Legislation on medical research involving human subjects in the Netherlands

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After the end of the Second World War many western countries drafted legislation for research with human subjects. The primary aim of this legislation was to protect those who participate in medical research whilst ensuring the integrity of research data. However, it took the Netherlands many years to pass such legislation – only in 1999 did it come into force.

The late legislation does not mean that human subjects in the Netherlands were not protected before 1999. Just as in other western countries, at the end of the 1960s and ‘70s Dutch hospitals appointed Medical Research Ethics Committees (MRECs) to review research proposals submitted by their colleagues. At the end of 1998 the Netherlands had around 100 of these MRECs. The exact number was at the time unknown, as was the composition of these committees, the number and type of studies which they reviewed, and the number of human research subjects (healthy volunteers and patients) who participated in clinical research on a yearly basis. There was no overview and a legal framework which could lead to this and which could offer insight into medical research with human subjects was much anticipated.

The first bill
The first step in the process of legislation was made in 1982. This is when the Central Health Council (the predecessor of the Council for Health and Society, Dutch abbr: RVZ) published its advisory document regarding medical experiments (Dutch: ‘Deeladvies inzake medische experimenten’).

However, it wasn’t until 10 years later that the first version of the bill made its way to the Dutch House of Representatives where it was the cause of much debate. A major point of discussion was the so-called non-therapeutic research with minors and incapacitated research subjects. In a non-therapeutic study the research subjects cannot expect to derive direct benefit from participation in the study, for example in the case of an experimental medicinal product which is being tested for the first time in humans.

It is at that point still unknown if the medicinal product will have a positive medical effect. In contrast, in the case of therapeutic research there is a realistic chance that the research subject will clinically benefit from participation in the medical research. It is for this reason that stricter regulations apply internationally to non-therapeutic research with minors and incapacitated subjects, as these are deemed to be vulnerable groups.

An impending ban on non-therapeutic research
During the debate at the beginning of the 1990s members of the Dutch House of Representatives called for a complete ban on non-therapeutic research with the named vulnerable groups. They argued that (young) children and other vulnerable groups such as elderly patients suffering from severe dementia are unable to make their own informed decision on the risks, burden and lack of direct benefit resulting from participation in a non-therapeutic study. They would therefore be unable to provide informed consent for participation.

The research community makes its case
The discussion in the House of Representatives only really gains momentum in the nineties.
politicians’ attention the importance of non-therapeutic research for developing new medicinal products and therapies specifically for minors and incapacitated patients as some illnesses are exclusive to these groups, for example certain forms of child cancer such as neuroblastoma, and Alzheimer’s Disease in adults, respectively. For new medicinal products for these types of illnesses to be developed they have to be tested on patients at a stage where the safety and effectiveness is not yet clear. At that developmental stage the patients cannot expect to derive therapeutic benefit from the experimental product.

The government appoints a committee
The debate demonstrated a clear discrepancy between the opinions and views of the parliamentary members on the one hand and the medical professionals on the other. For this reason, the government decided in 1994 to appoint an advisory committee named after its chair, the Meijers Committee. The committee publishes its report timely in 1995 in which it advises not to prohibit non-therapeutic research for this target group. The committee does however come up with supplementary criteria which are included in a revised bill which was given the name the Medical Research Involving Human Subjects Act (Dutch: Wet medisch-wetenschappelijk onderzoek met mensen, abbreviation WMO), not to be confused with the Dutch Social Support Act (Dutch: Wmo: Wet maatschappelijke ondersteuning). The Act comes completely into force on the 1st of December 1999, more than 17 years after the advice of the Central Health Council.

The introduction of the WMO led, amongst others, to the establishment of the Central Committee on Research Involving Human Subjects (Dutch abbreviation: CCMO). This multidisciplinary committee, which comprises experts from the medical research field, is given many significant legal tasks. This includes the accreditation of the MRECs and the reviewing of non-therapeutic intervention research with minor and incapacitated research subjects and clinical research for which the special expertise is required such as gene therapy.

CDA calls for a total ban
A few citations from the representative of the Dutch Christian Democratic Party CDA from the minutes of the House of Representatives meeting on the 2nd of October 1992: “In the case of non-therapeutic experiments the primary question is whether such experiments should be carried out at all. [...] The current Dutch legislation does not allow experiments with incompetent subjects if they are not in their own interests. [...] The consideration that a fundamental viewpoint, in this case a ban on non-therapeutic experiments with incompetent subjects, should stand in the way of science, does not form a justified argument for allowing these experiments to be carried out. [...] Making an exception to this rule presents problems when determining how to limit the exception. Not only do exceptions have the tendency of being unclear in when to apply limitations, they also often become precedents for new exceptions and can contribute to the danger of moving in the direction of the so-called slippery slope.”
Many changes for the MRECs

The arrival of the WMO in 1999 brought many changes for the more than 100 MRECs. To qualify for accreditation the MRECs had to comply with legal obligations with regards to the composition of the committee: each accredited MREC had to have an expert physician, a clinical statistician, an ethicist, a legal expert, and a so-called ‘research subject member’ (or lay member). This was later extended to include a clinical pharmacologist and a hospital pharmacist for the review of clinical research with medicinal products.

