

Clinical trials in developing countries

Introduction

This activity looks at some of the issues raised by conducting clinical trials in developing countries. It allows students to review some of the ethical principles involved and to discuss the difficulties.

The activity

This activity is intended to be used in small group or whole class discussion, with the text and questions stimulating the ideas.

This is a difficult topic to handle because of the political context. It is however an important one as more and more trials are being conducted in developing countries. Very polarised views exist, both in pressure groups and in the pharmaceutical industry. The activity is intended to provoke discussion and raise awareness, not provide correct answers. Students may need some help to imagine how conditions might be different in India.

Part 2

Suggested answers

1. What are the advantages to the Indian patients taking part in the trial?
Free health care, 50% chance of getting a drug that might combat the HIV
2. Why might patients with the same health problems in Europe be less willing to volunteer for a trial?
They would already receive healthcare and HIV treatment and would therefore have less to gain as well as more to lose from possible side effects. In other words their personal cost benefit balance would be different.
3. What are the advantages to the pharmaceutical company of doing the trial in India?
Access to more patients. Because the patients are not already receiving an HIV drug they do not have the expense of providing the standard treatment to the control group. Some would also argue, that there is less regulation controlling what they do.

How Science Works

Hc Society exercises controls on the development and application of science and technology. Official regulations apply to many kinds of scientific activity (e.g. levels of emission of radioactive materials or other hazardous chemicals; use of human tissue in research; use of animals in research, etc.). Regulatory bodies are set up to implement these controls.

Hj Some decisions involve balancing the rights of certain individuals and groups against those of others.

Hk A utilitarian approach is to argue that the right decision or choice is the one that leads to the greatest good for the largest number. It can also be argued, however, that some actions are wrong, even if they lead to good outcomes.

Hi Scientists have an individual responsibility to ensure that their practice is ethical. This may be detailed in a professional ethical code. Such codes may also form the basis of regulatory decision by ethics committees. National or international regulations that apply to scientific activity may have an ethical basis.

Resources

The World Medical Association produced the Declaration of Helsinki and modified it in 2000. This sets out the standards to be applied to any research on human subjects.
<http://www.wma.net/e/policy/b3.htm>

There was discussion of this in the BMJ in 2004
<http://www.bmj.com/cgi/content/extract/329/7471/876-a>

4. What is the alternative to the use of a placebo as a control?
In a UK trial it would be considered unethical to use a placebo when there was an existing standard treatment. Whether this also applies in a country where the standard treatment has not in fact been available has been the subject of much debate and is unresolved.
5. How is the trial proposing to monitor the risk of serious side effects?
There is no evidence that they are, although the information provided here may not be complete
6. There are several reasons why an ethics committee in Europe would not approve this trial without insisting on some changes. Describe **two** changes you think such a committee would demand.
- *The informed consent is perhaps the weakest feature. There is no guarantee that the patients are literate or even speak the language used. An ethics committee would demand a verbal explanation with opportunities to ask questions and that this was witnessed by someone without a vested interest.*
 - *The selection of subjects seems rather haphazard with incentives to doctors to enrol as many as possible perhaps resulting in them putting pressure on patients to join.*
 - *The issue of availability of the drug when the trial ends is another much debated issue and many would consider this trial unethical on these grounds. The Helsinki Declaration says that "Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research". It also says "At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study".
<http://www.wma.net/e/policy/b3.htm>*
 - *Care for those who suffer harmful side effects should be an essential part of any trial, even to the point of stopping the whole trial if these are serious.*
7. Do you think the same ethical standards should be applied to trials in India as those applied in Europe?
One's opinion will partly depends on a utilitarian versus a rights based approach to ethics. Experts have different opinions on this issue. Clinical trials are never designed to benefit the subjects, they are for the greater good. However the rights of participants must be protected as far as is compatible with the scientific aims.
- Most people believe that informed consent is essential. However they differ on whether the normal lack of availability of the standard treatment means that it is acceptable to use a placebo, as this is the standard in the local area. The lack of care when the trial ends seems very heartless in a situation such as that described. Whilst the trial continues the subjects on the treatment arm may well benefit, but they are also taking a risk. The drug may have serious side effects. Should they be compensated for this risk?*
8. Trials with designs not dissimilar to the invented description here have taken place in India. Do you think this is acceptable?
Most relevant points have been made above. This is where students can express their own opinion.
9. Is it the responsibility of the pharmaceutical company or the Indian government to ensure that trials are ethically responsible?
Most people believe that businesses have to be regulated to avoid them putting profits before care. Some believe that this can be done by a voluntary professional code, others that the interests of the people have to be protected by legally enforceable rules. This would cost the Indian government a lot to enforce.

