D7 | THE ETHICAL COST OF OFFSHORING CLINICAL TRIALS

Clinical trials represent a crucial stage in the R&D process in new drug development. Between 60 and 70 per cent of the R&D budget is allocated to them, or $80–90 billion out of the $130 billion spent annually by the pharmaceutical industry worldwide (Clark 2009). Efficacy and safety of newly discovered compounds are tested on humans. Companies do this in three phases of trials, which serve as the basis for the marketing authorization of a drug (i.e. licensing). A fourth phase is sometimes undertaken for the purposes of complementary research following licensing.

Although the majority of clinical trials are conducted in the United States and Europe, there is a movement towards offshoring to low- and middle-income countries (LMICs) and countries in eastern Europe. The proportion of trials conducted in LMICs increased from 10 per cent in 1991 to 40 per cent in 2005. Between 2006 and 2010 it continued to increase, while the proportion of clinical trials conducted in western Europe and the United States fell from 55 to 38 per cent (Mroczkowski 2012). These figures are broad estimates as there are no international norms for reporting clinical trials. However, all current estimates indicate that offshoring is increasing, particularly for the most expensive Phase III trials (Thiers et al. 2008). Major new destinations for clinical trials include China, India, Brazil, Russia, Argentina, Ukraine and South Africa (Mroczkowski 2012).

Offshoring leads to a significant reduction in the costs of clinical trials (ibid.) – the overall cost in China is a third of that in the United States (Homedes and Ugalde 2012). Recruiting in LMICs can also reduce the length of a trial by up to six months on average (ibid.). Licence to market a drug early leads to enormous benefits for pharmaceutical companies – each additional day of marketing a drug in a monopoly situation (i.e. protected by a patent) can be worth in excess of a million dollars (IMS Health 2012).

However, this 'globalization of clinical trials' does not result in better access to treatment in LMICs and, further, entails major ethical violations. This chapter examines the major issues related to the ethics of offshoring clinical trials.

Offshoring: at what price?

A number of international ethical standards have been drawn up over the years. These include: the Declaration of Helsinki (DoH), adopted by the World

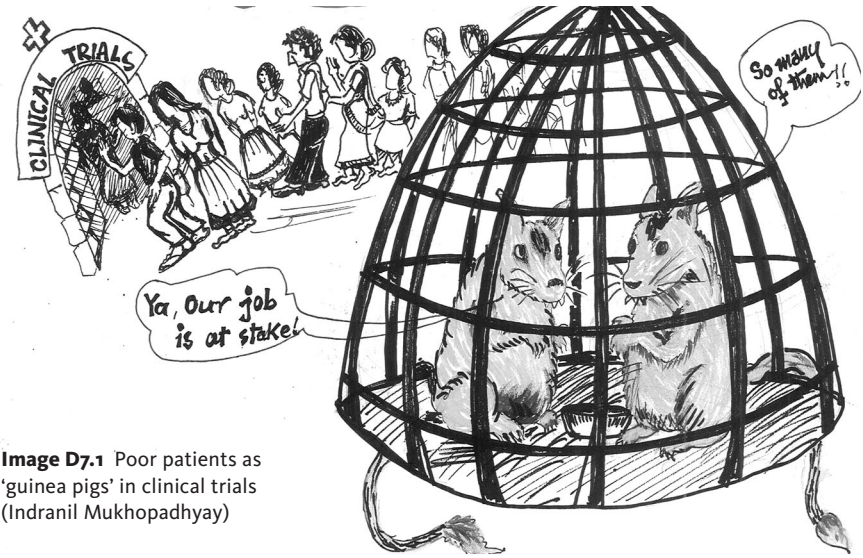

Image D7.1 Poor patients as 'guinea pigs' in clinical trials (Indranil Mukhopadhyay)

Medical Association in 1964 and subsequently amended several times (WMA n.d.); and the Guidelines on Good Clinical Practice (GCP) published in 1996 by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH 1996). The Council of Europe and the Council for International Organizations of Medical Sciences (CIOMS) have also developed ethical rules governing biomedical research on human subjects (Council of Europe 1997; CIOMS 2002). All these texts place the rights of trial subjects above those of science and society.

A major section of the people in LMICs and eastern Europe do not have access to social security and universal healthcare. Thus, often, taking part in a clinical trial represents for many the only hope of receiving some form of care (especially in the case of conditions which have few treatment options, and/or where medicines required are very expensive). The recruitment of vulnerable subjects is a clear ethical violation as trial subjects are presumed to be 'volunteers', and is tantamount to the exploitation of the vulnerability of local populations (Aultman 2013).

