The legacy of scandals and non-scandals in research and its lessons for bioethics in India

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A case study entitled "Observational study of cervical cancer", on research undertaken in a south Asian country, published in a compilation of case studies by Cash and others (1), is the subject of a collection of commentaries in this issue of *IJME*. The range of responses reflects the commentators' individual disciplinary orientations and views on the state of medical practice in those times, and the ethical standards that applied.

While reviewing this compilation of case studies, Macklin critiqued the use of historical case studies as they may not resonate with knowledgeable physicians and researchers who would want material that is relevant to their current or future experience (2). Another possible criticism is that case studies based on developed world scenarios may not seem as relevant to researchers from developing countries working within developing world settings. They may respond with "What if this happens in our setting?" rather than the more evocative "There but for the grace of God, go I!" which facilitates changes in perceptions and practices.

Bioethics training and international case studies

Indeed, the case studies employed in bioethics training within India, as well as in other parts of the world, are often "international research cases" from developed countries on issues relevant in their contexts. They may also describe the experiences of researchers from developed countries in the developing countries. As there are very few case studies identifying an Indian location and research sponsored by Indian agencies, trainees from the Indian subcontinent may feel that violations in ethics primarily occur elsewhere, and are perpetrated by "others" on our people.

This belief results in the reiteration of faith in our own morality and ethics, without the realisation that we can learn from such scandals only after in-depth inquiries, research and debate. The history of the Belmont Report is rooted in the inquiry into the Tuskegee study. This report initiated reforms in the way clinical research was conducted in the United States of America. It is also part of the bioethics literature. However, inquiries and scandals that occurred in India are not the subject of bioethics teaching in India. This is not because they do not occur, but because they are not written about, debated or discussed. This shortcoming needs to be corrected and the truth needs to be told as part of the development of the bioethics movement in India. We need to retell history, not as part of a witch hunt to blame or punish those involved, but to teach ourselves and set the record straight, based on the adage: "Those who cannot remember the past are condemned to repeat it".

The case study presented in this issue had women in different stages of dysplasia who were followed up for an extended period, without treatment; even after evidence for offering such treatment became available. The research was based on the rational assumption that it was important for a country with limited resources for health to determine which of the dysplasias would develop into carcinoma in situ (CIS), thereby identifying the high risk cases who could be given preference in provision of treatment. The study lasted 12 years. This again is reminiscent of the observational study of syphilis in African-American males in Tuskegee, Alabama, USA. In the Tuskegee study syphilis patients had been observed for 40 years, without providing treatment.

Research similar to that described in the case study

We know of two research studies conducted in the 1970s and 1980s on carcinoma cervix that are similar to the case study discussed in this issue. One well documented study that was acted upon and followed up was done in New Zealand. The other was carried out in India.

The research project that was a matter of public debate in New Zealand was on carcinoma cervix but with slightly different objectives and possible outcomes than the case study published in this issue. This was an observational study on the invasive potentiality of cervical CIS initiated in the mid 1960s at the National Women's Hospital in Auckland; the patients were not offered standard treatment. This study was brought to light in 1987, by two women's health activists and journalists, Sandra Coney and Phillida Bunkle, through an article in New Zealand's Auckland-based magazine *Metro* (3). Following a public outcry, this study became the subject of a judicial enquiry by Judge Silvia Cartwright (4). The public hearings took place between August 1987 and January 1988 and the report was released on August 5, 1988.

The findings of this inquiry set the pace for reform in medical research in New Zealand, and the understanding of ethics in health research within the country (5). A system of research ethics committees in which 50% of members came from the lay public was

established; their functions included the supervision of clinical observational studies. A successful population-based cervical screening programme based on cytological smears began. New Zealand enacted the Code of Patients Rights as a part of the Health and Disability Commissioner Act, 1994. This provided an independent external enforcement system in the Office of the Health and Disability Commissioner (6). Thus, the controversy, the inquiry, and subsequent follow-up created a lasting legacy that enhanced patients' rights and reformed medical practice.

