Clinical trials in developing countries

Unethical practice or a product of necessity?

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Kano, Nigeria, early 1996.
An outbreak of cerebral spinal meningitis kills 15 000. Médecins sans Frontières (MSF, Doctors without Borders) are the first NGO to arrive and work around the clock to treat the over 115 000 infected. The epidemic constitutes a severe public health crisis to the Nigerian government.
A few weeks after the onset of the outbreak, Pfizer, the largest pharmaceutical company in the world, sends employees to Nigeria to conduct a clinical trial with the newly developed antibiotic trovafloxacin (Trovan®). Pfizer aims *to bring Nigeria a life saving, innovative, less painful and cost effective form of antibiotic that could be used effectively to treat epidemic meningococcal meningitis, including in children*. Almost 200 children are included in the study. Half of them receive trovafloxacin, the others are treated with the 'best practice medication', ceftriaxon.
At least eleven of the children in the study group die, many others develop mental or physical disorders during or after the treatment.
In 2001, the Nigerian federal government starts a lawsuit against Pfizer, claiming $7 billion for the victims and their relatives. The government declares that the authorities did not approve this clinical trial and the patients and their families did not give informed consent before treatment. Pfizer denies all accuses. The court case proceeds until today.

The Trovan® case has become famous as the illustration of negative consequences of clinical testing in developing countries. Although exact numbers are unknown, it is clear that an increasing part of clinical trials by pharmaceutical companies is conducted in low-income countries. Large companies such as GlaxoSmithKline, Wyeth and Merck report to perform 29-70% of their trials in 'non traditional research areas'; scientists estimate this number to be 40% on average for all pharmaceutical trials.

Nigeria

144 720 00
inhabitants

$/
1 410
income per year

♂ 48yrs ♀ 49yrs
life expectancy

$
3.9%
of GDP for health

/
0.28
doctors/1000 people

Reasons for testing in developing countries

The main reason for the companies to choose new locations for their trials is that costs are 10-50% lower than in traditional research areas. Furthermore, less strict (or lack of) legislation helps research protocols to be easier and earlier accepted. If preparatory procedures take less time, more years for profit making within the patent period remain. Another pull factor is the fact that volunteers for trials are more easily found. This is partly because populations are larger and thus more patients with a certain disease are available. Yet, in many cases participation in a trial is the only chance for a patient to receive any treatment at all, and often the (financial) incentives form an important encouragement. A medical argument for testing in developing countries is that the outcome of research has a higher validity if the subjects of study have received less medication (similar to the one studied) before participating in the trial. Finally, there are high economical benefits for hosting governments, an important incentive to relocate trial venues to their countries. For example, India receives an estimated income of $1.7 billion in 2010, when 2 million Indians are estimated to take part in clinical trials.

Informed consent?

Non Governmental Organizations (NGOs) critically follow this transition to trial locations in developing countries. Their main argument against most of the clinical trials is that they are unethical, for they do not comply with the Helsinki Declaration, a document adopted by the World Medical Association stating ethical principles regarding human trials (see box on page 9).

One of the concerns is the issue of informed consent. Due to analphabetism, language difficulties and a hierarchic doctor-patient relationship, informed consent is complex to obtain. Furthermore, poverty and dependency on the offered treatment make informed consent a subjective matter of discussion and question the voluntarism of the participants. Moreover, the Helsinki Declaration states that after the trial ends, the participants should be assured access to the best proven therapy identified by the study. This is often not the case in developing countries and was true for the meningitis outbreak in Kano, Nigeria, too.

Social and public health aspects of the debate include the shortages of educated health personnel in developing countries. Working for

the trials means a large burden on the already heavy workloads of doctors and nurses. On a larger scale, it is often argued that most drugs on trial are developed to combat welfare diseases (as this entails greater profit) and to a lesser extent to combat tropical diseases that local residents mostly suffer from.

Responsibility

A large responsibility is with the local medical ethical committees that approve the research protocols. Assessment of these local committees has shown that 25% of the clinical trials in developing countries has had no ethical evaluation at all and that less than a quarter of the ethical committees follow the existing guidelines when reviewing a proposal. If guidelines are in place, there is often a lack of legislation to support them.

Large differences between the committees make it easy for pharmaceutical companies to choose the lenient ones to send their protocols to. They should promote responsible behaviour among themselves to comply with international guidelines and regulations.

NGOs urge stronger stakeholders to take responsibility in this matter. The European Union and the US Food and Drug Administration (FDA), as drug approving institutions, should help local governments to comply with the Helsinki Declaration. Strict control of medical ethical committees will

force them to review their protocols critically. Development support (e.g. training of health care workers) could also strengthen local health care systems. Another recent development is an (online) database of clinical trials that are being conducted worldwide. This ensures an easier method of control for NGOs and Western governments, as well as making sure no double research is conducted.

Because of the lower costs, lack of ethical evaluation, guidelines and supporting legislation, it remains attractive for pharmaceutical companies to conduct clinical trials in developing countries. Informed consent procedures that are adhered to are inadequate. Also, patients are often denied the best available care after trial completion. Responsibility for changing this situation is shared by local ethical committees, pharmaceutical companies, NGOs, the EU and the FDA.

Further reading

- Pfizer: Trovan fact sheet http://www.pfizer.com/files/news/trovan_fact_sheet_final.pdf
- SOMO: Ethics for Drug Testing in Low and Middle-income Countries
- SOMO: Examples of unethical testing
- Wemos: "A bitter pill"
- WMA: Helsinki Declaration
- Nuffield council of bioethics: The ethics of research related to health care in developing countries (2002)

The Helsinki Declaration

The World Medical Association (WMA) compiled a document with ethical principles regarding clinical trials on human subjects. The Helsinki Declaration is regarded as the basis of human research ethics for all doctors, researchers and other health care workers worldwide.

A summary of relevant paragraphs is listed below.

2. It is the duty of the physician to promote and safeguard the health of the people.
5. The well-being of the human subject should take precedence over the interests of science.
8. Vulnerable research populations require special protection.
13. The protocol for a clinical trial should be reviewed by an independent ethical review committee.
20. Participation in a trial must be voluntary and participants must be informed.
29. A new method should be tested against the best current method.
30. At the conclusion of the study, all trial participants should be assured access to the best proven therapy identified by the study.

In developing countries, it is often difficult if not impossible to comply with all guidelines. Therefore, alternatives have been proposed. For example, the Nuffield Council of Bioethics, London, has recommended to test against the best available treatment for a disease in that national public health system.