Indian Internet Journal of Forensic Medicine & Toxicology
Vol. 9, No.3, July-September 2011, 63-70

Review Article

Medical Research and Clinical Trials – Indian Scenario

Dr. Karunakaran Mathiharan

Formerly Head and Associate Professor, Forensic Unit, Faculty of Medicine,

University of Malaya, 50603 Kuala Lumpur, Malaysia

e-mail id: legalmedicine@gmail.com

ABSTRACT

Recently, the Government of India ordered suspension of clinical trials on tribal girl students carried out by a non-governmental organisation, for a pharmaceutical company for HPV (human papilloma virus) virus to prevent cervical cancer. The final report of the committee appointed by the Government of India to enquire into alleged irregularities found enough evidence to suggest that there were large-scale ethical violations during the conduct of "post-licensure observational study." In August 2010, Health and Family Welfare Minister, Government of India stated that the number of incidents involving clinical trials is increasing. Upsurge in the incidents involving clinical trials and medical research evidently points to the ineptness of the ethical and statutory provisions that are currently available in India.None of the issues concerning newer therapeutic measures and medical research except the organ transplantation have evoked a widespread public anxiety in India. Had there been public debates on medical research and clinical trials, it would have led to an energetic and prompt governmental response in the seform of rules and regulations. The need of the hour is transparency and accountability in conducting medical research and clinical trials. To achieve this, there should be a reappraisal of the ethical and legal policies concerning medical research and clinical trials which take into account the safety of the human volunteers and the establishment of a statutory authority with adequate powers to monitor and supervise the medical research and clinical trials.

Keywords: Medical research, Clinical trials, Medical law, Medical ethics, Bioethics

INTRODUCTION

India has five statutorily recognised systems of medicine and innumerable unrecognised systems. The recognised systems have their Codes of Ethics specific to the training, practice and research. But their implementation and monitoring by the respective medical councils leave much to be desired. There is an increase in the number of reported and unreported research projects in all the recognised systems with less or absent regulations. India's indigenous systems of medicine are Ayurveda and Siddha. Ayurveda has specific Codes of Medical Ethics such as *Caraka Samhita* and *Susruta Samhita* similar to Hippocratic Oath that essentially deal with the practice of medicine and the training of the new entrants. But they do not say anything about the ethics in medical research. The other statutorily recognised medical systems in India are Homoeopathy, Unani and Allopathic Medicine.

Practitioners and academicians of Allopathic Medicine in India are expected by the Medical Council of India (MCI) [1] to adhere to the guidelines of the Indian Council of Medical Research (ICMR).

MEDICAL RESEARCH AND CLINICAL TRIALS IN INDIA

The average cost of a clinical trial in the United States is US$180 million. Whereas, the average cost in India is US$100 million. Multinational companies are not the only ones to benefit financially from these studies — India does too. The consultancy firm McKinsey estimates

that US and European pharmaceutical companies will spend US$1.5 billion per year on clinical trials in India by 2010.[2]

India has several advantages as a host for such trials. Since around 40% of drug development costs are related to trials, it is felt that India with its vast reservoir at 60% less than the costs in a developed country will hugely benefit the big drug companies.[3] Its biggest asset is probably the size of its population at more than 1 billion. For instance, India with its 70 million heart patients, 40 million asthmatic patients, 35 million diabetic patients, 8-10 million people HIV positive, 8 million epileptic patients, 3 million cancer patients[4] provide a vast testing populace for the multinational drug companies and Indian outsourcing firms. In addition, Indians are increasingly suffering from the same illnesses as Americans and Europeans — diseases for which companies are desperate to find cures. Further, it also has the edge over most developing countries because of its sophisticated hospitals with many of its medical personnel speaking English.[5]

With virtually no or minimal government funding for the treatment of people with HIV/ AIDS in India, joint research ventures between care providers and physicians in India and US – based universities are fast becoming the norm. Ethical considerations in such ventures depend on the Indian partner who implements and coordinates the project. When it comes to people coming with HIV, this issue becomes a little tricky as issues such as an informed consent and confidentiality have very little meaning in India. Most such collaborations between Indian care givers and foreign universities are highly unethical and are being conducted without any approval.[6]

