

Human Experiments

By Duncan Vere

Ways to help sick people have rarely been found by accident, by inspired guesses or by hit-or-miss trials. Scientific testing with human volunteers is a key stage in work to find new or better treatments, or discover how illnesses work. For this research to be ethical, it must be conducted in a way that respects each human participant. The international codes that regulate medical research either draw from, or reflect, a biblical understanding of the value and intrinsic dignity of human life.

An enthusiastic doctor experiments on homeless people in New York. Many of the people die, but he continues, hoping to finding a cure for people with damaged nerves. It's the foundation of the plot of *Extreme Measures* the film starring Hugh Grant and Gene Hackman.

At the end of the film we are left asking questions about the ethical use of humans in research, and what to do with data that are derived from unethical research. The individual situation may have been fictional, but the issues are very real.

Contemporary medicine tries to understand how a healthy human body works and what can go wrong. It then looks for ways of restoring good health or helping the person live with the disease or disability.

To gain this understanding, doctors and scientists need to observe what naturally happens when a person is healthy and see how this changes when they are ill.

While the results of this observation-based research give valuable insights, the data will always be imprecise. To get a clearer idea of what is happening in health, disease or therapy, doctors need to set up an experiment.

In experiment-based research the researchers attempt to control

the situation so that they can pin-point the effect of a particular intervention. They ask a carefully framed question and then make observations that reveal the answer.

The advantage of experiment-based research is that the results are often clearer to understand. In controlling the situation, however, the experimenters may alter it so that the results are less applicable to real life.

Human experiments must be performed ethically. The work should be governed by safeguards that establish high levels of safety and create a system of honesty between the doctors and the volunteers.

These demanding standards reflect a philosophy of the high value of individual human life that has its roots in biblical thought.

What is an Experiment?

To some extent all medicine is an experiment. A doctor sees a patient, makes a diagnosis and then recommends some course of treatment. The doctor and patient

then wait to see what happens. They can never be certain that the treatment will have the desired effect because life processes are so varied.

Consequently, the reasons why people become ill and the effects of treatment can never be predicted with certainty. All a doctor can do is predict the likelihood of success.

There are, however, two important differences between ordinary therapy and experiment. First, routinely used therapies should have a large amount of experimental evidence to show that they work, while experimental treatments will always have less certain outcomes.

Secondly, therapy given in an experiment is more rigorously defined, controlled and observed than medical treatment in general. It is easy to assume that the uncertainty in the outcome of an experiment suggests negligence on the part of the medical team, however in good experiments this is more than compensated for by the increased level of scrutiny.

It is worth noting that medical experiments can be divided into two broad categories. Therapeutic research aims to find ways of combating disease or disability, and non-therapeutic research tries to increase our ability to diagnose

disease, or understand how the disease is altering the body's normal function.

Some critics say that biological systems are far too variable for experiments to yield meaningful results. They claim that you can only perform a good experiment in the 'hard' sciences like physics or chemistry. This problem is, however, overcome by performing the same procedure on a large group of people and pooling the data.

participants

No one should be tricked, deceived or imposed upon to take part in an experiment. They should be 'volunteers', or knowing and willing 'participants'. They should not be offered inducements like being moved up a waiting list, or payment beyond reasonable expenses.

Participants must be able to leave at any time without giving reasons and they should not be exposed to needless risks, or risks that are out of proportion to potential benefits.

Anyone who agrees to take part must have a good understanding of what is involved. Doctors should explain all risks and tell the person about any areas of uncertainty. The person should also know what will happen if anything goes wrong and what compensations are available. This explanation must be part of a full written protocol. Taken together this is called 'informed voluntary consent', and the concept is embodied in the guidance of the World Medical Association Declaration of Helsinki (see box).

