EDITORIALS

New regulations on compensation for injury and death in drug trials

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In 2005, the government amended Schedule Y of the Drugs and Cosmetics Act, 1940, and Rules, 1945, to liberalise the conduct of global drug trials in India. Proponents of this policy had asserted that we needed less, and not more, regulation, in order to expand the business of drug trials. Many from the medical profession, the bioethics community and civil society groups have been critical of this policy. Instead of establishing a robust system of supervision and monitoring of drug trials to protect participants, the drug regulator, the Central Drugs Standards Control Organisation (CDSCO) of the Ministry of Health and Family Welfare (MoHFW), converted itself into a facilitator for industry. Its critics were called anti-science, anti-business and sometimes even anti-national.

Thus, it is no wonder that, since 2005, drug trials have been marred by numerous scandals and a public outcry about alleged violations of research ethics and participants' human rights.

The MoHFW and the CDSCO have now woken up and are trying to reclaim the status of regulator. They have announced everywhere that their job is to protect people and public health. They have enacted new regulations on compensation for injury and death in drug trials (1), set up a panel of 48 experts and committees to examine drug trial deaths (2), and made the registration of research ethics committees mandatory (3). Some more changes are in the making. This is a good development; it is also an admission of guilt that, by intention or default, for eight long years, the regulators gave a free hand to violations in drug trials and colluded with pharmaceutical companies and their contractors, the contract research organisations (CROs).

Forces propelling change

Many developments in the recent past have forced the MoHFW and the CDSCO to rediscover their powers to formulate appropriate regulations, and to commit themselves to discharging their legal and ethical obligations – to protect trial participants' rights and interests.

Firstly, civil society activists, using the right to information and often conducting investigation in the field, brought out information and reports on the violations and sufferings in drug trials. The media provided prominence to such reports. These reports could not be dismissed as mere media sensationalism, for the number of drug trial participants suffering injuries and death was mounting. The CDSCO was forced by the questions raised in Parliament and by the Supreme Court to collate data which provided evidence of what was earlier suspected or alleged.

In January 2013, a Deputy Drugs Controller submitted an additional affidavit in the Supreme Court (4). It states that from January 1, 2005, to June 30, 2012, in the trials of 475 new chemical entities approved by the Drugs Controller General of India (DCGI), 14,616 serious adverse events (SAEs) were reported by companies, of which 2,644 (18%) resulted in death. Of the 2,644 deaths, the companies admitted to only 80 (3%) as being "related' to, or caused by, the trials and only 40 of the victims' families were paid compensation. On the other hand, of 11,972 SAEs that did not result in death, but caused temporary or permanent injuries or required hospitalisation, or prolongation of hospital care, only 506 (4.2%) were accepted as "related" to the trials. But there was no information on compensation for these non-fatal SAEs.

Secondly, it emerged very clearly that the officials at the CDSCO had not applied their minds to the reports on injuries and deaths received from the companies. For instance, in April 2011, it provided detailed individual information on each death that took place in drug trials in the year 2010, to the Parliamentary Committee on Government Assurances (5). According to this document (available with us), in 2010, 670 deaths took place, of which the companies reported only 25 (3.73%) as "related" to the drug trials. However, we found that there were an additional 92 (13.7%), or nearly four times more, deaths for which the companies had reported an indeterminate causality relation to the drug trials. Such indeterminate causality was expressed as "possible", "possibly", "probably", "probable", "unlikely", "implied", "suspected", "suspected to standard therapy", "dubiously suspected", "not suspected" and "doubtful". Moreover, in relation to 30 deaths, the information on the causality relation to the drug trial was missing.

Clearly, the data show that there are very large numbers of injuries and deaths of participants in drug trials. At the same time, we find that for every death or injury accepted by the companies as "related" to the drug trials, there are four which are not accepted, as they could not conclusively determine any relation or non-relation to the drug trials. This creates a genuine suspicion that

companies are perhaps testing the relationship of deaths and injuries only to the adverse effects of investigational drugs and not for all interventions in a drug trial. The CDSCO was, therefore, duty bound to launch independent investigations and scrutinise the claims of companies that most of the SAEs recorded were not related to the trials and that therefore, they did not have an obligation to pay compensation. It was also required to verify that all of them, irrespective of relatedness, were provided the best free medical management. But the CDSCO failed in its duty. This not only further dented the credibility of the CDSCO, but also raised serious doubts in the public mind about the safety of participants in drug trials.

Thirdly, the much maligned parliamentarians had no choice but to display some sensitivity to the public outcry with respect to injuries and deaths in drug trials. The health ministry was forced to answer many questions in Parliament and to repeatedly give assurances that something was being done. This culminated in the publication, in May 2012, of the 59th Report of the Department Related Standing Committee, which provided evidence of the CDSCO's shoddy working, its neglect of people's safety and health and, above all, of the nexus between the sponsor companies, the CROs and doctors providing expert opinions to the CDSCO (6).

