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

KHUSHBOO CHOUDHURY[1], RAVINDRA GHOOI[2]

[1] Post Graduate Student, [2] Professor, Symbiosis School of Biomedical Sciences, Symbiosis International University, Lavale, Mulshi, Pune 412 115 INDIA Author for correspondence: Ravindra Ghooi e-mail: ravindra.ghooi@gmail.com

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.

In clinical trials, investigational drugs are compared with standard drugs, such a comparison is essential since we do not know if the former an\re better than the latter. The failure of new drugs to provide the intended benefit is an inherent risk of research on new drugs, and should not be held against the drug under test.

The First Amendment

According to the First Amendment to the Drugs and Cosmetics Rules the definition of trial-related injury or death includes the following:

a) Adverse effect of investigational product/s

b) Violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator

c) Failure of investigational product to provide the intended therapeutic effect

d) Use of placebo in a placebo-controlled trial

e) Adverse effects due to concomitant medication, excluding standard care the use of which is necessitated by the approved protocol

f) Injury to a child *in utero* because of the participation of the mother in the clinical trial

g) Injury due to any clinical trial procedures involved in the study .

This clarification is most welcome since hitherto, there was no acceptable definition of 'trial-relatedness.' Whether the injuries and deaths falling under the above classification qualify for compensation is questionable. The amendment clarifies that the sponsor shall pay compensation for the treatment of any injuries or deaths suffered by trial subjects, and provide compensation if these are trial-related.

Section 5(b) of the amendment makes it binding on the sponsor to pay when injuries or deaths have been caused by the "violation of the approved protocol, scientific misconduct or negligence by the sponsor or his representative or the investigator".

It may be noted that the investigator is to give the regulators an undertaking that the trial will be conducted as per the protocol and that the sponsor's permission is required for any deviation or changes to the protocol (Appendix VII 7. [ii]). The investigator must comply with all the other requirements, guidelines and statutory obligations applicable to clinical investigators participating in clinical trials' (Appendix VII 7 [xii]). It may not be acceptable to the sponsors to have to pay for violations of the above conditions by the investigators. The British guidelines (13) specifically mention this as a limitation as far as the payment of compensation is concerned, stating that "no compensation should be paid if the injury has arisen due to significant departure from the agreed protocol."

In the USA, participants in trials can seek remedy against the investigator's negligence or failure to adhere to the protocol by resorting to the law of 'torts' The Indian amendment which, as already mentioned, requires the sponsor to compensate for such negligence or failure runs contrary to the principles of natural justice. This may lead sponsors to sue investigators in case the subjects in a trial are harmed through their misconduct.

Section 5(c) states that the failure of an investigational drug to provide the intended therapeutic effect will also render a subject eligible for medical management and compensation. The position adopted in the British guidelines again runs counter to this: "No compensation should be paid for the failure of the medicinal product to have its intended effect or to provide any other benefit to the patient."

Section 5(d) states that injury or death in the placebo-treated arms of a trial is also eligible for compensation. On the other hand, the British guidelines are clear that no such compensation should be paid. In any case, as per the Declaration of Helsinki (clause 32), the use of placebo is not allowed in trials in which there is a risk of death. Unlike the USA, we in India are bound to follow the Declaration of Helsinki scrupulously.

The first amendment makes it essential to include the information on compensation in every informed consent form (ICF). The changes that have been made in the ICF will make the subjects aware of their right to compensation and are most welcome. These changes are also in line with 21 CFR 50.25 (6), which states:

> *For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.*

Currently, in the USA, sponsors have no obligation to pay for patients' medical care if they are harmed during a clinical trial, although a handful of organisations voluntarily agree to do so (14). A close examination of 21 CFR 50 suggests that sponsors are not required to pay compensation for trial-related injuries. The US National Advisory Committee has taken no steps towards implementing no-fault compensation and participants in research need to resort to the tort system for compensation (15).

While compensating the patient's nominees for a death is a good act on the part of the sponsor, a number of deaths will take place due to the natural progression of the disease. There are actually very few drugs that can block the natural progression of diseases like cancer. If such patients die in the course of the accepted therapy, they are not eligible for compensation. However, if they die during the testing of new anti-cancer drugs, they would be eligible. There is a need to do away with this dichotomy because this practice adds to the cost of developing new drugs, and hence, to the price of the new drugs. This is not in the interest of patients.

The payment of compensation to subjects enrolled in trials on cancer could theoretically become an incentive for participating in trials. Patients diagnosed with cancer are not

eligible for insurance cover, as their illness becomes a pre-existing condition. The availability of compensation could serve as an alternative to insurance. Moreover, in a poor country such as India, some patients could be forced into trials by their relatives to earn compensation from their deaths.

There are therapeutic areas in which the rules relating to compensation should not apply. In palliative care, drugs are intended not to cure patients of their disease, but merely give them comfort or relief. Three trials are in progress in India (CTRI/2009/091/000336, CTRI/2012/11/003160 and CTRI/2012/11/003169) on Sativex, a cannabinoid, on cancer patients. It is expected that there will be a number of deaths in this trial, since the drug is not meant to prevent death. Would all these deaths be eligible for compensation?

