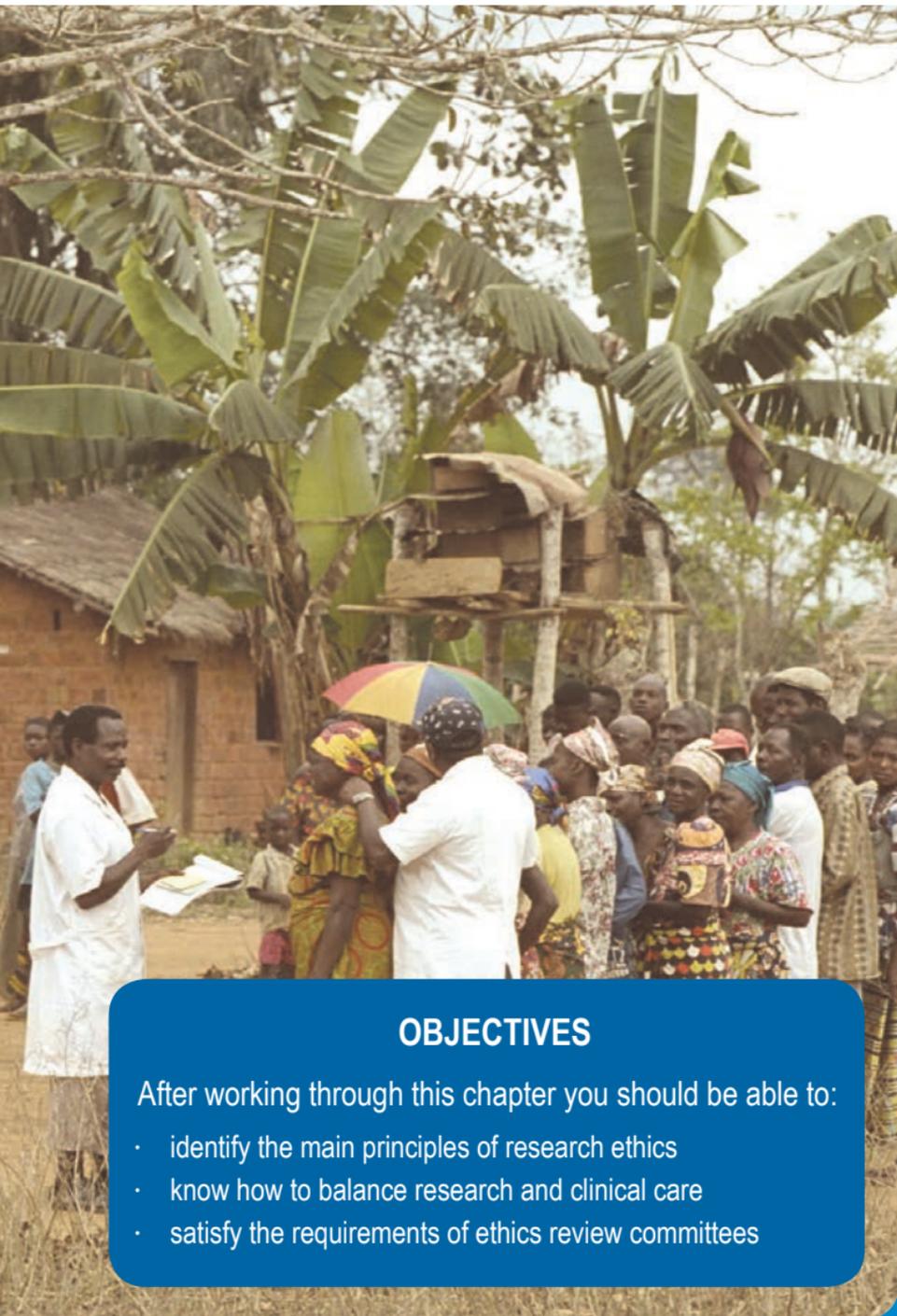


## CHAPTER FIVE – ETHICS AND MEDICAL RESEARCH



Sleeping sickness is back  
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## OBJECTIVES

After working through this chapter you should be able to:

- identify the main principles of research ethics
- know how to balance research and clinical care
- satisfy the requirements of ethics review committees

## CASE STUDY #4

Dr. R, a general practitioner in a small rural town, is approached by a contract research organization (C.R.O.) to participate in a clinical trial of a new non-steroidal anti-inflammatory drug (NSAID) for osteoarthritis. She is offered a sum of money for each patient that she enrolls in the trial. The C.R.O. representative assures her that the trial has received all the necessary approvals, including one from an ethics review committee. Dr. R has never participated in a trial before and is pleased to have this opportunity, especially with the extra money. She accepts without inquiring further about the scientific or ethical aspects of the trial.