The research carried out in India, like that in the case study published in this issue, observed women with cervical dysplasia, without offering treatment. It was supported by public funds and carried out by Indian researchers, and it lasted over a decade. The Indian medical and scientific community was aware of the research when it was being carried out. After its completion in 1987, its findings were reported in international journals. At the time it was on in the 1970s and 80s, researchers would have been aware of the international furore generated by the revelations about the Tuskegee trial. When the findings of the Indian study were being published, the controversy regarding the New Zealand study was being reported in the medical literature. Yet, there was no critical reflection within the community of Indian researchers on what was not done; nor were measures taken to provide recompense to the participants in the study. Instead, the country waited long for a public controversy. Ten years after the completion of the study, when some participants started reporting to hospital with cervical cancer, a newspaper report revealed that those participants were the ones who had not been provided treatment during or after the study, nor followed up in the long term (7). The report described it as "the use of women as guinea pigs". The researchers defended the study by saying that "no one died" (8) due to any medical intervention as there was none. However, like any other big scandal on health and research, this one too died down, was soon forgotten, and hardly anything has been written on it since then.

The perils of ignoring history

Among the cancers in India, carcinoma of the cervix is a major killer of women. There is absolutely no doubt that more research for its prevention and treatment is needed in the country. Ours is also a resource-poor setting, and so the argument in justification as given in the case study can be applicable to the research that was done in India. Indeed, the identification of dysplasia that would most likely turn into CIS makes the intervention selective and thus resource saving. In the absence of evidence to the contrary, we may assume that such good intentions motivated the researchers to undertake the study in India.

However, a research design based on observing the progression of disease in patients over a period without offering standard treatment during or after the research exposes patients to the risk of suffering from that disease. Such a research design does not offer any benefits to patients who are recruited only for the benefit of science and the benefit of future patients. This produces a serious imbalance in the risk-benefit ratio. This imbalance does not get corrected even when researchers are confident of obtaining written and witnessed informed consent from patients for participation. This inherent imbalance in risks and benefits to participants caused harm to patients; and so the public furore it aroused was fully justified. This situation could have been prevented only by questioning this harmful research design, which could have forced the researchers to look for alternative research designs to generate the kind of evidence they needed.

It has been argued that research of the kind described in the case study was essential for making treatment available to those who needed it the most. However, the government, which sponsored the research, did not follow this up with a genuine implementation of the universal cervical screening programme. Even a quarter century after the completion of the research, and 15 years after the reporting of the ethics controversy in the media, the universalisation of cervical screening with the provision of treatment to those who need it the most remains a distant dream. If the research is described as "sacrificing a few now in order to save many millions later" – an argument deeply problematic in ethics and indeed unacceptable – in this case "sacrifice" did not usher in the provision of real care for all women who needed it, though some did benefit from it.

Unethical research, even when it is on correctly identified health problems and produces useful outcomes, not only poses potentially serious harm to the participants, but also sometimes affects the priority accorded to these health problems. When a few scientists and physicians show lack of respect for vulnerable participants, future potential participants and society in general become suspicious of the motives and credibility of all researchers. Therefore, a short-lived media controversy on such research is not sufficient to correct the situation. What is needed is efficient and transparent investigation of such cases to bring out the facts in public, making those responsible for violations accountable. Further there is a need to use the findings of these inquires to improve the governance of research and ethics education of all stakeholders. Apparently, nothing of the sort that New Zealand did was done in India. And despite the numerous other controversies in biomedical research after this study – more so after 2005 when corporate- sponsored clinical trials increased in number – the governance of research and ethics education remain abysmal in India.

We have recently witnessed another controversy about ethics violations arising out of research into carcinoma of the cervix. This relates to the manner in which the phase IV clinical trials and demonstration project on HPV vaccines used for the prevention of carcinoma of the cervix were conducted. The public outcry surrounding it resulted in the suspension of the project and institution of an inquiry to investigate ethics violations and the deaths of participants. Of course, the institution of an inquiry is a step forward

when compared with the handling of the earlier controversy on the research into this disease. However, the report of the inquiry has still not been made public, though it was formally submitted to government by the committee. The facts of that research still remain disputed due to such secrecy; nobody is held accountable for violations, and of course no learning for researchers emerges from even such a controversial case (9).