On the other hand, risks of ethical violations are higher as regulations are generally lax in LMICs and capacity to monitor compliance is less developed (Glickman et al. 2009). A number of recent investigations by the media and civil society organizations (CSOs) have reported serious deficiencies in the process of obtaining the informed consent of trial participants, the problematic use of placebos as proof of efficacy, failure to pay compensation in cases of serious adverse events, and access to treatment at the end of trials[1] (see Box D7.1). While pharmaceutical companies deny the existence of double standards with regard to protection, ethical violations have been confirmed by recent investigations conducted by the Berne Declaration in Argentina, Russia, India

and the Ukraine (Berne Declaration 2013d; Berne Declaration n.d.), and by the Wemos Foundation in South Africa and in Kenya (WEMOS n.d.). As trials often take place simultaneously in several different locations internationally, if one branch of a trial is tainted by ethical violations or lack of scientific reliability, the entire clinical trial is compromised (Lang and Siribaddana 2012).

Box D7.1 The most frequent ethical violations in LMICs

Exploitation of people's vulnerability Trial participants often agree to be part of trials because this could be the only option available to receive treatment, and/or there is a small monetary incentive. We need to question whether it is ethical to exploit the vulnerability of people in LMICs (because they are poor and because they may not have easy access to healthcare) in order to test drugs at the lowest possible cost. Research carried out within vulnerable populations is justified only if the trial sponsor (usually a pharmaceutical company) ensures that the treatment will be available and accessible to those volunteering (Declaration of Helsinki (2013), Arts 20 and 34). This is seldom the case as a new product, marketed after successful clinical trials, is usually covered by a patent and is prohibitively expensive for patients in LMICs.

Absence of free and informed consent Any person taking part in a trial must give his/her free and informed consent.[2] This requirement is often not met in LMICs, where trial subjects could be illiterate or semi-literate, and unaware of the risks involved. Sponsors of trials and contract research organizations (CROs) recruit doctors to in turn recruit trial subjects. Such doctors often exert inappropriate influence on patients to become part of clinical trials (Berne Declaration 2013d; Hirschler 2011). Trial subjects are frequently unaware that they are part of an experiment (Glickman et al. 2009; Homedes and Ugalde 2012).

Improper use of placebos The use of a placebo makes it easier to obtain clear results and allows the efficacy of a drug to be evaluated in a patient receiving no treatment. However, if drugs exist that have already been used and are known to be effective for the type of pathology being studied, and if the absence or interruption of treatment represents a risk, using a placebo constitutes an ethical violation (Declaration of Helsinki (2013), Art. 33).[3]

Absence of compensation norms in cases of serious adverse events When injury or death occurs in the context of clinical trials and is linked to the drug

being tested, financial compensation must be provided.[4] Frequently, any link between the injury caused and the drug being tested is not evaluated independently but by those responsible for the trial. Compensation is almost never offered when the cause of death or injury is uncertain, even when there are indications that it is trial related (Berne Declaration 2013d).

No access to treatment at the end of the trial A person who agrees to participate in a study should be guaranteed access to the treatment when the trial ends if the drug was found to be beneficial during the trial, or to any other treatment or appropriate benefit (Declaration of Helsinki (2013), Art. 34). In reality, treatment is often stopped at the end of the trial, a problem which is all the more acute in countries where access to medicines is limited (Berne Declaration 2013d; Berne Declaration n.d.; WEMOS n.d.).

Lack of transparency and accountability

Data from clinical trials is routinely used to obtain marketing authorization of drugs (Barlett and Steele 2011). However, it is impossible to know, solely on the basis of information in the public domain, upon which clinical trials the marketing authorization of an individual drug is based, nor the details of such decisions (Berne Declaration 2013c). Worse still, half of all clinical trials conducted in the world are never published, particularly those presenting unfavourable results (Goldacre 2012). In the case of those that are made public, unfavourable data is concealed or minimized in order to present the drug being tested in a better light (ibid.). This leads to drugs of dubious efficacy and/or safety being marketed (Gøtzsche 2011). Given that 80 per cent of all clinical trials are industry-sponsored (Clark 2009), there are virtually no avenues available for public scrutiny of decisions by regulatory agencies (Doshi et al. 2012). In 2010 the European Medicines Agency adopted a more open policy on access to clinical trial data. However, its full implementation has been regularly challenged by the pharmaceutical industry (Hai Europe 2013).

