Journal of medical ethics, 1978, 4, 81–83

Testing new drugs—the human volunteer

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Professor Duncan Vere lays before us the idealised guidelines used for recruiting volunteers on which to try and test new medicines. He points out that if these were followed rigidly, few, if any volunteers would be found for this vital work. Inducements are used, but the size of these determines whether society deems it right or wrong. However, the aim is to help and advise volunteers of the need for such tests and the risks involved and therefore the information leaflet reprinted as part of the article indicates how the drug testers are attempting to encourage volunteers in as ethical a way as possible. To abandon human tests with new drugs may be unethical. A balance is sought.

Experience of trying to recruit volunteers, both normals and patients, for trials of potential new drugs has convinced me that the obstacles to ethical success are insuperable in some ways.

The idealised facts are these:

1) It must be accepted that new drugs are needed to fight disease (the 'medical mandate' for new drug development).

2) It must also be accepted that, given proper conservation, 'recycling' and the like, drug development is a proper use of the natural world (the 'dominion over the earth' mandate, if you so wish to call it).

3) The limiting step, the 'scarce resource', in this work is the human resource – volunteers, clinical trialists, expertise.

4) There are very small risks in single dose drug studies. There are much greater risks in prolonged courses of treatment with new drugs. Again, the determining step is often the human, not the pre-human (animal) tests.

5) Risks are taken by everyone. It can be altruistic to undergo risk on behalf of someone else provided the nature of the risk is known and understood, and it is undertaken with due consideration for self and others and not in a spirit of foolish recklessness.

6) No inducements should be offered to persuade people to undergo risks in drug testing.

7) No relevant information about risks should be withheld from volunteers before they make their decisions.

8) The supervision of the tests should be in the best possible scientific and clinical hands.

These ideas are embodied in the Tokyo amendments of the Helsinki agreement on human research by the World Medical Association (1976).

But what actually happens?

If the guidelines just mentioned are followed literally, one gets few if any volunteers. Many people take the attitude that they want drugs if and when they are ill, they want them pure, safe, effective and fully tested – but not tested on themselves.

There are five major obstacles to dealing with risks. First, most members of the general public have no means to understand them. They mistake them for odds or luck, or they insist on thrusting the decision upon the doctor who explains it to them. Second, whatever the Tokyo–Helsinki rules may or may not say, in paragraphs 7 and 9, in *this* context one cannot anticipate the risk or explain it to the volunteer. The experiments are being done to *discover* the risks. Their merit lies not in any anterior understanding of risk, but in the fact that they are the best available way to develop a posterior knowledge of risk in the safest possible surroundings. Drug safety is not absolute, nor is it understood prior to making human tests. It is minimised drug hazard.

Third, risks are presented statistically, as a proportion of a population that may be at risk from damage. But the risk to the individual is quantal, not quantitative. He may, or may not sustain severe injury; though the risk is very small the injury might be very great, even were he the only one of a million exposed persons to experience it.

Fourth, risk is relative, relative to the risk of a similar injury occurring in those never exposed to the drug under test.[1] The fifth point is that attitudes to risk are hopelessly biased. People will react vigorously against the least scintilla of evidence of drug risk, but will drink, smoke and drive themselves to death in large numbers, whilst paying huge sums for the privilege. This is partly because drugs have been and are expected to be, so safe. It is also because people fear unknown risks far more than they fear known risks. It is also because people cannot accept risks put upon them unknowingly by others, though they are prepared to accept great risks foolishly for themselves.

Inducements to volunteer

The inducement argument is a practical nonsense. If no payment or present is offered, very few people value the well being of others sufficiently to volunteer. If large payments, enough to 'be an inducement', are offered people would volunteer and the inducement would be wrong. But, if *small* payments or presents are offered, just enough to compensate for inconvenience suffered, not large enough to 'be an inducement', these are right in most peoples' eyes. If they are offered, people do volunteer. Why do they volunteer? Though there can be no proof of this contention, and it can only remain a personal suspicion, I do not believe they volunteer because their inconvenience is compensated. I believe that our society is so conditioned to payment for every service rendered that any gift may be a token which elicits a favourable response whether it is commensurate with the personal loss incurred or not. In short, people may respond to the symbolic value of any token of appreciation as a purely conditioned response regardless of its moral worth, whether relative or absolute. If that were so, then the idealised ethical considerations already discussed are reduced to nonsense. For it is not what people might, or should do, but what they do that matters in real life ethical decisions. To be really provocative, I am suggesting that the gifts may not induce but seduce the prospective recipients.

It is sad that the gap between perceived benefit to the sick, and the social obligation to volunteer for trials, is so great in time and in distance. It would be easier if people could see and appreciate more of how drugs are used and their benefits. There is also much bias in deciding these things. One amusing example was to see some local shop stewards (not among the greatest natural friends of the drug industry), so strongly recruiting volunteers as an act of social benevolence that they had to be restrained, whilst a group of senior academics sent back the dusty message that it was not part of their function to support the profits of the drug industry.

How the drug testers can help the volunteer

What then should we do, those of us with experience and, hopefully, some understanding of the risks involved? First it seems important never to deceive ourselves, and never knowingly or carelessly to deceive potential volunteers. Nor would it be right, even if there are problems, to abandon attempts to test drugs in the best possible ways.

