

# World Health Organisation biomedical research guidelines and the conduct of clinical trials

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## Editor's note

*The increasing importance, recognised by WHO, of prospective randomised clinical trials has led to discussion of the need for their careful regulation in the interests of maintaining high professional ethical standards. Ethical problems which do arise—for example where biomedical research in developing countries is sponsored from abroad—may best be handled by specially established professional scientific/ethical committees.*

## Introduction

The International Federation of Surgical Colleges has been associated for a long time with WHO as a non-governmental and non-profit organisation. Our representatives have had many chances to attend the World Health Assembly, the Regional Meetings of WHO and the meetings of WHO Executive Board. It was interesting to note that a great deal of WHO discussion has been devoted to biomedical research. WHO's firm conviction is that continued success is critically dependant upon advances in large-scale biomedical research and their application in the community. In 1978 the International Conference of WHO held in Alma-Ata, USSR, reaffirmed health as a fundamental human right and a worldwide social goal. At the same time 22 specific recommendations were adopted requiring new skills in the philosophy of educational and research needs for the era of health science up to the year 2000.

Looking at the activities of the Research Advisory Committees of WHO in Europe, the following five priority areas of research promotion and development can be distinguished:

- a) Standardisation of methods, measurements and terminology in biomedical and health services research.
- b) Prevention, prophylaxis, and early detection of certain diseases.
- c) Evaluation of drugs and other therapeutic and diagnostic substances.
- d) Problems of health care delivery.
- e) Economic aspects of health care.

The discussion on these priorities indicates that an important part of this programme includes both biomedical and organisational aspects of the

practice of medicine and surgery. The special groups of Advisory Committees for Medical Research appointed in the Headquarters and Regional Offices of WHO, emphasised the world-wide importance of standardisation, measurement and terminology in biomedical research. The most important need at present is to identify ways of providing a comprehensive assessment of the need for medical and surgical research.

## Randomised clinical trials

I think that WHO has a continuing interest in prospective randomised clinical trials, regarding them as one of the greatest scientific advances in our time and sometimes the only logical method of choosing a method of therapy or prevention. Clinical trials have contributed much to the advancement of therapy and play a substantial role in the medical care of the sick.<sup>1</sup> The widening use of clinical trials has stimulated broad discussion and reflection on the subject of human rights in clinical research on humans.

For this reason WHO sponsored the XII Round Table Conference of International Organisations of Medical Research in Lisbon on 1 December 1978, under the general headline 'Medical experimentation and the protection of human rights'. During this meeting several interesting papers were presented which could be classified as follows:

- a) Statutory regulations and ethical conduct.
- b) Concepts of clinical trials, and decision making in large scale comparative studies.
- c) Other values and limitations of clinical trials.

It has been emphasised that in clinical trials two distinct groups must be considered—the general public and the individuals participating in trials. The balance of interests between that of the patient involved in a clinical trials and the general public good may, at times, be extremely delicate. There are ethical controls of various sorts emerging from the Declaration of Helsinki, 1964, and the international code expressed in the Tokyo Declaration 1975, through the national system of modification of clinical trials to safeguard the patients, healthy volunteers and the reputation of the profession and institutions in matters of clinical investigation. It is now generally advised to set up ethical

committees and to refer to them all proposed clinical research investigations. The World Medical Association's Helsinki Declaration initiated the setting-up of scientific and ethical committees.<sup>3</sup> These created the terminology recently used in clinical research, the scientific and medical qualifications, and the experimental protocol. The composition of the committees, their activities, range of responsibility and authority were presented by Professor Giertz in accordance with WHO views. To my mind more conscious efforts should be made to bring about some forms of unified approach at international level.

I think that at this symposium it is worthwhile to quote two definitions: biomedical research and experimental protocol. According to Riis<sup>3</sup>, by biomedical research is understood all systematic collections of data with man as the research object. This way the field covers not only basic scientific projects but also social, medical and epidemiological research. By experimental protocol is understood a comprehensive collection of all documents describing a given scientific project. The following items have to be included: the original concept of the trial, the approach, design and planning, methods of observation and the information sheet given to patients.<sup>3</sup>