### IMPORTANCE OF MEDICAL RESEARCH

Medicine is not an exact science in the way that mathematics and physics are. It does have many general principles that are valid most of the time, but every patient is different and what is an effective

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treatment for 90% of the population may not work for the other 10%. Thus, medicine is inherently experimental. Even the most widely accepted treatments need to be monitored and evaluated to determine whether they are effective for specific patients and, for that matter, for patients in general. This is one of the functions of medical research.

Another, perhaps better known, function is the development of new treatments, especially drugs, medical devices and surgical

techniques. Great progress has been made in this area over the past 50 years and today there is more medical research underway than ever before. Nevertheless, there are still many unanswered questions about the functioning of the human body, the causes of diseases (both familiar and novel ones) and the best ways to prevent or cure them. Medical research is the only means of answering these questions.

In addition to seeking a better understanding of human physiology, medical research investigates a wide variety of other factors in human health, including patterns of disease (epidemiology), the organization, funding and delivery of healthcare (health systems research), social and cultural aspects of health (medical sociology and anthropology), law (legal medicine) and ethics (medical ethics). The importance of these types of research is being increasingly recognized by funding agencies, many of which have specific programs for non-physiological medical research.

## RESEARCH IN MEDICAL PRACTICE

All physicians make use of the results of medical research in their clinical practice. To maintain their competence, physicians must keep up with the current research in their area of practice through Continuing Medical Education/ Continuing Professional Development programs, medical journals and interaction with knowledgeable colleagues. Even if they do not engage in research themselves, physicians must know how to interpret the results of research and apply them to their patients. Thus, a basic familiarity with research methods is essential for competent medical practice. The best way to gain this familiarity

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is to take part in a research project, either as a medical student or following qualification.

The most common method of research for practising physicians is the clinical trial. Before a new drug can be approved by government-mandated regulatory authorities, it must undergo extensive testing for safety and efficacy. The process begins with laboratory studies followed by testing on animals. If this proves promising, the four steps, or phases, of clinical research, are next:

- Phase one research, usually conducted on a relatively small number of healthy volunteers, who are often paid for their participation, is intended to determine what dosage of the drug is required to produce a response in the human body, how the body processes the drug, and whether the drug produces toxic or harmful effects.
- Phase two research is conducted on a group of patients who have the disease that the drug is intended to treat. Its goals are to determine whether the drug has any beneficial effect on the disease and has any harmful side effects.
- Phase three research is the clinical trial, in which the drug is administered to a large number of patients and compared to another drug, if there is one for the condition in question, and/or to a placebo. Where possible, such trials are 'double-blinded', i.e., neither research subjects nor their physicians know who is receiving which drug or placebo.
- Phase four research takes place after the drug is licensed and marketed. For the first few years, a new drug is monitored for side effects that did not show up in the earlier phases. Additionally, the pharmaceutical company is usually interested in how well the drug is being received by physicians who prescribe it and patients who take it.

The rapid increase in recent years in the number of ongoing trials has required finding and enrolling ever-larger numbers of patients to meet the statistical requirements of the trials. Those in charge of the trials, whether independent physicians or pharmaceutical companies, now rely on many other physicians, often in different countries, to enrol patients as research subjects.

Although such participation in research is valuable experience for physicians, there are potential problems that must be recognized and avoided. In the first place, the physician's role in the physician-

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patient relationship is different from the researcher's role in the researcher-research subject relationship, even if the physician and the researcher are the same person. The physician's primary responsibility is the health and well-being of the patient, whereas the researcher's primary responsibility is the generation of knowledge, which

may or may not contribute to the research subject's health and well-being. Thus, there is a potential for conflict between the two roles. When this occurs, the physician role must take precedence over the researcher. What this means in practice will be evident below.