The investigators for clinical trials, particularly when drugs are to be tested, are chosen by sponsoring companies. All manufacturers want that their products should be found safe and effective. There cannot be a better way to ensure positive results than to select friendly, obliging and ever-willing investigators to do the bidding. Many investigators who conduct clinical trials are, or have been, beneficiaries of largesse from the pharmaceutical manufacturers. The financial ties include paid speaking engagements, equity of the sponsoring companies, expensive gifts such as cars, refrigerators, air conditioners, medical equipment, attendance at sponsored scientific conferences, paid consultancy work, authoring 'ghost-written' scientific articles, and travel grants for domestic and foreign travel. In 2002, a Mumbai-based company marketing erythropoietin had obliged some 300 senior nephrologists to visit Singapore on an expense-paid jamboree, an effective strategy not only to garner more prescriptions but also to ensure positive results of future clinical trials. Neither the regulatory authorities nor the ethics committees seek conflict of interest information from investigators.[7]

In the recent past, many drug trials have been conducted in India by many foreign universities and pharmaceutical companies because conducting such trials are cheaper and there are not much of any legal or ethical restrictions. Some such incidents have been listed below.

- To study rates of progression of uterine cervical dysplasia's to malignancy; the Indian Council of Medical Research during 1976-88 allocated 1158 women with varying degrees of cervical dysplasias to long term follow up. The study was conducted to observe the natural course of precancerous uterine cervical lesions without treatment in women who had not given written consent to take part. The development of carcinoma in situ was defined as the end point for treatment. In at least nine women the lesions progressed to invasive cancer, and 62 women developed carcinoma in situ of the cervix before they were treated. The investigators, from the Institute of Cytology and Preventive Oncology in New Delhi, said that they did not obtain written consent on the grounds that most of the women in the study were illiterate and that written consent was not mandatory when the study was launched.[8]
- Quinacrine, a synthetic anti-malarial belonging to the acridine group of drugs, was used in the treatment of malaria during the 1930s and 1940s, till it was replaced by better drugs such as chloroquine. It has also been used successfully in the treatment of giardiasis and systemic lupus erythematosus. Later, it was discovered that it could be used for the

chemical sterilisation of women. These trials took place in 19 third world countries - all countries of south Asia. The procedure involved the trans-cervical introduction of pellets of quinacrine into the fundus of the uterus in the early proliferative phase of the menstrual cycle using a modified copper-T inserter. The most common technique used was the insertion of seven pellets of 36 milligramms of quinacrine performed either once or twice. Following insertion, the pellets dissolved in the uterus in about half an hour and then, it was suggested that quinacrine set up a local inflammatory reaction specifically in the fallopian tubes. The fibrosis and scar tissue that ensued led to tubal occlusion and thus sterilisation. Since tubal occlusion took up to 12 weeks to be complete, an additional contraceptive was usually provided for this period along with the first insertion of quinacrine. Typically, a long-acting injectable contraceptive such as the controversial Depo Provera was used. In India, quinacrine sterilisation was carried out with "hundreds of doctors involved". Mullick, who ran a NGO named Humanity Association in Calcutta, admitted to have sterilised 10,000 women over two decades. He also claimed to have trained over 200 village health workers from all over the country in quinacrine sterilisation even as he frankly admitted that financial constraints prevented follow-up of his cases. In Bangalore, between July 1994 and July 1996, Pravin Kini, Sita Bhateja and B Rajagopal completed trials on 600 women. The September 1995 issue of the Family Health International's newsletter Network reported that three out of four studies on quinacrine showed it to be mutagenic. Mutagenicity, the capacity to induce somatic changes in cells, is indicative of possible carcinogenicity or cancer causation. The Government of India denied granting approval to any of these trials. In the parliament, in reply to a question tabled by Ashok Mitra, the minister of state in the department of legal affairs stated that the Government of India was aware that the WHO had specifically recommended that pending further studies, trials with quinacrine on human population's be stopped forthwith. He stated that the government had only permitted the Indian Council of Medical Research to carry out a study in 1992 but that the high failure rate early in the study compelled its termination. Subsequently, "approval for clinical trials of quinacrine pellets had not been granted to any investigator by the Drug Controller General of India."[9] After a writ petition was filed in the Supreme Court by the All India Democratic Women Association against the quinacrine trials, the Drug Control Administration invoked the provisions of Sections 10-A and 26-A of the Drugs and Cosmetics Act, 1940, to prohibit the import, manufacture, sale and distribution of quinacrine in pellet form and for its use as a contraceptive.[10]

