CT regulation in India: Science or social justice?

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Clinical researchers in India and the pharmaceutical and biotechnology industry are well aware of the various restrictions and regulations imposed by the Supreme Court and the Ministry of Health since early 2013. These restrictions and regulations include, among other things, a requirement for audio and visual recording of all informed consent discussions in clinical trials; mandatory provision by trial sponsors of "ancillary care" for medical conditions experienced by clinical trial participants even if those conditions are unrelated to the trial; and most importantly, mandatory compensation for all injuries experienced by clinical trial participants that are "related to" their participation in a trial. These measures have, quite predictably, imposed large new costs and additional uncertain future liabilities on the planning and conduct of clinical trials in India, and have caused a fall-off in interest among both sponsors and investigators, with clinical trial approvals declining from about 500 in 2012 to about 70 in 2013 and 150 anticipated in 2014.


Dr Barbara Bierer

When one considers the causes of the adoption of these measures, one sees – in the media reports, the opinions of the Supreme Court, and in public statements – a repeated concern that citizens of India may be enrolled in clinical trials without appropriate and fully informed consent, and once enrolled, may be harmed with no compensation provided for the injury. The response to these concerns has produced measures that, we believe, are overly broad and do not surgically and precisely address the real risks to subjects. Mandatory audiovisual recording of informed consent discussions was mandated for all participants, not for those who either are at some defined disadvantage (e.g., illiterate, decisionally impaired) or for those who wish to be recorded in this way. Instead, this broad mandate includes every consent procedure for every trial, independent of religious and cultural preferences, the sensitivity of the disease being studied (e.g. HIV, mental illness), the social norms of the community, and the degree of privacy desired by the participant.

Similarly, the requirement that compensation be paid to any participant who has suffered an injury "related to" the trial seems sensible – until one looks further at the definition of "related to," which is broad enough to encompass even injury from being run over on a busy road or injury from antecedent illness. Why should the sponsor of a clinical trial be required to pay for the expenses of heart problems suffered by a participant enrolled in an oncology drug trial, when the heart problems preceded that person's entry into the trial? Why should a sponsor be required to pay for the lifetime medical care of breast cancer when the study addressed only the effective treatment of multi-drug

resistant tuberculosis?

The overbreadth of these requirements, and how poorly tailored they are to achieve the specific goal of protecting clinical trial participants from risks directly caused by trials themselves, leaves one wondering whether the regulatory authorities fully comprehend the clinical trial process and the nuances of complex medical and biological processes. One further wonders whether what animates these measures may be less a concern for specific justice in individual cases than the goal of righting social wrongs and achieving social justice, unrelated to but prompted by clinical trial experiences. Achieving social justice and a more just allocation of social resources may be completely laudable – even desirable – as social or political policy, but unconsciously using the clinical trial context to promote this agenda threatens to corrupt science and to undermine health, with results that may create more social distress than social justice.

To understand the threat here, take the example of compensation mandated for injuries "related to" a trial, and the current regulatory definition of "related to" that is so broad as to include nearly anything adverse, from any cause, that may happen to a clinical trial participant. While the social justice result of such a mandate for compensation may be to transfer some defined amount of financial resources from companies, nonprofit organisations and academic medical centers that sponsor trials to people – often poor or of modest means – who participate in trials, the specific concepts used to operationalise this financial transfer do nothing but distort critical scientific concepts.

In clinical trials, the efficacy of a new drug, device or vaccine, and their safety profile, are being actively investigated and tested. Assessments of both safety and efficacy are, in turn, largely dependent on the clinical results, good and bad, and the carefully monitored adverse effects of the test agent. But sick and ill patients enrolled in trials experience many adverse health events. Most of them, typically, are related to the underlying illness that the test agent is meant to treat and not to the test agent; other bad health events are due to intervening causes that have nothing to do with the test agent or with the underlying disease – such as falling off a motorbike or drowning in rough seas.

In order to assess what adverse health effects are actually caused by a test agent and not by other factors, best practices in clinical trials (and international clinical trial standards) call for each investigator and the trial sponsor to analyse each adverse effect or unanticipated problem for its potential for having been caused by the test agent, and to record that probability finding in the clinical trial record, which is then reviewed by the ethics committee and ultimately presented to drug and device control authorities to support an application for approval of the test product. To assess causation, different variables must be carefully considered, such as the proximity in time between administration of the product and the appearance of the adverse condition, and similar patient experiences with other products whose mechanisms of action are similar to those of the test product. To understand a test agent's efficacy and safety, therefore, the assessment must adhere closely to objective data, and make judgment based on facts, not sentiment or on an understandable desire to assist an afflicted individual.

Yet these recent compensation regulations, in order to assure that injured participants get some compensation and assistance, require that compensation be given only when injuries are "related to" a trial, when in reality, "related to" is defined so broadly as to include nearly every bad event in the life of a trial participant. The result is that in India, when a trial concludes and the data are analysed, it may appear as though there have been multiple compensated injuries that were "related to" the trial, when in fact, the adverse health effect was unrelated to the trial or the test product.

There is no current method to compensate individuals for humanitarian reasons, independent of a finding of relatedness of the injury to the trial. Thus, the law and regulation—in order to achieve a beneficial social justice purpose—threaten to contaminate the reporting and scientific causality assessment of these health conditions. CDSCO may not be able to ignore multiple compensated injuries in a trial, when considering a new drug for approval. And attorneys who seek to sue drug companies for injuries allegedly caused by an approved marketed drug will reference evidence from injuries compensated during the trials of the drug (because they were found "related to" the drug being tested) to establish that injuries after marketing were also caused by, or related to, that drug.

Finally, because of these multiple compensation events for injuries "related to" the trial and the test drug, the safety profile of drugs tested in India will appear more problematic than in the rest of world, leading to the conclusion that there are biological, genetic, or environmental differences in the Indian population that might explain the adverse event profile, when in fact there is no difference.

Forever after, the mistaken conclusion will be that specific trials must be conducted on Indian populations powered to detect differences, when in fact the faulty regulatory framework—not biology —undergirds the findings.

In this way, the best of social justice intentions can adulterate science, by establishing, in law, false links between apparent causes and ill effects. The paramount concern here is that India, which has every human potential to become a world leader in science, not allow its laudable commitment to social justice inadvertently to be implemented under false concepts, the predictable effect of which will be to adulterate scientific discourse and hinder science itself.

In this case, the danger has come in the guise of clinical trial compensation regulations, but this risk could appear in regulations related to, for example, scientific funding, technology export controls, or intellectual property. In this recent experience, a regulation quickly drafted, without nuance or refinement, misleadingly has labeled all injuries in a trial as "related to" or caused by the trial.

If this shows us anything, it is that legal concepts should follow and respect science and not contradict it; social justice goals ought to be overt, explicit and appropriately defined and not embedded in unrelated or only tangentially related regulations and laws. In short, honesty in science, accuracy in scientific terminology, reasoning, evidence and integrity must be respected, or else science itself will be at increasing risk in India.

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