COMMENTS

India's regulatory reforms on compensation for clinical trial injuries and deaths: urgent need for revisiting

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Financial compensation to participants in clinical trials for the immediate and long-term medical treatment of injuries sustained while participating in the trials, and payment to their next of kin when such injuries result in death, is a relatively neglected subject, particularly in developing countries. Some countries do not require investigators and/or sponsors to indemnify research participants against trial-related injury or death through insurance cover, while others do. In the case of the latter, the indemnity limit and determination of the quantum of compensation is dependent on the terms outlined in the insurance contract, assuming one exists. Furthermore, any actual compensation is ultimately left to the discretion of the sponsor or clinical trial insurer. The recent promulgation of regulations on such compensation by India (1) is thus noteworthy. While the new regulations are a reaction to the Indian Supreme Court's finding that India's Central Drugs Standards Control Organisation (CDSCO) failed to protect the rights of participants in trials (2) and are intended to enhance the rights of the participants, the regulations are deficient in several respects and may have unforeseen consequences for India's wider population.

Impact on research sponsorship and India's population at large

Since India's promulgation of the aforementioned regulations, the number of approvals for clinical trials and applications by sponsors for such approvals in the country has dropped drastically (3). It is clear that the regulations are having a dampening effect on research in India. Put differently, research sponsors seem to regard the regulations as barriers to conducting clinical trials. While the authorities should always view the welfare of the participants in clinical trials as being of paramount importance, they also need to be mindful of the fact that India has many health needs, as well as gaps in the areas of policy and knowledge of practice. Research is crucial for addressing these needs and gaps, and inspiring evidence-based practice and policy reforms at a wider population level. The enactment of impractical or illogical regulations will impede such research and could inadvertently facilitate and entrench gaps in knowledge. Apart from discouraging the sponsorship of research, and by extension, research in the country, the regulations are also deficient in several other respects.

Should placebo-controlled and investigational product trials be discouraged?

India's new regulations provide for the compensation of injury or death arising from "the failure of [an] investigational product to provide intended therapeutic effect" [Rule 122-DAB (5)(c)] and from "the use of a placebo in a placebo-controlled trial" [Rule 122-DAB (5)(d)]. Both provisions are counterintuitive and violate the principle of equipoise.

Investigational products are *investigational* for a reason. While a therapeutic effect may be *hoped for* at the initiation of a study, the efficacy of an investigational product is not known, or not supposed to be known, until a study's conclusion. The apparent requirement that an investigator has to ensure that the investigational product possesses an "intended" therapeutic effect would imply that the investigator must know, with reasonable certainty, the efficacy of the product *before* its employment in the trial. The possession of such knowledge would violate a basic tenet of research—the principle of equipoise—which dictates that there must be *genuine uncertainty* at the outset on the part of the investigator regarding the purported efficacy or effectiveness of an investigational drug, device, or product. India's new regulations thus place investigators in an untenable position: they are to ensure that the investigational drug "provides intended therapeutic effect" or pay compensation for its failing to do so. This provision could lead to interpretation bias on the part of the investigator and would detract from the credibility of the results of Indian trials.

With regard to the regulations' provision on placebo-controlled trials, the very nature of a placebo is its confirmed inert / inefficacious state. Placebos are *not* supposed to demonstrate efficacy or effectiveness. It is thus counterintuitive and illogical to compensate trial participants for injuries or deaths that "arise from the use of placebo in a placebo-controlled trial." It would appear that India's new regulations are aimed at discouraging placebo-controlled trials. This is contrary to the position of the Declaration of Helsinki (4) and the Council for the International Organisations of Medical Sciences (CIOMS) Guidelines (5), both of which endorse placebo-controlled trials in particular circumstances, such as if no known intervention exists for the health condition under investigation.

Who decides eligibility for compensation and quantum?

While insurance cover for participants in clinical trials is not mandatory in many countries, some countries require investigators and/or sponsors to have a no-fault insurance cover for the participants in their trials to comply with good clinical practice (GCP), on the basis of the guidelines published by the International Conference on Harmonisation (6) or national versions thereof. This relieves the participant of the burden of proving negligence on the part of the investigator or sponsor to win the award of compensation. Thus, the mere occurrence of a trial-related injury or death, regardless of whether or not it is the fault of the sponsor or investigator, will trigger a pay-out. However, the quantum of compensation and actual pay-out are ultimately dependent upon the discretion of the insurance company. In some instances, should the parties disagree on the quantum, the insurance contract sometimes provides for a mediation process.