Lastly, in the public interest litigations (PILs) filed on drug trials, the Supreme Court has taken on a very proactive role and relentlessly demanded information and accountability for injuries and deaths during drug trials from the MoHFW. On January 3, 2013, in a PIL filed by Swasthya Adhikar Manch, the Supreme Court reiterated that all new drug trials must be carried out under the direct supervision of the Health Secretary (7).

Who are "experimental subjects" in drug CTs?

The ethical debates on compensation in trials are not only about the participants' right to compensation. Even in the USA, where the law does not provide for such compensation, all commissions on ethics, right from the 1970s until the present, have strongly recommended inclusion of free medical management and compensation for trial participants (8). Yet, there are many, who even after accepting the principle of free medical management of all SAEs by the sponsors, may not agree to compensation for injuries and deaths of all in drug trials. At the heart of this debate is our understanding of who are the participants experimented upon in drug trials, whose injuries and deaths are eligible for compensation.

The sponsors of drug trials are only interested in looking for the "relatedness" of SAEs to study drugs and comparing them to the SAEs in the control arm. Such data are needed to prove the efficacy of the experimental drug, relative to the standard drug or placebo, and form the basis of the marketing approval of the new drug. However, this is also extended by them into the realms of law and ethics; and thus, they entertain claims for compensation – if at all – only if the SAEs were caused by the study drug. This implicitly, and erroneously, assumes that only participants in the "experimental" arm of a drug trial are experimental subjects; those in the "control" arm are not; and thus do not deserve compensation for their injuries and deaths.

Clinical research is different from clinical practice. In clinical practice, the doctor provides individualised care in the best interests of a particular patient. All risks involved in the provision of such care are justified solely on the basis of anticipated benefits to the particular patient. Thus, the doctor has the latitude or flexibility to design interventions, and make changes in them, as per the specific needs of the patient (9).

On the other hand, in clinical research, the main objective is to produce new knowledge. A typical drug trial has, at least, an "experimental arm" where participants are randomised to receive the experimental drug; and a "control" arm where participants receive standard care (or placebo, in case there is no standard care for the disease). While the principle of clinical equipoise (genuine or evidence-based uncertainty about which treatment is better) ensures that patients in both arms may derive benefits, clinical research still departs from the clinical practice setting in certain important ways. The scientific method for clinical research makes it necessary to use fixed protocols of treatment for patients who are randomised to receive the experimental or the standard drug/treatment, and both sides (doctor and patients) may be blinded about who is receiving what. This means, the doctor is no longer making clinical decisions about the patients according to the individualised needs of each, and there is no flexibility available to adjust the intervention to the specific individual needs. Since they are all participating in research, all of them are under regimes or protocols that are standardised for the purpose of research. Besides, drug trials may require additional procedures on patients of both arms of a study in order to obtain good scientific data. In short, "although patient–participants may benefit from research participation, that is not the primary purpose of research" (9).

Thus, we must never forget that all participants, and not only those who are in the "experimental drug arm" of the trial, are involved in the experiment and, therefore, exposed to risks. Thus, *a priori* dismissal of injury or death of control arm participants as "not-related", or reduction of "relatedness" only to the adverse effects of the experimental drug, would not satisfy ethical and legal standards.

Ethics and law cannot narrow their focus only to the consequences of the new product being tested, but ought to look at the consequences of *all interventions* used on *all participants*, as all of them are part of an experiment and face various degrees of risk.

Advances in ethical standards in the new regulations on compensation

The new regulation on compensation enacted by the CDSCO on January 30, 2013 (1) represents a definite advance in ethical standards in India. On first reading we were impressed by two strong norms. First, it reiterates, without ambiguity, the principle that the sponsors have the unconditional ethical obligation to provide free and complete medical management of all adverse events in drugs trials. This is irrespective of their "relatedness" to the experimental drug or even broadly, the trial. It makes no distinction between medical management of "original disease", some other illness a participant may get, or co-morbidities, or an accident. Besides, it refuses to count the expenses for such medical management as compensation. Thus, it elevates free medical management of all participants of drug trials to the status of an unconditional right. Indeed, it reiterates an ethical principle, and translates it into a law.

Second, for determination of eligibility of injuries and deaths for compensation, it effectively knocks down the reductionist and narrow interpretation of "relatedness" (accounting only for adverse effect of the experimental drug). It expands the concept of "relatedness" to the entire clinical trial. Thus, implicitly, and in principle, it reiterates, what we argued earlier, that *all* participants in drug trials are experimented upon, and *all* of them are taking various degrees of risks. So, the SAEs suffered by all of them should be considered for compensation, and not merely the SAEs caused by the experimental drug.