In an attempt to improve the information offered to volunteers, and accepting that they will not always be the most informed or intelligent of men, we have drawn up a little leaflet for them, and evolved a 'patient's, or subject's friend' procedure to help them. The text follows and explains both the advice and the procedure offered.

HELPING TO TEST NEW MEDICINES

Better remedies are needed for people who are ill and one day that may include any one of us. Before a new drug can be given to patients it must be thoroughly tested, first in animals, and later in healthy people. People are grateful for effective safe and pure medicines, but seldom see how they can help with their development.

This leaflet explains how this can be done, and invites your help.

WHO CAN BE THE SUBJECTS FOR TESTS OF NEW DRUGS?

We believe that it is morally wrong to induce people to volunteer for these tests by persuasion or by any form of personal or financial pressure. This means that we must rely on volunteers to come forward of their own accord. If they do not, the drugs will probably be tested in countries where standards and facilities are not so good. The authorities in this country may then not be able to judge the validity of the results and might be misled. We are convinced that, in general, drugs which are going to be used here should be tested here. Usually any healthy adult up to the age of 65 can volunteer but occasionally tests are done on more restricted groups of subjects.

WHAT ARE THE RISKS TO THE SUBJECTS?

In centres where there are experts in drug testing ('clinical pharmacologists'), these risks are exceedingly small. Most of these people have tested drugs for many years without any trouble. It must be clearly said that there will always be some possible risk in taking *any* drug, and this is bound to be greater when the drug is new. However, it must be remembered that the tests start with a tiny dose and work up towards the dose needed for treatment using a large number of volunteers and usually each volunteer takes only one dose. This is much safer than taking a whole course of tablets at full dose, as a sick patient might need to do. Also it is true that volunteers are watched far more closely for all possible effects than would be practical even for hospital patients. The risk of such tests must be less than that of crossing the road.

WHO ARE THE VOLUNTEERS AT PRESENT?

They cannot be patients, except in certain severe diseases like cancers for which it is impossible to give the drugs to normal volunteers. The reasons for this are obvious – it would not be justifiable to inflict the worry and inconvenience of drug tests on patients. Adding to their problems would be like taking a penny from a poor man's hat. It is in general better for the strong to help the weak.

At present, the volunteers are mainly members of drug firms, doctors and University staff. Because there are so few of them, some are taking many new drugs in their lifetime, so exposing themselves to higher risks – like someone who spends his

whole life repeatedly crossing the road. And there are scientific reasons why they should not do this. Do you think it is fair to expect them to go on doing so in the interests of the community at large?

HOW CAN YOU BE SURE YOU WILL NOT BE EXPLOITED?

Almost all new drugs are developed by the pharmaceutical industry. Most drug firms have high ethical standards – and welcome the co-operation of clinical pharmacologists who are employed by the hospital service or by universities. They are independent, and will not test any drug which they think is not worth developing. They scrutinise all the animal test results and scientific information available about a drug before they agree to take it further. So the best safeguard is to contribute to tests conducted by these independent people. There may be a few unscrupulous manufacturers, but they tend to work only with those who are dependent on them, or lack the expertise to notice these problems.

WHAT WOULD BE THE INCONVENIENCE FOR YOU?

For some drugs this is trivial, perhaps a blood or urine test. For others, one or two working days in the laboratory are needed because a continuous watch can then be kept, for example, on the electrical activity of the heart. Usually, the subject of an experiment can read a book while it is going on. The only tests which may cause any pain are blood samples, but the discomfort is no more than that of giving blood for transfusions. You will get all your expenses back, including loss of earnings, and a small payment may be made to cover any inconvenience or loss of free time. No payments are made which could induce people to volunteer. Your general practitioner is told about the proposed tests and asked if he has any objection. If you agree, your industrial medical officer will also be contacted in advance. You will be told the result of the tests, and get the benefit of a full medical examination as part of the procedure.

WHAT IS 'INFORMED CONSENT'?

It has been accepted that no one should be asked to volunteer for drug tests unless he or she has been told what is to be done and the possible risks and effects. It is sometimes difficult to explain these facts to volunteers who are not scientists. We get over the problem by discussing the experiment with possible volunteers in the presence of a third party, the 'subjects' friend'. This is someone who is highly qualified to judge but who is not a member of our department and who is asked to put himself entirely on the subjects' side. This person is asked to ensure, by asking questions, that an adequate explanation has been given and understood.

HOW CAN I BE SURE THE TESTS ARE REALLY NECESSARY, AND NOT MADE JUST FOR SCIENTIFIC INTEREST?

The tests proposed have to pass the scrutiny of one or even two independent ethical committees. So the decision to go ahead is not made solely by those who have a direct interest in the tests. Also, the tests are generally too expensive to use them purely to settle some point of scientific interest. But the basic safeguard can only be the integrity of the investigator.

Many people take the attitude that when they become ill they want medicines which are pure, effective and safe – but they are unwilling for new drugs to be tested on themselves. We know that not everyone will be so selfish, and that some, like blood donors, will be public spirited enough to meet a human need, if only because they may one day have to take medicinal drugs themselves.

Reference

[1] Vere, D W (1976). Risks of everyday life – Drugs. *Proceedings of the Royal Society of Medicine*, **69**, 105–107.