India published its GCP in 2001(7). Paragraph 2.4.7 of the GCP Guidelines governs compensation for accidental injury and states:

> *Research subjects who suffer 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 IEC. In case of death, their dependants are entitled to material compensation.*

Paragraph 2.4.7.1 also obliges sponsors to pay compensation in instances of trial-related injury or death. It states:

> *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.*

These provisions did not prevent the apparent systemic non-payment of trial-related compensation by Indian trial sponsors and/or their insurance companies (8), which highlights that the country's GCP Guidelines were inadequate to protect the interests of participants in clinical trials. The codification of a compensation process for clinical trials amounts to the removal of the discretionary power of trial sponsors and/or their insurance companies to stipulate the terms and conditions of coverage and to determine the quantum.

India's new regulations entitle injured clinical subjects to "free medical management as long as required," as well as financial compensation "over and above any expenses incurred on the medical management of the subject." While this is a welcome measure, it is not clear if the latter compensation is for the time spent on, inconvenience associated with and reimbursable expenses (such as transport costs) related to the patient's medical management and/or for the pain, suffering and mental anguish experienced by the participant in the trial or the surviving next of kin (if applicable). The authorities should clarify this issue so that the participants in trials (and sponsors) know the scope of the potential study-related claims, especially since proving that such a claim exists or determining the quantum of compensation in the case of non-reimbursable claims (such as pain and suffering) generally requires the testimony of expert witnesses and other evidence. If such matters are not governed by the regulations, the injured parties or the next of kin of the deceased participants will have to institute such claims through civil proceedings.

Another problematic feature of India's new regulations is that they leave the determination of the quantum of compensation to the discretion of research ethics committees (RECs) and an "independent expert committee" (IEC) constituted under the auspices of the licensing authority. The regulations require the governing REC to forward its opinion on compensation (if applicable) to an IEC, whose mandate includes determining the quantum of compensation to be paid out. Traditionally, such determination has been the domain of judicial officers well-versed in civil law and in determining the quantum of compensation to be awarded, and not of multidisciplinary RECs or IECs (unless such bodies are to be trained in/ staffed by judicial officers or legal experts skilled in the determination of the quantum of compensation). Given the already overburdened state of most RECs, it is not clear how the onerous task of forwarding quantum-related opinions will influence their turn-around times and what impact it will have on their staff turnover.

Conclusion

India's attempt to regulate the issue of compensation for injuries and deaths arising from clinical trials is laudable, given the years of indifference on this subject. However, in their current form, the regulations are deficient and counterproductive and thus, merit urgent reconsideration. As they stand, they will dissuade sponsors and investigators from engaging in clinical trial activities. Without such sponsorship, the gaps in knowledge in the area of health will persist, and sub-optimal practice and policy will continue to cause suffering to millions. This is counter to the interests of India's people, who need responsible health research governance and intensified research that is locally responsive.

Acknowledgements

Jerome Singh receives support from the Ethical, Social, and Cultural (ESC) Program for Global Health at the Sandra Rotman Centre. He also receives support from the Centre for the AIDS Program of Research in South Africa (CAPRISA), which forms part of the Comprehensive International Program of Research on AIDS funded by the National Institute of Allergy and Infectious Disease at the National Institutes of Health (NIH) and the US Department of Health and Human Services, as well as support from the NIH HIV Prevention Trial Network (HPTN). The author would like to thank Shane Green for his comments on an earlier version of the manuscript.