The Declaration came in response to previous disastrous abuses of human research, such as in Nazi Germany and in public health tests in the USA, where people were exposed to dangerous infections or radiation without proper consent.

controls and placebos

All experiments involve some form of comparison between two or more situations. Participants may be divided into groups and given

World Medical Association Declaration of Helsinki

The Declaration of Helsinki was initially adopted by the World Medical Association in 1964. Since then it has been amended on five occasions, the most recent being in Edinburgh, October 2000.

The declaration aims to be 'a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects'. The opening paragraphs establish grounding principles for ethical research:

Paragraph 2 says that a physician should use his or her knowledge and conscience 'to promote and safeguard the health of the people'.

Paragraph 3 reminds physicians of The Declaration of Geneva of the World Medical Association's statement that 'The health of my patient will be my first consideration', and the International Code of Medical Ethics which declares that, 'A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient'.

Paragraph 5 states that in medical research the well-being of each human subject should take precedence over the interests of science or society.

Paragraph 8 points out that people who are particularly vulnerable need special protection. These include people who:

- are economically and medically disadvantaged
- cannot give or refuse consent for themselves
- may be under pressure to take part

The Declaration also reminds researchers to be particularly careful where the participant will not benefit personally from the research and where the research is combined with routine care.

Paragraph 9 reminds investigators of their obligation to be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. It also states that 'no national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration'.

different treatments, enabling a comparison to be made between the groups. Alternatively, the different treatments may be given to each participant and a comparison made in each person between the periods having each treatment.

One group or part of the experiment will be called the 'control' and in this part of the experiment the normal course of events is allowed to occur. The control provides a background against which the experimenters can judge the success of their treatment.

A control is needed because a patient's symptoms will sometimes improve simply because they believe they are being given a drug or surgical treatment. This makes it hard to know what effect is caused by the therapy and what is the result of the patient's own emotional response to it. Control groups can separate the physical from the psychological effects of treatment.

On occasions the control group is given a dummy treatment called a placebo. In this case the volunteers do not know whether they are taking

the treatment or the placebo. The aim is to separate the effects caused by a person's simple belief in the value of the therapy, from the genuine physical effects of the treatment.

bias and blinding

Medical experiments are made in ways which aim for as little bias as possible. Bias can occur when the observers want to see a particular expected outcome and choose the result closest to this. Participants can also bias results by falsely reporting that the treatment is working.

The way to avoid this is to 'blind' both the volunteer and the doctor. In these experiments codes are used so that no one knows which treatment is being given at any one time. The codes are only 'broken' at the end of the experiment.

This cannot always be done. For example, you can't have hip surgery without everybody knowing what has happened. But in many trials, like those on new drugs, 'blinding' can be extremely useful.

phases 1 to 4

Over the years a standard pattern has developed in the way that new ideas are tested in human experimental research.

Once laboratory studies have shown that a treatment has a high chance of success a Phase 1 trial will start, when the treatment will be given to a human being for the first time. In a Phase 1 trial, the treatment is tested on healthy volunteers. This of course is restricted to treatments that are not hazardous.

Phase 1 studies aim to find effective and safe doses for medicines, to see if there are unexpected effects of treatments, and to measure the amount of the medicine that is absorbed. If no problems occur, the researchers move on to a Phase 2 study, where the treatment is given to a small group of patients who have the target disease. The idea is to see if there is any indication that it has a beneficial effect.

In Phases 3 and 4 the treatment is given to larger groups of patients, establishing the extent of any benefit and keeping track of all adverse effects. Tests must be stopped in any of the Phases if there is harm. Work cannot be published if the experiment is unethical.

enough to count

The numbers of volunteers needed for experiments must always be calculated. Too few volunteers gives a weak test that lacks the power to lead to a result that is believably different from chance. Having too many volunteers can waste resources and risk more people.

Setting standards

People volunteering for a human experiment will very often not be able to evaluate fully how well the study has been designed. For this reason there are national and international rules that should govern all experiments involving humans. The Declaration of Helsinki forms an international framework that underpins national legislation.

In addition, British law states that all proposals for medical experiments must be submitted in advance and reviewed by a competent panel that is independent from the investigators.