- An investigational drug M4N, a derivative of the natural product nordihydroguaiaretic acid (NGDA) (derived from the creosote bush (*Larrea tridentatia*)) was injected into cancer patients between November 1999 and April 2000 at the Regional Cancer Centre (RCC) in Thiruvananthapuram before its safety was established in animal tests and without clearance from the Drug Controller General of India (DGCI), and without approval from the institutional ethical committee. NGDA had been used as a herbal remedy but was known to cause liver and kidney damage. Subsequently, a 60-year-old woman was again included for a trial in which the RCC provided five doses of the experimental drug. The woman's condition turned critical before the fifth dose but she survived. Clearance from the Drugs Controller was first received in 2001. However, it was claimed that the approval was given in November 1999 for topical drug administration but not for injection. Each patient was given three injections into one area of their tumour. The tumour was surgically removed after three or four days for microscopic examination of the injected region. It was clear that the injection was done not with the aim of producing any tumour regression. Three patients whose tumours could not be removed were given radiation therapy.[11] The patients were not informed that they were taking part in an experiment or that they were being denied an established treatment, as a result of which two of

them died. Under pressure from media and NGOs, the government was forced to take action on this incident, hence, ended up only suspending the research for six months. The ICMR conducted an inquiry into this trial, but the results were not made public. The John Hopkins University admitted that previous drug safety testing and the trial's consent forms had been inadequate and barred the involved scientist from serving as principal investigator on any future research involving human subjects.[12-13]

- The protocol of the drug Tacrolimus, submitted by Panacea Biotec and Cilostazol (Pletal), a product of Otsuka, were cleared by the DCGI (probably around 1999), based on incomplete and inadequate information on its adverse effects. Common serious side effects such as angina and myocardial infarction were not mentioned.[14]
- Phase III trials involving Cilansetron, a new molecule of Solvay Pharmaceuticals, not approved anywhere in the world were cleared by the DCGI (probably around 2000) even though only Phase II trials had been conducted abroad. At that time, trials of foreign drugs were permitted in India only at one step below the phase completed abroad.[15]
- The DCGI approved the Phase III trial of Pfizer's zoniporide (probably around 2000), while Phase II trials had not been completed in the USA and carcinogenic and reproductive studies on animals mandated by Indian law had not been completed.[16]
- In 2002, Dharmesh Vasava, a 22-year-old healthy 'volunteer' from Bharuch in Gujarat, died while participating in tests on citalopram, an antipsychotic drug sponsored by Mumbai-based Sun Pharmaceuticals. Dharmesh Vasava was among a number of daily wage workers who were given a psychiatric drug as part of a bioequivalence study sponsored by the Mumbai-based Sun Pharmaceuticals. He developed pneumonia and died. According to another participant of the same trial, the subjects were lured with money by agents working for the company. Incidentally, bioequivalence studies are conducted by drug exporters, to prove that their product is as effective as the approved branded version. They are not needed by the Indian regulatory authorities.[17]
- In 2002, the multinational company Novo Nordisk conducted multi-centre phase III clinical trials of a diabetes drug before receiving the results of animal studies. The study report found that the drug, ragaglitazar, caused urinary bladder tumours in rats — and this should have been known before the drug went for phase I trials, let alone phase II and phase III. Ragaglitazar was developed by Dr Reddy's Laboratories, Hyderabad, and licensed to Novo Nordisk which conducted the trials. The trials were conducted on 650 people from North America, 200 from Latin America, 100 from Australia / New Zealand, 800 from the European Union, and 200 from non EU Europe and 550 from Asia - including 130 people from eight centres in India. Half of these people received the experimental drug. Novo Nordisk defended its stand by stating that long-term carcinogenic study data were only required when filing a marketing application. The Indian scientists questioned the ethics of the phase III clinical trials of the drug Ragaglitazar, before it was fully tested on animals. The trials were suspended in July 2002 by the company after it discovered that a mouse (and several rats) treated with the drug had developed urinary bladder tumours.[18]
- Letrozole, which belongs to the group of aromatase inhibitors, was tested by Sun Pharmaceuticals to induce ovulation. The drug has been approved globally for the treatment of breast cancer in post-menopausal women, but it is not approved for any other use in any country. More than 400 women who had been trying in vain to conceive were enrolled in 2003 without their knowledge or consent to take part in clinical trials conducted at nine or more centres across India. Subjects were not informed they were participating in a trial and informed consent was not obtained. They then publicised the doctors' reports to other doctors as "research", using their network of medical representatives. A complaint on the letrozole case was filed in the Supreme Court by the

