 45 days after publication. In addition, the draft guidelines for compensation were posted for comment by the Indian Council of Medical Research (ICMR), where bioethicists have been responsible for developing and updating the *Ethical guidelines for biomedical research on human participants*, last revised in 2006. These guidelines state that research participants who suffer an injury as a result of participation in research are entitled to compensation for impairment or disability (2). It is commendable that the Government of India through the Ministry of Health and Family Welfare is taking steps to safeguard the rights of research participants and emphasise the responsibility of sponsors, investigators and institutional ethics committees engaged in conducting or reviewing clinical research in India. The proposed rules include several provisions for ensuring that study participants who suffer injury, permanent injury, or their heirs in case of the participants death, will be entitled to timely and just compensation. These rules highlight the need to ensure that research participants' needs in case of injury, are given primacy, as they should be.

Unlike the basic principles of autonomy, justice, beneficence and non-maleficence that underlie the practice of biomedical ethics worldwide, there have been contrasting views in the area of biomedical research, on the needs of participants and the

responsibilities of sponsors and investigators. One view holds that routine compensation is not required because subjects are made aware of the risks through the process of informed consent, and they understand these risks and voluntarily agree to participate. The other view is that sponsors and institutions are obligated to compensate injured subjects, particularly in trials with commercial sponsors, regardless of who may be to blame. The former view has been widely applied in the United States, where payment for participation in clinical trials is generally practised and where compensation for injury is implemented largely through the courts (3). This approach is not favoured in Europe and several other parts of the world, where guidelines mandate the provision of clinical-trials insurance, through which subjects are often covered regardless of fault.

There is always some risk in participation in most clinical trials, but serious injury or death as a result of participation is rare, particularly for healthy volunteers. Unfortunately, despite the requirement to report serious adverse events to sponsors, institutional review boards and regulatory authorities, there are few systems in place to quantify the severity, frequency and types of injuries and the associated costs of managing medical care or rehabilitation in any country. Injuries can and do occur, and may result from the research procedure (e.g. bruising at the site of a phlebotomy or a spinal headache after a lumbar puncture), or from the drug or device being tested (such as post-antibiotic diarrhoea or because an investigator failed to follow the protocol or to perform the procedures correctly). In addition, there can be completely unforeseen and unrecognised severe side-effects, such as in the TGN1412 trial (4). In all of these, the severity and permanence may vary, but some harm has resulted, and in the 'no-fault' approach, the onus of looking after the research participant should be with the investigative team and the sponsor. Particularly in India, where the conduct of clinical trials is fraught with the issues of properly informed consent and the lack of availability of quality medical care except in a trial setting, and the lack of easy recourse to an appellate authority, the idea of 'no fault' and prompt compensation needs implementation.

However, because of the phrasing of several clauses in the draft guidelines published in the Gazette, there are concerns that the draft in its current format will make it extremely difficult to carry out clinical trials in India, whether investigator-initiated or sponsored by the pharmaceutical industry. The main issues which require reconsideration as stated, possibly in error, are: the statement in Clause 4(d) regarding failure of the investigational product to produce the desired therapeutic benefit and Clause 4(e) on the administration of placebo showing no therapeutic benefit.

With all drugs, whether used in a clinical trial or for therapy, some people do not derive benefit. So it is entirely possible that, in a trial, many people in the investigational arm may not show therapeutic benefit; and as with cancer trials, which recruit patients in advanced stages of disease, several patients may die. This is to be expected, and if compensation were to be paid in such cases, by extension, any patient who failed therapy with a licensed drug could also be considered entitled to compensation. Similarly, a placebo is not expected to show therapeutic benefit in all treated individuals and the same logic applies. If these clauses were to become law, no investigator-initiated clinical trials would be possible, nor would therapy. Therefore, urgent reconsideration is required.

In Clauses 5 and 6, the draft guidelines go on to state that the amount of compensation should be specified prior to the clinical trial and included in the consent form. Given that many trials are minimal- and low-risk trials, specifying the amount of compensation to be paid in case of death in such trials would be inappropriate and more likely to induce fear of participation in such studies. This would obviously be appropriate in high-risk studies with the potential for harm. It may be worthwhile for the government to lay down both general and specific criteria for determining the amount of compensation in studies that are judged to be low risk studies by the institutional review board or ethics committees, in the event that temporary or permanent injury occurs. It is also possible that prior mention of the amount for compensation might induce both participation in a clinical trial with a significant risk, and a lower threshold for reporting real or perceived injury. These are complex issues and need discussion with stakeholder groups before decisions on policy and implementation are made.