Another potential problem in combining these two roles is conflict of interest. Medical research is a well-funded enterprise, and physicians are sometimes offered considerable rewards for participating. These can include cash payments for enrolling research subjects, equipment such as computers to transmit the research data, invitations to conferences to discuss the research findings, and co-authorship of publications on the results of the research. The physician's interest in obtaining these benefits can sometimes conflict with the duty to provide the patient with the best available treatment. It can also conflict with the right of the patient

to receive all the necessary information to make a fully informed decision whether or not to participate in a research study.

These potential problems can be overcome. The ethical values of the physician – compassion, competence, autonomy – apply to the medical researcher as well. So there is no inherent conflict between the two roles. As long as physicians understand and follow the basic rules of research ethics, they should have no difficulty participating in research as an integral component of their clinical practice.

## ETHICAL REQUIREMENTS

The basic principles of research ethics are well established. It was not always so, however. Many prominent medical researchers in the 19<sup>th</sup> and 20<sup>th</sup> centuries conducted experiments on patients without their consent and with little if any concern for the patients' well-being. Although there were some statements of research ethics dating from the early 20<sup>th</sup> century, they did not prevent physicians in Nazi Germany and elsewhere from performing research on subjects that clearly violated fundamental human rights. Following World War Two, some of these physicians were tried and convicted by a special tribunal at Nuremberg, Germany. The basis of the judgment is known as the Nuremberg Code, which has served as one of the foundational documents of modern research ethics. Among the ten principles of this Code is the requirement of voluntary consent if a patient is to serve as a research subject.

The World Medical Association was established in 1947, the same year that the Nuremberg Code was set forth. Conscious of the violations of medical ethics before and during World War Two, the founders of the WMA immediately took steps to ensure that physicians would at least be aware of their ethical obligations. In 1954, after several years of study, the WMA adopted a set of **Principles for Those in Research and Experimentation**.

This document was revised over the next ten years and eventually was adopted as the **Declaration of Helsinki (DoH)** in 1964. It was further revised in 1975, 1983, 1989, 1996, 2000, 2008 and 2013. The DoH is a concise summary of research ethics. Other, much more detailed, documents have been produced in recent years on research ethics in general (e.g., Council for International Organizations of Medical Sciences, **International Ethical Guidelines for Biomedical Research Involving Human Subjects**, 1993, revised in 2002) and on specific topics in research ethics (e.g., Nuffield Council on Bioethics [UK], **The Ethics of Research Related to Healthcare in Developing Countries**, 2002).

Despite the different scope, length and authorship of these documents, they agree to a very large extent on the basic principles of research ethics. These principles have been incorporated in the laws and/or regulations of many countries and international organizations, including those that deal with the approval of drugs and medical devices. Here is a brief description of the principles, taken primarily from the **DoH**:

### **Ethics Review Committee Approval**

Paragraph 23 of the **DoH** stipulates that every proposal for medical research on human subjects must be reviewed and approved by an independent ethics committee before it can proceed. In order to obtain approval, researchers must explain

the purpose and methodology of the project; demonstrate how research subjects will be recruited, how their consent will be obtained and how their privacy will be protected; specify how the project is being funded; and disclose any potential conflicts of interest on the

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part of the researchers. The ethics committee may approve the project as presented, require changes before it can start, or refuse approval altogether. The committee has a further role of monitoring projects that are underway to ensure that the researchers fulfil their obligations and it can if necessary stop a project because of serious unexpected adverse events.

The reason why ethics committee approval of a project is required is that neither researchers nor research subjects are always knowledgeable and objective enough to determine whether a project is scientifically and ethically appropriate. Researchers need to demonstrate to an impartial expert committee that the project is worthwhile, that they are competent to conduct it, and that potential research subjects will be protected against harm to the greatest extent possible.

One unresolved issue regarding ethics committee review is whether a multi-centre project requires committee approval at each centre or whether approval by one committee is sufficient. If the centres are in different countries, review and approval is generally required in each country.

## Scientific Merit

“...medical research involving human subjects must be justifiable on scientific grounds”

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Paragraph 21 of the **DoH** requires that medical research involving human subjects must be justifiable on scientific grounds. This requirement is meant to eliminate projects that are unlikely to succeed, for example, because they are methodologically inadequate, or that, even if successful, will likely produce trivial results. If patients are being asked to participate in a research project, even where risk of harm is minimal,

there should be an expectation that important scientific knowledge will be the result.