Delhi-based NGO Social Jurist. Novartis, who was not involved with the study but marketed letrozole under the brand name Femara, sent a clarification letter to all infertility experts in India to remind them of the approved indication.[19-20]

- In Gujarat, during a trial (probably in 2003) sponsored by Johnson & Johnson, acute mania psychiatric patients were taken off their existing medication and told that it was no longer available. They subsequently received Risperidone or a Placebo. This was controversial because the patients receiving a placebo could suffer unnecessary harm by being taken off their medication. One patient explained that he signed a form because the doctor required it, but had no idea that he was participating in a clinical trial. Johnson & Johnson denied the allegations and stated that consent had been obtained from every patient.[21]
- In 2003-2004, Bangalore-based Biocon and Hyderabad-based Shantha Biotechnic were accused of conducting Phase III trials of genetically engineered drugs (insulin for diabetes by Biocon and streptokinase for heart attacks by Shantha) without prior approval of both the DGCI and the Genetic Engineering Approval Committee (GEAC). Reports said they applied for and got DCGI permission but applied to the GEAC only after the trials started. Some people died in the Shantha trial, conducted on seriously ill patients. The important question involved in this drug trial is whether the patients could have given their informed consent to participate in the trial in an emergency since streptokinase is administered as an emergency life-saving treatment to stroke patients. In September 2004, litigation was filed against the companies by a Delhi-based NGO Adar Destitute and Old Age Home and the Supreme Court of India admitted the PIL.[22-23]
- Responding to a Right to Information (RTI) query filed by Uday Foundation for Congenital Defects and Rare Blood Groups, a NGO on clinical trials, the AIIMS administration admitted that out of the 4,142 babies enrolled for clinical trials by the institute's department of paediatrics, 49 had died since January 1, 2006.[24]

ICMR AND STATUTORY REGULATIONS OF CLINICAL RESEARCH IN INDIA

In 2005, the Government of India liberalised the permission for conducting clinical trials by multinational pharmaceutical companies in India by amending the Schedule Y of Drugs and Cosmetics Act. After the amendment, the earlier guarantee of 'phase lag' in phase-II and phase-III trials was removed. Previously, the phase-II trials in India were allowed only when phase-II had been completed abroad and phase-III had been started. Now phase-II trials in India have no such protection and can be held concurrently with trials overseas. Similarly, earlier, phase-III trials in India were allowed only when the drug was being marketed for general use abroad, not experimental. Now, these trials have also been made concurrent.[25]This amendment was brought to facilitate India to become part of global trials. But even then phase I has to be repeated for safety. It is claimed that it would be helpful to India to demand a reasonable price for the new drug if it takes part in the global trial. But it also establishes that India's regulatory mechanism is more and more becoming accommodative to the advantage of the multinationals and their Indian associates.

A *Clinical Trials Registry – India* (CTRI) was officially launched on July 20, 2007 by the National Institute of Medical Statistics (NIMS) of the Indian Council of Medical Research and is supported by the Department of Science and Technology (DST) and the World Health Organisation (WHO). The clinical trial registry of India strives to ensure the following goals:[26]

- Transparency and accountability of clinical research
- Internal validity of clinical trials
- To oversee the ethical conduct of clinical trials
- Reporting of results of clinical trials

The Indian Government made registration of all clinical trials conducted in the country mandatory from June 15, 2009. The Drug Controller of Government of India (DCGI) brought out a notification to this effect informing the researchers to register the clinical trial in ICMR Clinical Trial Registry before initiating the trial process.

The new registration norm became applicable to the clinical trials started after June 15, 2009.

Also, the research scholars engaged in clinical research involving the living persons are expected to adhere to the Ethical Guidelines for Biomedical Research on Human Participants, 2006[27] issued by the ICMR (Revised version of Ethical Guidelines for Biomedical Research on Human Subjects, 2000).

