

THE DUTCH MEDICAL RESEARCH INVOLVING HUMAN SUBJECTS ACT IN PRACTICE

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1. Introduction

Medical research on human subjects is crucial to the progress of medicine. However, because individual rights are at stake and medical experimentation always poses uncertain risks, it is necessary to guarantee the protection of the rights and safety of the participants in clinical trials. As a result, several international instruments have been developed to ensure that research practices are ethically acceptable, such as the Declaration of Helsinki, the Clinical Trials Directive of the European Union and the (European) Convention on Human Rights and Biomedicine (Gevers et al., 2005). In addition, in most countries guidance on good research practices has been issued by a variety of legal and other regulatory instruments and guidelines. To review the ethical acceptability of research protocols Research Ethics Committees (further: REC's) operate on a statutory or a non-statutory basis.

In the Netherlands, the patient or healthy volunteer who participates in a medical experiment is protected by the Medical Research Involving Human Subjects Act (further: the MRIHS Act). The MRIHS Act requires medical research to be carried out in accordance with a research protocol that should have obtained a positive review from an acknowledged REC. The MRIHS Act came into effect on 1 December 1999. Five years after its enactment the Act has been evaluated: how does the Act function in practice, to what extent does the Act serve its purpose and which (desired and unwished-for) effects does the Act have on the main actors in the field of medical research and on the progress of medical research in general (Dute et al., 2004b)?

This paper presents the results of this evaluative study. First, a brief overview of the MRIHS Act will be given. Then the data collection will be explained briefly, followed by a description of the main findings. This paper will end with some concluding remarks. It should be noted that this study does not pertain to the major changes of law as a result of the European Union Clinical Trials Directive.

2. The Dutch Medical Research Involving Human Subjects Act

The MRIHS Act applies to medical research, which is defined as subjecting persons to acts or imposing a certain way of behaviour on persons. This includes intervention research as well as some types of observational research. Apart from purely medical research, it also encompasses paramedic and nursing research, and even certain forms of behavioural scientific research. Direct contact with the patient or the healthy volunteer is required. The MRIHS Act does not address research involving retained human material, which in the

future will be regulated by a special Act. Nor does it address medical research undertaken by reviewing patient health records, which is covered by (some provisions of) the Medical Treatment Agreement Act, the Data Protection Act and professional guidelines. In 2005, the Medical Research Act has been revised in order to implement the Clinical Trials Directive. As noted before, this major revision will not be dealt with here, because it fell outside the scope of the evaluative study.

The law requires a research project to be carried out in accordance with a protocol which describes the project in detail. This protocol should have obtained a positive review from an multidisciplinary composed REC, taking into account a number of aspects, such as the necessity of the research project; its design; the anticipated risks and benefits (the risk-benefit ratio); and the suitability of the researcher and the facilities. The REC will also ascertain whether the rules governing informed consent are complied with. Furthermore, research may only be carried out if insurance was taken out covering the test subject's death or injury caused by the research (Dute et al., 2004a).

For certain vulnerable groups, such as minors, incapacitated adults and persons in dependence relations, tightened rules are applicable. For this purpose the distinction between therapeutic and non-therapeutic research is relevant. Therapeutic research (research which may be of direct benefit to the subjects) with minors and incapacitated adults is, in principle, allowed. Non-therapeutic research with minors and incapacitated adults is prohibited, unless it concerns research which could not be conducted without the participation of persons of the same category as the subject. In addition, the risk associated with participation should be negligible and the burden minimal. Should the subject object to receiving treatment or behaving in the required manner, then this person has to be excluded from participation. A comparable regulation applies to research involving test subjects in a dependence relation, such as detainees, though in this case the additional requirement of negligible risks and minimal burden is not set.

The MRIHS Act sets requirements as to the composition and functioning of the REC's. They should consist of at least one or more doctors, a lawyer, an ethicist, a methodologist and a person charged with the task of examining protocols specifically from the subject's point of view. In case of a trial of medicines, experts on pharmaceuticals and clinical pharmacology should also form part of the committee. Furthermore, at least ten research protocols per year should be reviewed by each REC.

A special body has been introduced by the MRIHS Act, the Central Committee on Research Involving Human Subjects (further: Central REC), charged with various tasks. First of all, the Central REC reviews specific types of medical research, for instance interventional research with minors and incapacitated adults, gene therapy, xenotransplantation and so on. Besides, the Central REC is responsible for recognising the REC's, supervising their activities and drawing up guidelines for that purpose. A recognised REC is authorised to review all types of medical research on humans except those which have to be reviewed by the Central REC. An appeal can further be lodged with the Central REC against an assessment given by the local REC.

A researcher who fails to obtain REC approval for the conduct of a medical research project commits a criminal offence. The MRIHS Act states that it has to be evaluated every five years.

3. Method

Data were collected in various manners. Interviews were held with members of the Central REC and other key figures in the field of (the regulation of) medical research; questionnaires were filled in by (members of) all REC's, researchers, scientific associations and executive boards of hospitals; and a focus group interview was held with representatives of patients and trial nurses. The study was completed in December 2004.

4. Results

General observations

The most important finding is that the MRIHS Act by and large functions according to its purposes. The Act aims to protect participants in medical research against the risks and discomforts of medical research, without unnecessarily hampering the progress of medical research. Research protocols are reviewed by the REC's and the Central REC with due care. Especially medical research with minors and incapacitated adults has been scrutinized very carefully. In some cases it turns out to be difficult to assess competency and to recognize resistance offered by the one who lacks capacity, but the same goes for treatment situations.