To ensure scientific merit, paragraph 21 requires that the project be based on a thorough knowledge of the literature on the topic and on previous laboratory and, where appropriate, animal research that gives good reason to expect that the proposed intervention will be efficacious in human beings. All research on animals must conform to ethical guidelines that minimize the number of animals used and prevent unnecessary pain. Paragraph 12 adds a further requirement – that only scientifically qualified persons should conduct research on human subjects. The ethics review committee needs to be convinced that these conditions are fulfilled before it approves the project.

## Social Value

One of the more controversial requirements of a medical research project is that it contribute to the well-being of society in general. It used to be widely agreed that advances in scientific knowledge were valuable

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in themselves and needed no further justification. However, as resources available for medical research are increasingly inadequate, social value has emerged as an important criterion for judging whether a project should be approved.

Paragraphs 16 and 20 of the **DoH** clearly favour the consideration of social value in the evaluation of research projects. The importance of the project's objective, understood as both scientific and social importance, should outweigh the risks and burdens to research subjects. Furthermore, the populations in which the research is carried out should benefit from the results of the research. This is

especially important in countries where there is potential for unfair treatment of research subjects who undergo the risks and discomfort of research while the drugs developed as a result of the research only benefit patients elsewhere.

The social worth of a research project is more difficult to determine than its scientific merit but that is not a good reason for ignoring it. Researchers, and ethics review committees, must ensure that patients are not subjected to tests that are unlikely to serve any useful social purpose. To do otherwise would waste valuable health resources and weaken the reputation of medical research as a major contributing factor to human health and well-being.

## Risks and Benefits

**“If the risk is entirely unknown, then the researcher should not proceed with the project until some reliable data are available”**

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Once the scientific merit and social worth of the project have been established, it is necessary for the researcher to demonstrate that the risks to the research subjects are not unreasonable or disproportionate to the expected benefits of the research, which may not even go to the research

subjects. A risk is the potential for an adverse outcome (harm) to occur. It has two components: (1) the likelihood of the occurrence of harm (from highly unlikely to very likely), and (2) the severity of the harm (from trivial to permanent severe disability or death). A highly unlikely risk of a trivial harm would not be problematic for a good research project. At the other end of the spectrum, a likely risk of a serious harm would be unacceptable unless the project provided the only hope of treatment for terminally ill research subjects. In between these two extremes, Paragraphs 17 and 18 of the **DoH** require researchers to adequately assess the risks and be sure that they can be managed. If the risk is entirely unknown,

then the researcher should not proceed with the project until some reliable data are available, for example, from laboratory studies or experiments on animals.

## Informed Consent

The first principle of the **Nuremberg Code** reads as follows: “The voluntary consent of the human subject is absolutely essential.” The explanatory paragraph attached to this principle requires, among other things, that the research subject “should have sufficient knowledge and comprehension of the elements of the subject matter involved as to enable him to make an understanding and enlightened decision.”

“The voluntary consent of the human subject is absolutely essential.”

The **DoH** goes into some detail about informed consent. Paragraph 26 specifies what the research subject needs to know in order to make an informed decision about participation. Paragraph 27 warns against pressuring individuals to participate in research, since in such circumstances the consent may not be entirely voluntary. Paragraphs 28 to 30 deal with research subjects who are unable to give consent (minor children, severely mentally handicapped individuals, unconscious patients). They can still serve as research subjects but only under restricted conditions.

The **DoH**, like other research ethics documents, recommends that informed consent be demonstrated by having the research subject sign a ‘consent form’ (paragraph 26). Many ethics review committees require the researcher to provide them with the consent form they intend to use for their project. In some countries these forms have become so long and detailed that they no longer serve the purpose of informing the research subject about the project. In any case, the process of obtaining informed consent does not begin and end with

the form being signed but must involve a careful oral explanation of the project and all that participation in it will mean to the research subject. Moreover, research subjects should be informed that they are free to withdraw their consent to participate at any time, even after the project has begun, without any sort of reprisal from the researchers or other physicians and without any compromise of their healthcare (paragraph 31).