However, in spite of maintaining a registry for clinical trials and the establishment of Hospital ethical Committees subsequent to the introduction of ICMR guidelines, there is no effective and sustained centralised monitoring of the research projects for ethical violations. In India, medical practitioners are traditionally held in high esteem and blind faith of the patients to their physician is not uncommon. This fact coupled with the availability of vast illiterate and semiliterate population often tempt the men behind the clinical research involving human subjects to be complacent about adhering to the ethical guidelines.

Recently, the Government of India ordered suspension of clinical trials on tribal girl students in Andhra Pradesh and Gujarat, carried out by a non-governmental organisation, Path-International, for U.S-based pharmaceutical company MERCK for HPV (human papilloma virus) virus to prevent cervical cancer. The final report of the committee appointed by the Government of India to enquire into alleged irregularities in the conduct of studies using HPV vaccine found enough evidence to suggest that there were large-scale ethical violations during the conduct of "post-licensure observational study," in obtaining the consent of the young girls on whom the trial was conducted, or on issues related to safety, follow up, and reporting of adverse events.[28]

In August 2010, Health and Family Welfare Minister Ghulam Nabi Azad stated that the number of incidents involving clinical trials by foreign pharmaceutical companies is increasing.[29]

At present the Ethics Committee — whether at the national, State or institutional level can only suspend trials in case of violations. If any doctor is directly involved in the trial, his license can be cancelled. Law does not prescribe any punishment for this offence. The Board of Governors of the Medical Council of India has set up a working group on medical ethics reforms that would recommend strictures against medical malpractices. Similarly, the Union Health and Family Welfare Ministry is in the process of amending the Drugs and Cosmetics Act to make violation of medical ethics an offence punishable under law. This is likely to be done by adding a separate chapter on medical ethics in the Act, which would also prescribe punishment for such offences.[30]

REGULATING MEDICAL RESEARCH

Upsurge in the incidents involving clinical trials evidently points to the deficiency of the legal and ethical provisions that are currently available in India. Few years back, introduction of an Act (Biomedical Research on Human Subjects (Regulation and Protection) Bill, 2005) to regulate the medical research and clinical trials was discussed. However, subsequently no further progress has been made in this direction.

In general, the urgency of the medical ethos in relation to a particular issue is proportional to the interest taken by the public in that issue.[31]None of the issues concerning newer therapeutic measures, medical research and clinical trials except the organ transplantation have evoked a widespread public anxiety in India. Had there been public debates on medical research and clinical trials, it would have led to an energetic and prompt governmental response in the form of rules and regulations. Public apathy is mainly due to the ignorance of the ethical issues embroiled since many of the biomedical research projects and modern therapeutic techniques do not form a major part of the healthcare delivery in India. Nevertheless, public apathy breeds insecurity, which in turn leads to confusion and contradictory attitudes whenever these issues are flashed in the media. Therefore, any effort to regulate the ethical aspects in medical research and clinical practice should include educating the general public and getting the opinion of civil society.

Further, before introducing any of the international or

national ethical standards, the plural ethical concepts sanctified by religions permeating the Indian society should be taken into consideration. Instead of totally relying on the international codes on medical research such as World Medical Association's (WMA) Declaration of Helsinki[32] which is founded on the Judaeo-Christian principles and the experiences of the Second World War by the European and North American countries, the exact guidelines for medical research should include the socio-economic and socio-cultural aspects of India.

The Helsinki Declaration is an international code which is relatively detailed and which had tremendous beneficial effects, at least in Europe and North America. Nevertheless, it is difficult even in a limited field, to reach a reflective equilibrium, and the guidelines for medical research must be worked out on a national and not on an international level. Also a code of medical ethics must reflect among other things the organisation of the health service, the level of education of the population, and not to forget, the state of medical knowledge and technology. The moral code which was developed by doctors in ancient Greece cannot be expected to provide sufficient guidance to 21st century doctors, and even today medical ethics must of necessity change gradually, as new technological advances create new ethical problems.[33]

CONCLUSION

The need of the hour is transparency and accountability in conducting medical research and clinical trials. To achieve this, there should be a reappraisal of the ethical and legal policies concerning medical research and clinical trials which take into account the safety of the human volunteers and the establishment of an authority similar to that of the Human Tissue Authority of U.K. with adequate statutory powers to monitor and supervise the medical research and clinical trials and also to address the grievances of the affected volunteers.