Local human research ethics committees usually perform this 'peer review'.

Britain also has a national ethics committee, along with groups that handle specialised areas such as the Human Fertilisation and Embryology Authority and the Committee on the Use of Human Fetal Material.

Other groups have established standards for psychological and genetic experiments and the Medical Research Council publishes a series of booklets that set standards for medical research.

While the UK has a system of ethics committees, many parts of the world have no formal regulation.

vulnerable participants

Difficult problems arise with vulnerable minorities (see box), especially in gaining informed consent. With such people external peer review needs to be especially strict, and extra rules apply such as gaining consent of parents or guardians when working with children. Third parties may need to assist volunteers and ensure that all the information is presented in a way that they can understand.

honesty and openness

A major moral issue is honesty and 'transparency'. For example, dead children's organs should not be kept for research without the parents' consent to a full and true account of what is proposed. Concern here has

Vulnerable minority groups

- Embryos, fetuses and children
- Ethnic minorities
- Poor people in developing countries
- Demented patients and people with severe learning difficulties
- Groups under potential duress, or open to inducements, such as prisoners, members of armed forces, malnourished people, students and employees
- Aged or dying patients
- Pregnant women and those who might conceive during tests
- People with inherited diseases

led to opposition to research with children, thus slowing down the scientific discovery of effective remedies for childhood illnesses.

Another example concerns companies' use of industrial confidentiality to conceal unethical tests or dishonest test results, or to suppress findings which are accurate but might damage sales. Even negative findings should be published.

value the individual

In human research there is often a tension between the desire to benefit humanity and the need to help and protect those who suffer illness now.

It is never right to sacrifice present sufferers for the sake of those who may come in the future.

balancing risks

Risks must be weighed against possible benefits. A volunteer should only be exposed to major risk if the risks of non-treatment exceed those of therapy.

Risk, however, is hard to judge. One person may see a particular risk as trivial, while another may do everything to avoid it. In addition, a 1-in-a-million risk becomes a 1-in-1 reality if it affects you.

what then?

There is also the issue of what happens when an experiment stops. People may receive magnificent therapy while they are involved, but the treatment ceases at the end of the protocol. Sometimes this may leave them worse off than before.

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placebo and deception

Trials that use placebos have a particular ethical problem – that of the potential for deceit. The person may think they are receiving a treatment for their disease, but in fact they are only taking a placebo.

The Declaration of Helsinki (para 29) only allows placebos to be employed in human experiments where there is no existing treatment that can be used to give an appropriate comparison.

Christian principles

A number of features that can be derived from Biblical teachings can assist in setting up ethical experiments with human beings.

neighbour love: Jesus talked of the need to treat others with the high degree of respect that we would like ourselves (eg. Luke 10:25-37). In an experiment the participant's needs should come first and the experimenters' interest in the experiment should be secondary.

sanctity of human life: Because all human beings are made by God in his image, everyone has equal value in God's sight (Genesis 1:27). It is therefore always wrong to use someone as a means to an end, however desirable that end may be. Even in an experiment, everyone should be treated for their own benefit.

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choice: No one should force another into performing any action. Each human being has been given autonomy of decision-making.

attempt to heal: A theme of healing runs throughout the Bible. Jesus commanded his followers to go and heal people (eg. Matthew 10:1), so being involved in finding ways of making people well is an integral part of Christianity.

no modification: The Bible gives no mandate to experiment with human life in a way that will change it from what is normal. The mandate is to restore to health.

Conclusion

The moral duties placed on medical researchers have been agreed worldwide on the grounds of human justice and individual rights. Christians agree, but go further because of their belief that all creation, and the knowledge gained about it, are seen to be 'given' by God. People are his creatures, not ours to manipulate for our own or other's gains - even if the research aims to improve the wellbeing of many other human beings.

Further Reading

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- Smith R. Research with Children. British Medical Journal, 2001;322:1377-8*
- The Declaration of Helsinki*
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