## Confidentiality

As with patients in clinical care, research subjects have a right to privacy with regard to their personal health information. Unlike clinical care, however, research requires the disclosure of personal health information

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to others, including the wider scientific community and sometimes the general public. In order to protect privacy, researchers must ensure that they obtain the informed consent of research subjects to use their personal health information for research purposes, which requires that the subjects are told in advance about the uses to which their information is going to be put. As a general rule, the information should be de-identified and should be stored and transmitted securely. The WMA **Declaration on Ethical Considerations Regarding Health Databases** provides further guidance on this topic.

## Conflict of Roles

It was noted earlier in this chapter that the physician's role in the physician-patient relationship is different from the researcher's role in the researcher-research subject relationship, even if the physician and the researcher are the same person. Paragraph 14 of the **DoH** specifies that in such cases, the physician role must take

precedence. This means, among other things, that the physician must be prepared to recommend that the patient not take part in a research project if the patient seems to be doing well with the current treatment and the project requires that patients be randomized to different treatments and/or to a placebo. Only if the physician, on solid scientific grounds, is truly uncertain whether the patient's current treatment is as suitable as a proposed new treatment, or even a placebo, should the physician ask the patient to take part in the research project.

## Honest Reporting of Results

It should not be necessary to require that research results be reported accurately, but unfortunately there have been numerous recent accounts of dishonest practices in the publication of research results. Problems include *plagiarism*, data fabrication, duplicate publication and 'gift' authorship. Such practices may benefit the researcher, at least until they are discovered, but they can cause great harm to patients, who may be given incorrect treatments based on inaccurate or false research reports, and to other researchers, who may waste much time and resources trying to follow up the studies.

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## Whistle-blowing

In order to prevent unethical research from occurring, or to expose it after the fact, anyone who has knowledge of such behaviour has an obligation to disclose this information to the appropriate authorities. Unfortunately, such whistle-blowing is not always appreciated or even acted on, and whistle-blowers are sometimes punished or avoided for trying to expose wrong-doing. This attitude seems to

be changing, however, as both medical scientists and government regulators are seeing the need to detect and punish unethical research and are beginning to appreciate the role of whistle-blowers in achieving this goal.

Junior members of a research team, such as medical students, may find it especially difficult to act on suspicions of unethical research, since they may feel unqualified to judge the actions of senior researchers and will likely be subject to punishment if they speak out. At the very least, however, they should refuse to participate in practices that they consider clearly unethical, for example, lying to research subjects or fabricating data. If they observe others engaging in such practices, they should take whatever steps they can to alert relevant authorities, either directly or anonymously.

## Unresolved Issues

Not all aspects of research ethics enjoy general agreement. As medical science continues to advance, in areas such as genetics, the neurosciences and organ and tissue transplantation, new questions arise regarding the ethical acceptability of techniques, procedures and treatments for which there are no ready-made answers. Moreover, some older issues are still subjects of continuing ethical controversy, for example, under what conditions should a placebo arm be included in a clinical trial and what continuing care should be provided to participants in medical research. At a global level, the 10/90 gap in medical research (only 10% of global research funding is spent on health problems that affect 90% of the world's population) is clearly an unresolved ethical issue. And when researchers do address problems in resource-poor areas of the world, they often encounter

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problems due to conflicts between their ethical outlook and that of the communities where they are working. All these issues will require much further analysis and discussion before general agreement is achieved.

Despite all these potential problems, medical research is a valuable and rewarding activity for physicians and medical students as well as for the research subjects themselves. Indeed, physicians and medical students should consider serving as research subjects so that they can appreciate the other side of the researcher-research subject relationship.

## BACK TO THE CASE STUDY

Dr. R should not have accepted so quickly. She should first find out more about the project and ensure that it meets all the requirements for ethical research.

In particular, she should ask to see the protocol that was submitted to the ethics review committee and any comments or conditions that the committee put on the project. She should only participate in projects in her area of practice, and she should satisfy herself about the scientific merit and social value of the project. If she is not confident in her ability to evaluate the project, she should seek the advice of colleagues in larger centres. She should ensure that she acts in the best interests of her patients and only enrolls those who will not be harmed by changing their current treatment to the experimental one or to a placebo. She must be able to explain the alternatives to her patients so they can give fully informed consent to participate or not to participate. She should not agree to enrol a fixed number of patients as subjects since this could lead her to pressure patients to agree, perhaps against their best interests. She should carefully monitor the patients in the study for unexpected adverse events and be prepared to adopt rapid corrective action.

Finally, she should communicate to her patients the results of the research as they become available.