ACKNOWLEDGEMENT

The author thanks Prof. (Dr.) Amrit K. Patnaik, Former Director, Institute of Forensic Medicine, Madras Medical College, Chennai for his critical comments and valuable suggestions in the preparation of this paper.

REFERENCES

1. MCI. Indian Medical Council (Professional conduct, Etiquette and Ethics) Regulations, 2002. Gazette of India dated 06.04.02, Chapter 7, section 7.22.
2. Padma TV. India's Drug Tests. *Nature* 2005; 436: 485.
3. News report. The Hindu (Chennai Edition). 2006 January 3 p. 12 Col 7 & 8.
4. Sandhya Srinivasan. Indian Guinea Pigs for Sale: Outsourcing Clinical Trials. Available at http://www.indiaresource.org/issues/globalization/2004/indianguineapigs.html (accessed on 30 May 2010).
5. Supra 2
6. Bhandare Namita. HIV, Red Alert. The New Indian Express (Chennai Edition) Express Magazine: 2000 May 21; p- 2.
7. Gulhati C M. Needed: closer scrutiny of clinical trials. Indian *J Med Ethics* 2004;12(1).Availableat http: www. issuesinmedicalethics. org/121ed004.html (accessed on 10 June 2010).
8. Mudur G. Indian study of women with cervical lesions called unethical. *BMJ* 1997;314: 1065.
9. Rao Mohan. Quinacrine Sterilisation Trials: A Scientific Scandal? *Economic and Political Weekly* 1998; 33: 692-695.
10. A.I. Democratic Women Assn. Vs. Union of India, (1998) 5 SCC 214.
11. Jayaraman KS. Johns Hopkins embroiled in fresh misconduct allegations. *Nature* ;412: 466.
12. Mudur G. John Hopkins admits scientist used Indian patients as guinea pigs. *BMJ* 2001; 323: 1204.
13. Mudur G. Indian doctors defend 'unethical' anticancer drug trial. *BMJ* 2001;323: 299.
14. Supra 7
15. Supra 7
16. Supra 7
17. Supra 7
18. Mudur G. Researchers question ethics of diabetes drug trial. *BMJ* 2002; 325: 353.
19. Supra 2
20. Supra 7
21. Patel V. Ethics of a placebo-controlled trial in severe mania. *Indian J Med Ethics* 2006; 3 (1): 11-2.

22. SOMO briefing paper on ethics in clinical trials - Examples of unethical trials. February 2008 (updated) Available at http://somo.nl/html/paginas/pdf/Examples_ of_ unethical_ trials_ nov_ 2006_NLpdf (accessed on 10 June 2010).

23. News Report. Available at http://www.indianexpress.com/news/clinicaltrial&error/255582/0 (accessed on 01 June 2010).

24. NewsReport.Availableat http://timesofindia.indiatimes.com/articleshow/3374492.cms (accessed on 01 June 2010).

25. Supra 3

26. World Health Organisation, International Clinical Trials Registry Platform (ICTRP), List of Registers. (Cited 2007 10 Aug) Available at: http://www.who.int/ictrp/network/list_registers/en/index.html (accessed 22 May 2010).

27. *http://www.rewi.unijena.de/rewimedia/Downloads/LS_Ruffert/Ethical_Codes/ICMR_Ethical +Guidelines +for +Biomedical +Research+on+Human+Participants.pdf* (accessed on 04 Aug 2010).

28. Dhar Aarti. Final HPV enquiry report finds evidence of ethical violations. The Hindu: 2011 May 09. Available at http://www.thehindu.com/health/policy-and-issues/article2004146.ece (accessed on 09 May 2011).

29. http://www.thehindu.com/todays-paper/tp-national/article545280.ece (accessed on 01 Aug 2010).

30. Supra 29

31. Mason JK, McCall Smith RA. Law and Medical Ethics. 4th edn. London: Butterworths, 1994; p-8.

32. Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the: 29th WMA General Assembly, Tokyo, Japan, October 1975, 35th WMA General Assembly, Venice, Italy, October 1983, 41st WMA General Assembly, Hong Kong, September 1989, 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996, 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, 53rd WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added), 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added), 59th WMA General Assembly, Seoul, October 2008.

33. Wulff Henrik R., Pedersen Stig Andur, Rosenberg Raben. Philosophy of Medicine. Oxford: Blackwell Scientific Publications, 1986; p-177.