Reporting of serious adverse events (SAEs)

The First Amendment has detailed the procedure and timelines for reporting SAEs, harmonising all reporting to calendar days. The amendment differentiates between SAEs that lead to death and those that do not. There is, however, a drawback in the reporting procedure in that the investigator, sponsor and Chairman of the Ethics Committee are all supposed to send reports on SAEs to the licensing authority. The receipt of multiple reports may result in a single SAE being counted as three or four SAEs at the licensing authority level. A simplified reporting procedure that avoids duplication and subsequent confusion could be adopted. The countdown should begin from the time the investigator comes to know of the SAE rather than its occurrence. This is shown in Table 1.

Table 1. Suggested reporting procedure and timelines

Report by	Report to	Timeline
Investigator	Sponsor/head of institute	24 hours
Sponsor	IRB/EC chairman	7 days
IRB/EC chairman	Expert committee [a]	14 days
Expert committee	Licensing authority	21 days
Licensing authority	Sponsor	3 months (for passing orders)
Sponsor	Licensing authority	1 month (for compliance)

[a] When an SAE does not lead to death, the IRB/EC chairman reports to the licensing authority, bypassing the expert committee.

In the past, the IRB/EC was empowered to fix the quantum of compensation using a formula for the calculation of the amount (16).

There have been doubts regarding the competence of the ethics committees operating in India, but hopefully the registration of ethics committees (17) will help resolve this issue.

Effective date

Normally when new guidelines are issued, there is a date on which they become effective. As for laws, they become effective as soon as they are published in the gazette. In the case of the new rules (Rule 122 DAB), there is no information on the date from which they will become applicable. It is not clear as to whether they apply to all trials cleared after January 30, 2013, all subjects randomised after this date, SAEs occurring after this date or SAEs reported after this date. A clarification from the government would be most welcome.

Conclusions

The importance of drug trials in promoting health cannot be overemphasised. New drugs have had a tremendous impact on the life span and quality of life of patients. It is essential to continue with drug trials more vigorously than before, the more so in a country such as India. In the past, when the patent regime did not favour the discovery of new drugs, India had to depend on drugs developed abroad. With the new patent regime in place, the country will have to start its own drug development programme if the people are to have access to new and affordable drugs.

The government has notified rules for compensation for injury and death in clinical trials, the conduct of trials and registration of ethics committees. It is hoped that these will enhance the safety of the subjects and adequate compensation is paid in the event of injury or death. The rules should establish the primacy of the subject's rights and well-being. The possible negative effects of the rules also need to be considered.

The CR industry in India was a rapidly growing one, providing subjects for research and opportunities for the development of new drugs. As more subject-friendly rules are made, we should try to maintain a balance so that India remains an attractive destination for the outsourcing of clinical trials. An excessive increase in the cost of the trials will eventually affect the cost of the new drugs, which will not be in the interest of the patients who are suffering. Let us remember that it is finally the patient who pays for it all.

References

1. Bhatt A. Clinical trials in India: pangs of globalization. *Indian J Pharmacol.* 2004;36:207–8.
2. Thatte UM, Bavdekar SB. Clinical research in India: great expectations? *J Postgrad Med*. 2008;54:318–23.
3. Pandey A, Aggarwal AR, Seth SD, Maulik M, Bano R, Juneja A. Clinical Trials Registry – India: Redefining the conduct of clinical trials. *Indian J Cancer*. 2008;45:79–82.
4. Nagraj NM. Hospitals turn poor into guinea pigs. *Times of India* [Internet]. 2009 May 11[cited 2013 Jun 24]; Available from: http://articles.timesofindia.indiatimes.com/2009-05-11/bangalore/28155467_1_clinical-trials-clinical-research-india-drug-controller-general.
5. Sengupta A. Fatal trials: clinical trials are killing people. *Indian J Med Ethics.* 2009;6(3):118–19.
6. Central Drugs Standard Control Organisation. Guidelines for determining quantum of financial compensation to be paid in case of clinical trial related injury or death [Internet]. New Delhi:CDSCO;2012 Aug 3[cited 2013 Jun 23]. Available from: http://www.cdsco.nic.in/compention.pdf
7. Ministry of Health and Family Welfare (Department of Health). Drugs and Cosmetics (First Amendment) Rules, 2013. GSR No. 53(E) [Internet]. New Delhi: MoHFW, Govt of India; 2013 Jan 30[cited 2013 Jun 24]. Available from: http://www.manupatra.com/manufeed/contents/PDF/634969625902580076.pdf
8. The Berlin Code of Ethics 1900. Available from:. http://www.geocities.com/artnscience/00berlincode.pdf.
9. Nuremberg Military Tribunal. The Nuremberg Code 1947. *JAMA*.1996 Nov 27;276(20):1691.