When drugs are tested on volunteers, the results should logically be made available to society and considered a public good (Gøtzsche 2011). In making their bodies available in the interests of science, participants in clinical trials are in fact taking a risk. However, pharmaceutical companies consider trial-related data as proprietary and attempt to keep it confidential (Hai Europe 2013).

Most trial sponsors, i.e. pharmaceutical companies, are located in western Europe and the United States. Regulatory agencies in these regions have a

duty to demand that the same ethical standards that are mandated in their home countries are followed when trials are offshored. The European Medicines Agency has recently recognized the need to strengthen ethical controls on clinical trials conducted abroad and require that relevant information in this regard be submitted along with marketing authorization applications in the EU. This is designed to ensure that trials in non-EU locations have been conducted in accordance with the same ethical standards as applied in the EU (European Medicines Agency 2012). However, drug regulatory agencies in other high-income countries (prominently in the United States) do not follow this practice (Berne Declaration 2013c).

Case studies: deficient regulatory environments

Russia and Ukraine[5] Russia and Ukraine are host to an increasing number of clinical trials – recruitment of subjects is reported to be up to twenty times faster than in western Europe. Both countries are attempting to align their regulatory framework with that in western Europe, but effective changes are yet to be implemented. Both countries are characterized by a public health system in decline and plagued by corruption.

Ukraine has seen a rapid rise in offshored clinical trials for several reasons. It is situated at the gateway to the European Union, and its population is genetically close to that of western Europe. Patients are easy to recruit, given the decay in Ukraine's public health system and a deeply entrenched economic crisis. There has been a sharp rise in the number of facilities authorized to conduct drug trials, from 175 in 2001 to more than 1,300 in 2009 (although many of the municipal hospitals involved do not have the necessary infrastructure). Conducting a drug trial costs half of what it costs in western Europe.

The sudden rise in trials in Ukraine has been accompanied by an increased risk of ethical violations. Regulations are weak and regulatory mechanisms are not fully operational. Ethics committees (which are supposed to ensure that ethical violations do not occur during the conduct of a trial) are plagued with issues of conflict of interest – doctors in charge of trials are members of such committees. The agency in the ministry of health, responsible for overseeing clinical trials, ceased functioning in mid-2012.

Patients are at the mercy of a medical profession which stands to benefit financially, by conducting trials. Doctors are known to deliberately mislead patients by recruiting them in what they term a 'humanitarian programme that provides treatment free of charge'. Informed consent norms are frequently violated, with reports that hospital employees sign consent forms on behalf of the recruited patients. Such systemic deficits in the regulatory system have led to instances of gross violation of ethics (see Box D7.2).

In 2010, Russia legislated for the establishment of decentralized ethics committees. The central agency in the ministry of health, overseeing clinical trials, is poorly staffed and overworked. The inspectors at Russia's medicines

Box D7.2 Orphans as guinea pigs

In March 2013, members of the Ukrainian parliament claimed that three clinical trials – conducted by international companies between 2011 and 2012 on orphan children – clearly violated national laws. One of these trials was conducted by the Swiss firm Actelion, on a drug called Tracleer (a treatment for pulmonary arterial hypertension). Informed consent procedures were waived in the case of many children, though the national law mandates that in the case of orphans, a representative of the state must provide consent. In addition, the trials were said to have taken place at facilities not in possession of the necessary accreditations. The Ukrainian authorities denied the accusations, while the companies concerned remained silent. An official inquiry was launched, but its results were not published.

agency are powerless, owing partly to a lack of resources but mostly because the law does not permit serious sanctions to be imposed on doctors involved in research or on clinical trial facilities. Local ethics committees (just as in Ukraine) are plagued with the problem of conflict of interest, with doctors in charge of trials also sitting on ethics committees.

Patients are also recruited through misleading advertisements on the internet, where they are enticed by being asked to join an 'observation programme'. Doctors, who use unethical means to recruit trial participants, benefit financially from the clinical trials (up to several times their basic salary). The trials are often poorly supervised and the trial results are, thus, unreliable.

A number of ethical violations were reported during the conduct of a trial by Novartis of Gilenya (used to treat multiple sclerosis). Consent was not sought from several patients before the start of the trial and no compensation was provided to those who experienced trial-related side effects. In fact, between 2007 and 2009 not one of the more than 70,000 patients insured against treatment-related side effects received compensation.