The current normative and regulatory framework for medical research should be considered as a product of incremental development. In this respect the Act has especially codified already accepted ethical and legal rules. However, the enactment as such of these legal norms has brought about relatively major changes in the review procedure. The requirements for proper research are stated in more detail, and they are also elucidated and elaborated. Some new requirements were introduced, like for instance the need for an independent physician the participant can turn to for advice. In addition, the MRIHS Act has introduced a new, coordinating administrative body, the Central REC, that enjoys wide powers. This body initiated a drastic reduction in the number of REC's. Finally, general administrative rules have become applicable, which will be discussed below. All in all, the MRIHS has not only codified, but in a certain sense also modified the existing review system.

The statutory review procedure is to a considerable extent grafted onto research with medicinal products. For other types of research, for instance not-blinded research into the effect of primary care interventions, the legal system may appear to be less suited. It is doubtful whether randomised consent meets the statutory requirement of informed consent.

In practice, the scope of the law is not always clear. For instance, medical research involving questionnaires usually does not fall within the scope of the law, but sometimes it does, namely when questions are far-reaching and might infringe personal integrity. Furthermore, because not only medical research involving human subjects may entail risks and discomforts, but in fact all types of research involving human subjects, the more principal question arises whether the scope of the law should be extended.

Research Ethics Committees

Since the enactment of the Act the number of REC's has been decreased drastically, due to the requirement of ten research protocols per year set by the Central REC. In 2000, 81

REC's existed, in 2003 63 and in 2005 only 34 (8 of them have been set up by academic hospitals). In 2003, the REC's together reviewed more than 1700 research protocols. In practice, a REC has on average 12 members and meets twice a month. Every meeting takes 2.4 hours on average. In four out of five cases the review procedure requires only one session. The workload of the members of the REC's is high: an individual member spends an average of 13 hours per month on meeting and preparing the meeting. As a result of the high workload some REC's have difficulties in finding enough qualified physicians who are able to combine membership with their daily routine. Another point of particular interest is the somewhat vague profile of the member charged with the task of examining protocols specifically from the subject's point of view.

Though the REC's initially developed themselves on the basis of self-regulation, they now have a statutory basis. This implies that they have obtained a public-law status and should legally be considered as an administrative body. This entails that they are subjected to the general rules applying to the Government, such as the General Administrative Law Act and the Government Information (Public Access) Act. This has led to several important changes in the review practice. One of them is the time-limit of 8 weeks to which the review procedure is subjected. According to the REC's, 80% of all applications are decided within the prescribed period of time. It should be noted, however, that the further handling of the application is suspended for as long as required documents are missing or questions has to be answered by the researcher.

The focus of the review procedure is on the research protocol. Once the protocol has been approved by the REC, there is only limited supervision on how the research is carried out in practice. As a result it is not sufficiently monitored whether the research project actually meets the requirements of the research protocol.

Multi-centre research

In case of multi-centre research, the positive assessment of the REC of only one participating centre suffices. The executive boards of the other participating centres are expected to consider only issues relating to their particular locality. This task is not assigned to the REC's; however, in practice half of the executive boards asks their advice. A quarter of the REC's is of the opinion that this multi-centre research review procedure does not guarantee a careful examination of the protocol. They do not have sufficient trust in the quality of each other's judgment. Not surprisingly, many REC's do not limit their scope of control to local issues.

Central Research Ethics Committee

In the course of five years the Central REC has become a professional organisation. It is charged with a diversity of tasks, of which the task to review research protocols appears to be the most dominant one. Besides, the Central REC is responsible for recognising and monitoring REC's and requires them to review at least 10 protocols, which has led to a substantial decrease in the number of REC's. The Central REC issued a number of guidelines and brought them together in a manual. The REC's are satisfied with the advice given by the Central REC.

The MRIHS Act provides for legal protection in case a trial is not approved by a REC or, as the occasion arises, the Central REC. Between 1999 and 2003 21 appeal procedures from a REC assessment were instituted (three of them were considered well-founded by the

Central REC) and 16 notices of objection to a Central REC assessment were filed (two were upheld). No lawsuits were commenced.

Opinion of researchers

Researchers are dissatisfied with the length of the review process. In real time (but, as noted before, the further handling of the application is suspended as long as documents are missing or questions has to be answered), for one out of four protocols the review procedure requires more than 16 weeks, for one out of ten even more than 30 weeks. Furthermore, in the opinion of researchers bureaucracy has increased. To a large extent, however, this increase in bureaucracy is justified by the fact that the review procedure has been made more transparent.

Informed consent procedure

Consent is an important requirement of lawful research. The MRIHS Act requires the participant to be informed in writing of the aim, nature and duration of the research, the risks and the discomfort associated with participation and the risks of premature cessation of the research. The information should be provided in such a way that it is beyond reasonable doubt that it has been understood by the participant. Furthermore, he should have had sufficient time to properly consider the information and to reach a reasoned decision regarding consent. Consent should be in writing. The evaluation study shows that all parties involved attach great weight to the informed consent procedure. Mostly, the information given is very detailed. The information form is scrutinized by the REC. However, this does not ensure that the information is fully understood and the participant reaches a well informed and conscious choice. It is not standard procedure to apply sound educational principles like testing the information material on representatives of the target group. Close attention should be paid to the informed consent procedure in terms of developing more empirical knowledge on this topic and improving the information process.

5. Conclusion

As we have seen, the MRIHS Act by and large functions according to its purposes. In the review process quality and transparency, but also bureaucracy have increased. Some aspects of the law, more in particular the proper implementation of the informed consent requirement, the length of the review procedure and the review of multi-centre research, deserve close attention in the future. In 2009 the next evaluation of the MRIHS Act will be undertaken.

Literature

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