10. World Medical Association. The Declaration of Helsinki. Ethical principles for medical research involving human subjects [Internet]. 2008 Oct[cited 2013 Jun 23]Available from http://www.wma.net/en/30publications/10policies/b3/.
11. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report. Ethical principles and guidelines for the protection of human subjects of research. Washington, DC: US Govt Printing Office;1979 Apr 18[cited 2013 Jun 24]. Available from: http://www.fda.gov/ohrms/dockets/ac/05/briefing/2005-4178b_09_02_Belmont%20Report.pdf
12. Indian Council of Medical Research. Ethical guidelines for biomedical research on human participants [Internet]. New Delhi:ICMR;2006 [cited 2013 Jun 23]. Available from: http://icmr.nic.in/ethical_guidelines.pdf.
13. The Association of the British Pharmaceutical Industry. Clinical trial compensation guidelines. London:ABPI;1991[cited 2013 Jun 23]. Available from: http://www.abpi.org.uk/our-work/library/guidelines/Pages/ct-compensation.aspx.
14. Elliot C. Justice for injured research subjects. *N Engl J Med*. 2012;367(1):6–8.
15. Pike ER. Recovering from research: A no-fault proposal to compensate injured research participants. *Am J Law Med*. 2012;38(1):7–62.
16. Ramanathan M, Sarma PS, Mishra US. Compensation for trial-related injury: does simplicity compromise fairness? *Indian J Med Ethics*. 2012;9(4):232–5.
17. Ministry of Health and Family Welfare (Department of Health). Drugs and Cosmetics (First Amendment) Rules 2013. GSR No. 72(E) [Internet]. New Delhi:MoHFW;2012 Feb 8[cited 2013 Jun 23]. Available from: http://www.cdsco.nic.in/html/G.S.R%2072%28E%29%20dated%2008.02.2013.pdf

Theatre of the Oppressed in medical humanities education: the road less travelled

SETU GUPTA[1], ABHINAV AGRAWAL[1], SATENDRA SINGH[2], NAVJEEVAN SINGH[3]

[1] MBBS student, University College of Medical Sciences, New Delhi 110 095 INDIA, [2] Department of Physiology, Medical Education Unit and Medical Humanities Group, University College of Medical Sciences, New Delhi 110 095 INDIA, [3] Department of Pathology and Medical Education Unit and Medical Humanities Group, University College of Medical Sciences, New Delhi, 110 095 INDIA. Author for correspondence: Satendra Singh e-mail: dr.satendra@gmail.com

Abstract

Internationally, there is an increasing awareness of the need to include humanities in the medical curriculum. The Medical Humanities Group at the University College of Medical Sciences, Delhi, organised a series of events to explore this area. This paper describes our experience with Augusto Boal's "Theatre of the Oppressed" (TO). Twenty-six participants attended a 2-day workshop culminating in a "forum theatre", in which the spectators are transformed from passive observers to active participants or spect-actors. The participants' responses to our workshop indicate that TO provides a multitude of experiences and addresses a wide range of learning domains. TO challenges the senses and offers a promising and enjoyable option for learning medical humanities.

Introduction

Buried in the verbiage of the document regulating graduate medical education in the country, the Medical Council of India (MCI) (1) does attempt to include study of the humanities in the MBBS curriculum. Interestingly, it is clubbed with community medicine. Seemingly unconnected to this, elsewhere at the bottom of the list of "institutional goals", personal characteristics and attitudes required for professional lives of graduating students find mention, suggesting that clarity of thinking on the issue is still some way off. Small wonder, then, that any attempt to engage the teaching fraternity in a discussion of the subject only manages to raise the occasional curious eyebrow, amid a sea of frowning disapproval. However, a Google search using the phrase "medical humanities" demonstrates that world-wide there is a gathering storm of interest in this discipline. Journals (2, 3) are devoted to medical humanities, universities offer courses (4) and funding agencies (5) are keen to support research in the area. Clearly, priorities and perceptions differ across the globe.

At the University College of Medical Sciences, Delhi, we have attempted to introduce our students to the humanities. To achieve this, the Medical Humanities Group of the Medical Education Unit (6) has organised a series of events over the past few years relating to literature, philosophy, ethics, the visual and performing arts, street theatre, and the social sciences (7–12). This paper examines our experience with "Theatre of the Oppressed" (TO), a unique form of theatre devised in Brazil by the legendary Augusto Boal (13, 14). Designed to help communities to understand their social reality and find solutions to their own problems, TO has been used as a tool to bring about change in diverse environments; however, its use in a medical community has not been documented.

The personal characteristics and attitudes required for professional life specifically identified by the MCI for MBBS students are "personal integrity, sense of responsibility and dependability and ability to relate to or show concern for other individuals" (1). Considering that these lie squarely in the domain of philosophy and ethics, it is interesting to speculate on how these ends can be achieved.

We must explore how the student can be exposed to situations where such learning is facilitated, so that she may learn on her own. Importantly, to be effective, such learning, all learning really, must be perceived to be fun. It must not only attract the curiosity of the student, but must also have a lasting impact. The 2-day workshop in Theatre of the Oppressed that we organised was an attempt to achieve some of these goals.

The workshop

The 26 participants in the workshop included students from the University College of Medical Sciences (UCMS), the Army College of Medical Sciences and Amar Jyoti Institute of