Argentina: deceptive appearances[6] Argentina is listed third among countries hosting the largest number of drug trials in South America, behind Brazil and Mexico. Although it is often cited as a reference for best practice, investigations report serious problems in the conduct of clinical trials. Argentina has no national law on regulation of drugs trials, its national ethics committees are only nominally independent, and its medicines agency (Anmat) appears to lack rigour when permitting clinical trials.

In the absence of a public regulatory system governing ethics, 'independent ethics committees' are responsible for ensuring that ethical norms are followed.

These committees are not accountable to the public and appear to 'rubber-stamp' applications, without carrying out any serious evaluation of proposals that they receive. Two 'independent ethics committees' approve 80 per cent of the trials carried out in Argentina. One of them, the FEFyM, audits the protocols of 85 per cent of the clinical trials conducted by Roche and Novartis.

The quality of the FEFyM's work was called into question by an analysis of thirty-six clinical trial protocols (thirty of which were approved) received in 2005 and 2006. The analysis identified nearly a hundred points in 85 per cent of the protocols examined that did not comply with the standards in force. (See Box D7.3 and Box D7.4, which describe two cases of ethics violation.)

Moreover, there is a total lack of transparency surrounding the decisions of the ethics committees. There is no national public registry of clinical trials. 'Ethics committee shopping' is rampant – a practice where trial sponsors (whose protocol is rejected by a particular ethics committee) serially submit their application to several committees, till one of them accepts it.

The only major case where a trial sponsor has been found guilty (and fined) for ethics violations involves GlaxoSmithKline's (GSK) trial of Synflorix (a vaccine against pneumonia, otitis and meningitis). The trial was conducted between 2007 and 2011 on 14,000 infants. Fourteen babies died during the trial period, causing outrage and triggering an inquiry. The inquiry found that parental consent was often obtained by alarming parents about the health of their baby and ignoring their refusal to have their baby vaccinated. GSK paid $350 to researchers for each baby recruited, an enormous sum for doctors whose monthly salary was about $1,200–1,400. Even though it was not possible to prove a clear link between the vaccine and the deaths, the Argentinian authorities imposed a fine on GSK, for ethical violations. The decision was upheld by the Argentinian justice system.

Box D7.3 Schizophrenia patients denied treatment

Placebo trials, where an effective treatment is withheld to test a new drug against patients who receive no treatment, are a violation of ethics. Merck, in a clinical trial begun in 2010 in a number of countries in the southern and eastern hemispheres, tested the use of an anti-psychotic drug, Saphris (Asenapine), on adolescents suffering from schizophrenia. In Argentina, the trial placed many trial participants in grave danger by withdrawing all their medication (antipsychotic, antidepressant, etc.), and replacing them with a placebo. Anmat finally suspended the trial after this was reported by an anonymous whistle-blower. However, no legal proceedings were initiated and a veil of secrecy surrounds the case.

Box D7.4 Off-label use of a drug during a clinical trial

In 2008, Roche tested the use of an immunosuppressant, ocrelizumab, in the treatment of lupus nephritis (an autoimmune disorder causing kidney disease). Conducted in several countries, the trial was finally suspended owing to serious side effects. In Argentina, in addition to ocrelizumab or the placebo, patients also received CellCept (mycophenolate mofetil), an immunosuppressant used to prevent rejection of transplants. CellCept is not authorized for the treatment of lupus in Argentina, although doctors prescribe it unofficially ('off-label'). The 'off-label' use of a drug is a clear violation of Argentinian law.

India: taking advantage of a dysfunctional regulatory regime[7] Before 2005, foreign companies were not allowed to conduct clinical trials in India unless they repeated the trial from a previous phase in the country (called 'phase lag'). This dissuaded foreign sponsors from conducting trials in the country. However, the regulatory system was changed in 2005, and the 'phase lag' provision was amended. This led to a steep rise in the number of clinical

Box D7.5 Victims of industrial genocide as guinea pigs

Perhaps the worst industrial 'genocide' in the world took place in the central Indian city of Bhopal in 1984. Over three thousand people were killed because of a poisonous gas leak (methyl isocyanide) from a chemicals plant run by Union Carbide (since acquired by the chemical giant Dow Chemicals). Over ten thousand more people have died since because of long-term effects. Victims were left scarred for life, and 300,000 people who live in the vicinity of the Union Carbide plant now live with varying degrees of disability.