References

1. International Conference on Harmonisation. Guideline for good clinical practice [Internet]. ICH; 1996 [cited 2013 May 19]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6_R1/Step4/E6_R1__Guideline.pdf
2. Jesani A. New regulations on compensation for injury and death in drug trials. *Indian J Med Ethics* [Internet]. 2013Apr–Jun [cited 2013 May 28];10(2):76–9. Available from: http://ijme.in/pdfs/212ed76.pdf
3. PTI. Post stringent norms, clinical trials in India plummet *Thehindu.com* [Internet]. 2013 Apr 21[cited 2013 May 28]. Available from: http://www.thehindu.com/sci-tech/health/policy-and-issues/post-stringent-norms-clinical-trials-in-india-plummet/article4639976.ece
4. World Medical Association. Declaration of Helsinki—Ethical principles for medical research involving human subjects [Internet]. Geneva:WMA; 2008 [cited 2013 May 19]. Available from: http://www.wma.net/en/30publications/10policies/b3/
5. Council for the International Organisations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects [Internet]. Geneva:CIOMS; 2002 [cited 2013 May 19]. Available from: www.cioms.ch/publications/layout_guide2002.pdf
6. The Gazette of India Extraordinary. Part II- Section3-Subsection (i). Regd. No.D.L-33004/99.No. 47. Published by Authority [Internet]. New Delhi: Ministry of Health and Family Welfare (Dept of Health);2013 Jan 30 [cited 2013 May 19]. Available from: http://www.elsevierbi.com/~/media/Supporting%20Documents/Pharmasia%20News/2013/February/Clinical%20Trials%20Compensation%20Guidelines.pdf
7. Central Drugs Standard Control Organisation, Directorate General of Health Services, India. Good Clinical Practices for Clinical Research in India. Good Clinical Practices: Guidelines for Clinical Trials on Pharmaceutical Products in India [Internet]. New Delhi: CDSCO; 2001 [cited 2013 May 19]. Available from: http://cdsco.nic.in/html/gcp1.html
8. Mukherjee S. Compensation conundrum. *Perspect Clin Res*[Internet]. 2012 Jan–Mar [cited 2013 May 19];3(1):4–7. doi: 10.4103/2229-3485.92300PMCID: PMC3275993. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3275993/

New rules for clinical trial-related injury and compensation

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Abstract

The rules for compensation for injury and death in clinical trials have recently been notified. These rules clarify that medical management of all injuries in clinical trials is mandatory and in cases in which injury or death is related to the clinical trial, the subject (or nominee) is entitled to compensation over and above the medical management. They also specify procedures and timelines for reporting serious adverse events. These require simplification. The rules will hopefully make clinical trial safer for subjects and investigators alike. However, they suffer from certain inconsistencies that should be reconsidered. They need to be modified so that they do not damage the industry.

Introduction

The Indian clinical research industry is in the doldrums. Early in 2004, India was thought to be on the way to becoming the "hub of clinical research" and the advantages that the country had to offer were advertised (1). The government's efforts towards promoting the industry were widely applauded, but the fact that such research was poorly regulated was a matter of concern (2). In the eight years since then, the situation has changed for the worse. The growth of the clinical research (CR) industry has not reached the zenith that had been foreseen, but has actually plummeted. Despite the fact that the industry is overseen by the government (3), reports of unauthorised and unethical research appear in the media.

The dissatisfaction of patients with the compensation and services they have received in India has been highlighted worldwide, affecting the outsourcing of trials. The media has gone into overdrive, selectively reporting the negative aspects of the trial industry and ignoring the positive ones. The absence of any rules on compensation and the management of injury has been a source of additional trouble to the subjects. Many cases of trial-related deaths have not been adequately compensated, with the result that several press reports have branded trial subjects as guinea pigs (4).

Stakeholders in CR and ethicists have long been seeking guidelines on compensation (5). Last year, the Central Drugs Standard Control Organisation (CDSCO) released draft guidelines on the compensation to be paid for injury or death related to clinical trials (6). Following an examination of the comments and suggestions received, rules for compensation have now been formulated (7).

The need for testing of new drugs on human beings has been acknowledged since the early twentieth century, as also the fact that such testing is fraught with burdens and risks for the research subjects (8). The latter has been highlighted in the Nuremberg Code (9), the Declaration of Helsinki (10), the Belmont Report (11) and the Indian Council of Medical Research (ICMR) Guidelines (12). All these codes suggest that the investigators should maximise the benefits and minimise the risks of research to the subjects.

Clinical research is carried out both on healthy subjects and patients. While patients are likely to benefit from research, healthy subjects may not. The latter enrol due to either altruistic or monetary considerations. The possible benefits of trials could be an incentive for patients to enrol.

The society we live in comprises people whose state of health ranges from very bad to very good. It is axiomatic that healthier people will have a longer life span than the sick. Since drug trials are conducted mostly on sick individuals, the death rates in such trials will always be significant.