Formulation of the original concept and decision making are particularly important stages for scale comparative studies. Clinical trials often determine precisely the efficacy of treatment and the value of preventive regimen. These large studies 'may cost millions of dollars not only in terms of financial but also in other research resources: the large number of research facilities and personnel required.'<sup>4</sup> As you all know, WHO has no specialised research institutions except the International Agency Against Cancer in Lyons. WHO however has a very close co-operation with the leading medical research centres in the world. One of them is the National Institute of Health in Bethesda, where some principles of large scale clinical trials were elaborated and implemented. At the National Heart, Lung and Blood Institute, Levy and Sondik developed the specialised decision process to aid in the formulation, design, conduct, analysis and dissemination of the results of clinical trials. The progression of clinical trials from the initiation of an idea, through planning and the conduct of the trial, to the analysis and dissemination of the results can be divided into four phases. At each decision point a number of groups review the progress of the trial. According to Levy and Sondik,<sup>4</sup> these decision factors fall into four major categories.

- a) The state of science related to the trial.
- b) The feasibility of the effect.
- c) Potential impact of the trial on health care.
- d) Ethical considerations inherent in the use of human subjects.<sup>4-6</sup>

### Externally sponsored research

Another problem discussed at the Lisbon CIOMS Conference was externally sponsored research.<sup>5</sup> At the present time the power resources and technical equipment of most of the developing countries may not be sufficient to carry on biomedical research on their own. In these circumstances such research is often sponsored by external agencies. This is acceptable under the following conditions:

- a) Strict administrative and scientific control of the agreement on the trial by National Scientific Committees.
- b) The topic of clinical research must be relevant to the problems of the recipient country.
- c) The results of the investigations must lead to advances in that particular country and must be applicable in many developing countries.<sup>5</sup>

I think that WHO is looking very carefully at external sponsored research in developing countries and recommends very strict monitoring of investigations from a scientific and ethical point of view. All sponsored research in developing countries should be subject to an agreement on publication policy before the work begins.<sup>5</sup>

The value of controlled clinical trials is well known to all who apply scientific methods to clinical problems. Among others, especially among non-scientists and politicians there exist, however, many misunderstandings. The most common is that clinical studies are of an extremely experimental character and that assigning patients to one or another type of treatment protocol is completely randomised.<sup>1</sup> This is not true. A patient is assigned to undergo clinical study when, on the basis of our best judgment, an equal possibility exists that each of the compared methods of treatment will be of advantage to the patient.<sup>1</sup> Many people express some reservations if children or prisoners are subjected to clinical trials.<sup>6</sup> I think these doubts can be avoided by proper planning and decisions of ethical committees considering the ethical, moral and scientific issues.

Finally I would like to stress that a clinical trial, which is the application of scientific methods to clinical problems is distant from everyday clinical routine. Clinical trials are a continuous function: each stages relies on the previous one, taking advantage of its results and asking new questions which arise from them. It would not be fitting to consider any clinical trial a final step because no studies in surgery and in medicine will ever be final but will always be subject to revision and reevaluation. One should also never renounce clinical studies prematurely simply because another method of therapy has been introduced. Premature termination of clinical trials results in a waste of the contributions made up to that time and devalues the potential hazards to which the patient is exposed during the trial.<sup>1</sup>

In summary, I wish to emphasise that in planning and conducting clinical trials we involve the patients. Their cornerstone of trust rests in the faith that their rights, even those unknown to them, will be recognised and honoured by the physician. These rights were beautifully summarised and expressed by V Peters;<sup>7</sup>

- a) the right—to seek consultation
- b) the right—fully to understand treatment
- c) the right—to know the treatment alternatives and ramifications
- d) the right—to help with treatment decisions.

I am deeply convinced that the International Federation of Surgical Colleges is extremely sensitive to these basic human rights in medical experimentation.

### References

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- <sup>3</sup>Riis, P (1978) Ethical review committees: composition, authority and influence. XIIth CIOMS Round Table Conference. *Medical experimentation and the human rights*. Lisbon.
- <sup>4</sup>Levy, R I and Sondik, E J (1978). Decision making in planning large scale comparative studies. *Annals of the New York Academy of Science*, **304**, pp. 441–459.
- <sup>5</sup>Phillips, H H (1978). Externally sponsored research. XIIth CIOMS Round Table Conference. *Medical experimentation and the human rights*. Lisbon.
- <sup>6</sup>Cooke, R E (1978). Ethical considerations in the selection and recruitment of children for research. XIIth CIOMS Round Table Conference. *Medical experimentation and the human rights*. Lisbon.
- <sup>7</sup>Peters, V (1979). *Progress against cancer*, **32/2**, p 7.

### Further reading

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