Learning from history and ethics cases

On October 1, 2010, the United States secretary of state, Hilary Clinton, and the health and human services secretary, Kathleen Sebelius, expressed regret and tendered their apologies to Guatemalans who were harmed by the US Public Health Service sexually transmitted disease inoculation study of 1946-1948 (10). This was an outcome of painstaking research on the subject done by a historian, Susan Reverby, which exposed the deliberate inoculation of infective agents into many Guatemalan people as a part of a research project sponsored by US government agencies (11). One may say that an apology is insufficient to provide solace to those who suffered, and to bring back respect to the community and the country. But an admission of error, and the reaching out to those who suffered and their community, is a good beginning. One will want such apologies in all cases where nations have violated ethics in research.

However, ethical practices and review in research, and the ability to learn from past mistakes, cannot be limited to a first world initiative, when the potential for unethical practices is universal. If we do not dust off old books on our own medical research, identify lapses, document them and discuss them, we will fail the stakeholders of such research – those who will participate either as subjects or as researchers in future initiatives or as regulators of such research in India. It is for this reason that we decided to publicise this case study and initiate discussion on it-- many decades after the event -- to obtain a better understanding of the need for ethics in research, and to facilitate an understanding of the issues among future researchers within the country. A case study of the kind published in this journal may not be sufficient to go into all the issues in the actual research, but it should be a sufficient trigger for historians to re-examine these concerns.

References

1. Cash R, Wikler D, Saxena A, Capron A, editors. *Casebook on ethical issues in international health research* [Internet]. Geneva:World Health Organisation;2009 [cited 2011 Dec 13];124-5. Available from: http://whqlibdoc.who.int/publications/2009/9789241547727_eng.pdf
2. Macklin R. Casebook on ethical issues in international health research. *Bull World Health Organ* [Internet]. 2010 [cited 2011 Dec 13];88:716. Available from: http://www.who.int/bulletin/volumes/88/9/10-078469/en/index.html
3. Rosier P. The speculum bites back: feminists spark an inquiry into the treatment of carcinoma in Situ at Auckland's National Women's Hospital. *Reprod Genet Eng* [Internet].1989[cited 2011 Dec 13];2(2):121-32. Available from: http://www.finrrage.org/pdf_files/RepTech%20General/Carcinoma_In_Situ.pdf
4. Cartwright S. *The report of the committee of inquiry into allegations concerning the treatment of cervical cancer at National Women's hospital and into other related matters* [Internet]. Auckland (New Zealand): Government Printing Office, Auckland; 1988 Aug 5[cited 2011 Dec 13]. 288p. Report No.:ISBN0-473-00664-2. Available from: http://www.nsu.govt.nz/Current-NSU-Programmes/3233.aspx
5. Paterson R. The Cartwright legacy: shifting the focus of attention from the doctor to the patient. *N Z Med J* [Internet]. 2010 Jul 30 [cited 2011 Dec 13];123(1319):6-10. Available from: journal.nzma.org.nz/journal/123-1319/4239
6. Bunkle P. Patient-centred ethics, the Cartwright Inquiry and feminism: identifying the central fallacy in Linda Bryder, *A history of the'unfortunate experiment' at National Women's Hospital (2009, 2010). Women's Studies Journal* [Internet]. 2010[cited 2011 Dec 13];24(2):8-24. Available from: http://www.wsanz.org.nz/journal/docs/WSJNZ242Bunkle8-24.pdf
7. Mudur GS. ICMR let women guinea pigs get cancer. *The Telegraph* (New Delhi Ed). 1997 Mar 22.
8. Mudur GS. Gynaecologists refuse to buy "no one died" argument: Cancer trial stroke ethics debate. *The Telegraph* (New Delhi Ed). 1997 Mar 23.
9. *Sarojini N, Shenoi A, Srinivasan S, Jesani A. Undeniable violations and unidentifiable violators. Econ Pol Wkly. 2011 Jun 11;46(24):17-9.*
10. *US Department of Health and Human Services [Internet].Washington DC: US Department of Health and Human Services.* Joint Statement by Secretaries Clinton and Sebelius on a 1946-1948 study; 2010 Oct 1[cited 2011 Dec 13];[about 2 screens]. Available from: http://www.hhs.gov/news/press/2010pres/10/20101001a.html
11. Reverby SM. "Normal exposure" and inoculation syphilis: a PHS "Tuskegee" doctor in Guatemala, 1946-1948. *J Policy Hist.* 2011;23(1):6-28.