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Clinical trials in developing countries

Clinical trials are an essential part of the development of a new drug. They are often one of the most expensive parts. An increasing proportion of drug trials are now taking place in developing countries. It is alleged that some of them have not been conducted to the highest standards. This does not mean that all drug trials in developing countries are unethical. The activity is intended to help you think about some of the issues involved.

Some headlines about drug trials in developing countries

Unproven meningitis therapy 'killed 11 children'

A malaria vaccine has been found to be safe and effective, early results of an African trial suggest.

DRUG COMPANY SUED FOR £3.5 BN OVER ILLEGAL DRUG TRIALS

Part 1

The following quote is taken from the report Global Health and the Pharmaceutical Industry published by the ABPI. <http://www.abpi.org.uk/>

Conducting vital research in resource-poor settings represents practical difficulties, and sound ethical frameworks are vital to safeguard possible exploitation of research participants. Informed consent is the cornerstone of ethical clinical research and this becomes even more crucial in healthcare settings where participation in research might seem the only route to quality treatment.

Some commentators have suggested that, for medicines designed for developing countries, a less rigorous and therefore cheaper level of regulation could be applied and possibly get medicines to patients more quickly and at lower cost. The pharmaceutical industry rejects this view as well-intentioned but dangerous – the highest standards must be maintained for all patients. In fact, pre-launch testing is even more important in developing countries because they do not have the failsafe systems of side-effect monitoring that are a key part of developed healthcare systems.

The following quotes are taken from an article on the BBC web site.

Six years ago, an experimental drug from the US called M4N was injected into cancer patients in India without being properly tested on animals first. Later it was discovered that several patients had not known they were part of a clinical trial.

Giving informed consent to be part of an experiment is the golden rule of all clinical trials which goes all the way back to the Nuremberg Code.

But one doctor at the prestigious Lilavati hospital in Mumbai, Dr Shashank Joshi, says the idea of all patients giving informed consent in India is "a myth according to me... because I do not think it's truly informed in the language the patient understands.

"I was just told that the drugs were American. They used to give me the tablets and I used to eat them," says Parshottam Parmar.

"We just sign because I believe the doctor takes the signature to help us. That's why I sign it." He says he had no idea that he was part of a clinical trial.

"I didn't know that experiments were being carried out on me. I was told that the old drugs were discontinued and were no longer available in the pharmacies.

"I don't know a lot about all these things. I am poor and I live in a small hut and I don't understand many things. The doctors are intelligent. They write the drugs for me so I have to take them accordingly."

1. Whose interests are being served by the lax regulations on clinical trials described by the BBC?
2. How does it happen that the excellent principles expressed by the ABPI are not always carried out in practice?
3. Explain how the normal guidelines for clinical trials seek to balance utilitarian ethics with respect for individual rights.

Part 2

This looks in more detail at the design of a hypothetical trial.

Company X has a new HIV drug that looked promising in stage II trials and now requires a Stage III clinical trial.

They plan the trial as follows:

- It will be carried out in India as there are more people who are HIV positive than in the European country where X is based and where the stage II trials were done. Very few people in the part of India chosen have any access at all to HIV drugs because they are too expensive.
- Local doctors will be asked to recruit volunteers, and be paid for doing so.
- Whilst on the trial the drugs will be free to the volunteers.
- The local doctors will investigate the health status of the volunteers and select 3000 subjects for the trial.
- All those chosen will have to sign a consent form. This will be a translation into one of the local languages, with minor changes, of the form used in the stage II trial.
- The patients will be assigned at random to the treatment or control group. The control group will receive a placebo. Neither patient nor doctor will know who is receiving drug or placebo.

- The patients in both groups will get regular medical check ups and free treatment for any infections whilst the trial lasts. This will encourage them not to drop out.
- At the end of the trial, even if the drugs work, the company does not plan to continue to make them available to the subjects.

Discuss the questions below in a small group and then share ideas with the class and your teacher to clarify points on which you are uncertain.

1. What are the advantages to the Indian patients taking part in the trial?
2. Why might patients with the same health problems in Europe be less willing to volunteer for a trial?
3. What are the advantages to the pharmaceutical company of doing the trial in India?
4. What is the alternative to the use of a placebo as a control?
5. How is the trial proposing to monitor the risk of serious side effects?
6. There are several reasons why an ethics committee in Europe would not approve this trial without insisting on some changes. Describe **two** changes you think such a committee would demand.
7. Do you think the same ethical standards should be applied to trials in India as those applied in Europe?
8. Trials with designs not dissimilar to the invented description here have taken place in India. Do you think this is acceptable?
9. Is it the responsibility of the pharmaceutical company or the Indian government to ensure that trials are ethically responsible?