While this is a conceptual advance, it is likely to pose some technical challenges. Experts have recently argued that there are great difficulties in distinguishing SAEs due to the consequences of underlying diseases from those due to the experimental drug (10, 11). They also argue that the requirement of new regulations to relate causality to the entire clinical trial is going to be even more challenging (11). The difficulties and challenges need not make the task impossible. So if causality or relatedness is used as a criterion to determine eligibility for compensation; the experts have no choice but to overcome technical difficulties. Not only that, the CDSCO has an ethical obligation to ensure that a competent and efficient system is in place for the determination of relatedness of injuries and deaths to drug trial.

However, the new regulations do not take the acknowledgement of the principle that *all* participants are experimented upon and take risks in drug trials, and so have some right to compensation when they suffer injury or death, to its logical conclusion. While specifying the criteria to determine the relatedness of the injury and death to a drug trial, clearly the participants in the control arm have not received adequate consideration.

Seven specific criteria mentioned in the new regulation for determining relatedness of injury and death to the trial are: (a) adverse effect of investigational product; (b) violation of approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator; (c) failure of investigational product to provide intended therapeutic effect; (d) use of placebo in placebo controlled trial; (e) adverse effect due to concomitant medication, excluding standard care, necessitated as part of approved protocol; (f) for injury to a child *in-utero* because of participation of parent in clinical trial; (g) any clinical trial procedure involved in the study.

The provision of "failure of investigational product" would provide participants who are randomly assigned to the experimental arm expanded benefits of compensation, including the consequences of the disease that the investigational product was supposed to treat but could not. However, the same criteria are not applied to participants who are assigned to the control arm, as standard drug treatment is not included. As explained earlier, there is ample scope to argue that the "standard drug treatment", when converted into a "standard protocol" in a research setting, is not entirely the standard treatment as is practised in the individualised flexible clinical setting. Therefore, this appears to be an inconsistent application of the principle.

At the same time, the criteria also show some consistency. When the participants in the control arm are provided placebo, then all injuries and deaths are related to the trial and thus eligible for compensation. This may make some people hastily conclude that this provision is to deter the conduct of placebo controlled drug trials as the cost due to payment of compensation may increase. But conversely, it may also make the ethics committees lax in the implementation of the prohibition on the use of placebo when standard treatment is available.

It is known that the CDSCO does not have adequate human resources, finance and competence to handle the complex processes of determining the relatedness of injuries and deaths in drug trials. More panels and committees are only going to lead to more delays, thus seriously discrediting the good intention of providing compensation. When, in principle, a step has been taken to compensate for all injuries and deaths in drug trials, one wonders what pressure or consideration deterred the CDSCO or the MoHFW from introducing "no fault" compensation – where there is no need to look for relatedness, but all injuries and deaths during drug trials are provided compensation.

Need for vigilance

Several committees are still involved in drafting new guidelines related to drug trials in India. They are also under pressure to reconsider guidelines already in existence. It would therefore be premature to view the guidelines on compensation as a

finished product. There is still no clarity on how the new regime for examining injuries and deaths in drug trials would function in a transparent and accountable manner. The issue of how the quantum of compensation would be calculated still remains undecided.

Besides, the panel and committees of independent experts formed to examine SAEs (2) are strangely charged with investigation of only those SAEs that resulted in deaths and not others. It is also not clear whether they will be examining the tens of thousands of SAEs of the last eight years. It is indeed very important that justice for those who have already suffered should constitute the foundation of new regulations.

All those with the ethical commitment to provide protection, benefits and compensation for drug trial participants will need to show a high level of vigilance to propel the system forward and not allow it to regress.

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Trust in healthcare: an evolving concept

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Introduction

There has been increased interest over the past couple of decades in the public's trust in doctors and in the health system. The fundamental basis of a healthcare relationship is trust, which is the patient's voluntary acceptance of his vulnerability in the expectation that the healthcare provider will do the best for him (1).The changing socio-political and healthcare environment in India may be creating different types of provider-patient relationships. There is a need to look at what 'trust in healthcare' means in today's context. Do patients still have (a possibly naïve) complete faith that providers will give them correct treatment that is in their best interest?

In this essay, I will explore the notion that advances in medical technology and their diffusion through corporatisation of healthcare have affected the character of people's trust in healthcare providers and the system. Patients may have a modified trust in their physicians. I describe four types of trust in addition to what some have described as "blind trust": patients may weigh their options: they may verify the doctor's decisions; they may remain sceptical of the doctor, and they may place their trust in protocol-based treatment.

Trust in healthcare

First, we have to understand what trust in healthcare is. Some have defined patient trust in the physician as a collection of expectations that the patients have from their doctor (2). Others have defined it as a feeling of reassurance or confidence in the doctor (3). Yet another definition of trust, which is apt for the healthcare setting, is "an unwritten agreement between two or more parties for each party to perform a set of agreed upon activities without fear of change from any party"(4). A fourth definition of trust in healthcare is "an optimistic acceptance of vulnerability of the patient that the physician will do the best for their treatment