Other clauses that raise concern include 5 (3) where the ethics committee must decide the quantum of compensation within 30 days of receiving a complaint, and 5 (4), where, if no complaint is received, the ethics committee has still to decide on the amount of compensation for a serious adverse event. Given that institutional ethics committees are composed of scientific and lay individuals who may or may not have a financial or actuarial background, it would be inappropriate to lay the burden of such decision making regarding causality on these committees. In addition, ethics committees would find it difficult to set any kind of compensation without specific guidance from the government on situations and ranges of appropriate compensation.

Compensation in clinical trials is a complex issue which requires a careful assessment of causality. In any biological system, unequivocal establishment of causality is near impossible and it is for this reason that regulators, health experts and advisory bodies such as the Council for International Organisations of Medical Sciences and the World Health Organisation have graded the causality of adverse events in a classification that ranges through "not related", "unlikely", "possibly related" and "probably related" to "definitely related". On an individual basis, a causal relationship is difficult to establish and it is the cumulation of results comparing frequency of events between test and control groups that enables the determination of relationship of an effect with the drug or device being tested. There are also practical issues. For instance, it may be difficult to determine

whether a medical problem is related to participation in a clinical trial, particularly if it develops months or years later, or if a subject has other risk factors (5).

Although Indian guidelines necessitate the provision of insurance in order to manage research-related injury, the actual implementation of these guidelines needs to be specified in greater detail. Although not in a clinical trial setting, one example to consider might be the United States National Vaccine Injury Compensation Program, established in 1988. This is a “no fault” system covering all vaccines recommended by the Centers for Disease Control and Prevention for routine administration to children, which is similar to government and industry tax-supported programmes in other parts of the world (6). Another guideline which has been widely adopted is that of the Association of the British Pharmaceutical Industry on compensation for trial-related injuries, which recommends that subjects suffering from research-related injuries be compensated on a “no fault” basis, with seven basic principles. First, even in the absence of legal commitment, the company should pay compensation to patient-volunteers suffering bodily injury (including death). Second, 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. Third, children *in utero* are treated as volunteers. Fourth, compensation should only be paid for more serious and permanent injury, including exacerbation of an existing condition, and not for temporary pain or discomfort or less serious or curable complaints. Fifth, compensation should also cover the inadvertent effects of managing an adverse event and not just a test product administration. Sixth, the fact that the adverse reaction was foreseeable or predictable, and that informed consent was obtained, does not exclude the patient from consideration for compensation. Seventh, in order to avoid doubt, it is not necessary for the patient to prove negligence in procedure or defect in a product. These guidelines for phase II and III trials clearly state that they do not apply to phase I studies in non-patient volunteers or to licensed drugs or to independent trials initiated by doctors who are responsible for the health and welfare of their patients (7). The guidelines do not recommend compensation if the drug or placebo has no intended effect, and if the adverse reaction is due to concomitant medication. Unfortunately, despite the rational approach, even these guidelines are incomplete when it comes to early phase studies, volunteer studies and trials with licensed drugs, and are not a legal commitment (8).

A review of policies for injuries to research participants in India demonstrated that almost half of all surveyed investigators were not aware of their responsibilities and the procedures for the management of research-related injury (9). Even though a proportion of investigators and ethics committees and all sponsors had policies to manage compensation issues, these were mainly to provide immediate free medical care or reimbursement of expenses for the acute management of an adverse event. In this scenario, the efforts of the Government of India to develop regulations to protect research participants and compensate them for involuntary harm are welcome and necessary steps towards improving the conduct of clinical research in India. However, the description of the specifics of such procedures, the roles and responsibilities of investigators, institutions, ethics committees and sponsors, and the guidelines for benchmarking need to be considered carefully and discussed widely. This is necessary to ensure that ambiguities are eliminated before the introduction of these regulations which can effectively put the needs of patients first.

**Competing interests:** None.

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