In 2004, around ten firms, including Pfizer, GlaxoSmithKline and Astra Zeneca, conducted clinical trials in the hospital in Bhopal reserved for victims of the industrial genocide. The clinical trials were not of medicines that could treat the health problems that the gas victims are facing. The trials were called off in 2008 on the orders of the hospital's management. While the trials were under way, numerous irregularities had been recorded in procedures related to recruitment and consent. The conduct of trials on victims of a disaster, in a hospital where patients come to be treated free of charge, for drugs that are not even useful, is truly diabolical.

Box D7.6 India – pittance paid for deaths and serious adverse events

Adverse events during drug trials are seldom acknowledged, and weak regulatory systems rarely pick them up. Official data shows that, between 2005 and 2012, approximately 2,600 deaths were reported in 40,000 participants of clinical trials in India. More than half of those (1,317) were documented between 2010 and mid-2012.

Because of lax oversight it has not been possible to establish the cause of death in an overwhelming majority of cases. Evidence is available to link only twenty-two of these deaths to the drugs tested in 2010, and only sixteen in 2011. Families received compensation of around US$3,000–4,000 – a pittance in comparison to the millions earned from drug sales by companies. The situation is no better for those who suffered serious side effects, and patients have to go through a tedious process to prove a link between the adverse event and the drug tested.

The Indian lawmakers are now engaged in drafting fair compensation norms and procedures.

trials – from fewer than a hundred before 2005 to over a thousand within four years. While the floodgates were opened, regulatory structures did not keep pace with the virtual explosion of clinical trials in India. Trials in India are typically two to three times less expensive than in Europe, and there is a huge pool of potential trial subjects (driven, as in the case of Ukraine and Russia, by a poor public health system and widespread poverty).

In the wake of various scandals involving unethical clinical trials, the Supreme Court had to intervene in 2013 to virtually stop clinical trials (attempts are under way to persuade the court to modify its ban).

Many ethical violations have taken place since 2005, involving procedures related to recruitment, consent and compensation (see Boxes D7.5 and D7.6).

Trial participants in India are largely of rural origin (80 per cent) and tend to be poor. Most are recruited by their treating doctor, in whom they have blind confidence. In addition, there is the prospect of receiving treatment free of charge, treatment that would otherwise be unaffordable.

As in the other countries studied, there is an obvious conflict of interest when the doctor is at the same time the principal investigator of the trial and when he or she receives payment for every patient recruited. Ethics committees do little to combat such conflicts of interest.

Further, a large number of 'institutional' ethics committees in India are linked to health facilities that benefit financially from clinical trials. It is rare for these committees to verify consent procedures: they barely check whether the correct form exists. Such violations occur even though Indian law now

says that any deficiency in procedure is equivalent to a refusal of consent (including when the person responsible does not read the form, when it is not understood by the participant, or when any undue influence is exerted on the patient to sign).

Conclusion

The case studies reflect a common trend in some of the preferred destinations of offshored clinical trials. All the countries studied have weak regulatory systems and a vulnerable population constitutes a pliant pool of clinical trial subjects. Violation of ethics is rampant and increasing. The case studies collected by the Berne Declaration[8] are the proverbial tip of the iceberg. The gross rights and ethical violations are taking place owing to a nexus between multinational pharmaceutical companies, domestic regulatory agencies, pliant doctors leading clinical trials and regulatory agencies in the North. The continuance of the trend described in the chapter has several implications. Poor and vulnerable patients are dying because of unethical and poorly designed clinical trials. The data generated by these clinical trials is often unreliable, but is being used to get marketing approval in countries across the world, thereby jeopardizing the health of patients in both the North and the South. It is imperative that the health community takes cognizance of the very serious challenges to public health that are posed by the offshoring of clinical trials.

Notes

1 Among the NGOs, in particular, are Dutch-based Wemos Foundation, www.wemos.nl, and SOMO, www.somo.nl, as well as Swiss-based Berne Declaration, www.evb.ch/en.

2 This requirement is made explicit in all ethical and good clinical practice guidelines mentioned previously.

3 For some concrete cases, see the recent investigations carried out by Wemos and Berne Declaration (Berne Declaration 2013d; Berne Declaration n.d.; WEMOS n.d.).

4 This requirement is made explicit in all ethical and good clinical practice guidelines mentioned previously.

5 Based on Berne Declaration (2013e, 2013b).

6 Based on Berne Declaration (2013a).

7 Based on Berne Declaration and Sama (2013).

8 The case studies presented in this chapter were collected by Berne Declaration as part of a research project.

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