The arrival of the WMO also meant a change in the review by the committees. Many previously had the character of a local ethical advisory group, primarily concerned with the patient informed consent form, though once the WMO came into force the focus lay on an integral review with regards to the content of the scientific, medical and ethical aspects of the research proposals. This addressed the widely held view that exposing research subjects to a possible scientific inadequate medical research is unethical.

An accreditation meant that the position of the MREC shifted from being a hospital advisory committee to becoming an independent administrative body responsible for carrying out a governmental task issuing independent legal decisions on the reviewed research proposals.

The accredited MRECs also must adhere to the condition of reviewing an average of 10 or more research proposals per year measured over a period of two years. As many accredited MRECs could not meet this stipulation it led to a strong concentration of the number of MRECs in our country, from around 80 in 1999 to 23 in 2017.

Once again discussion on non-therapeutic research

The discussion on the review of non-therapeutic research with minors and incapacitated research subjects is a recurring theme, even after the introduction of the WMO. As a result of the parliamentary discussion in the 1990s extra restrictions were included in the legislation pertaining this type of research: the risks must be negligible, the burden minimal and the research must be group based. The last condition stipulates that if the research can be carried out in capable adult research subjects that it may not be carried out in minors or incapacitated subjects.
European legislation for clinical research with medicinal products

In the European Union (EU) in the 1990s the European Committee strives to draft a legally binding directive for the review of clinical research with medicinal products which will harmonize the regulations and procedures of all the member states. The idea behind this aim is to place the EU more prominently on the map for research of the pharmaceutical industry. After much discussion, the European Parliament and the European Council (which includes the EU ministers of Health) gave the go-ahead for the EU Clinical Trials Directive at the end of 2000, with the agreement that the directive will be implemented and enforced in the national legislation of all member states before or on May 1st, 2004. After the implementation of the EU Directive Good Clinical Practice there is much criticism. Hardly any improvements are made in the intended harmonized review of clinical research with a medicinal product. The directive primarily leads to higher costs for investigators and companies. The failure of the attempt to harmonization was in part the result of the choice to implement an EU Directive instead of an EU Regulation. A Directive is less imposing and each member state ‘translates’ it into its own (in many cases existing) legislation and procedures pertaining to review of clinical research with medicinal products. Because of this a kind of couleur nationale emerges; national interpretations which prevents harmonization within the EU. The research community and industry calls Brussels for a more strict instrument to be applied. The call is heard and after many years of preparation and discussion in 2014 the European Committee publishes the EU Regulation on clinical trials on medicinal products for human use.

In contrast to the EU Directive, the EU Regulation must be incorporated literally and in its entirety in the national legislation. The EU Regulation is expected to come into force in 2019. One of the significant changes concerns a reduction in the review timeline for clinical research with medicinal products from 60 to 45 days. This presents a huge challenge for the members of the CCMO, the accredited MRECs and their supporting staff. They will have to apply substantial effort to ensure a thorough independent review of the scientific, medical and ethical aspects of the often lengthy research proposals within the legal timeline.
As the CCMO has been assigned the task of reviewing all non-therapeutic intervention research with minors and incapacitated research subjects, it obtained an clear view on the pros and cons of the legal restrictions for this type of research. The advantage is that the extra restrictions stimulate investigators and the industry to find solutions to minimize the risks and burden for these vulnerable research subject groups. The disadvantage is that in a small number of cases important studies cannot be approved as the risks are not deemed to be negligible and/or the burden minimal.

It is for this reason that the CCMO calls for new debate on the legal restrictions in its Annual Report 2006. This is based on its seven year experience in reviewing clinical protocols on non-therapeutic intervention research with minors and incapacitated subjects up until this point. The then Deputy Secretary of Health Bussemaker pays heed to this call and together with the involved members of the cabinet appoints an advisory committee, the Doek Committee in 2007. The Doek Committee publishes its report at the end of 2009 in which it recommends changing the legislation. However, it took quite some time before the law is actually amended. The new legislation finally came into force on the 1st of March 2017 and allows for a broadening of the possibilities for non-therapeutic research with minors and incapacitated research subjects. This is more than 10 years after the call from the CCMO for a debate on the strict regulations on research with minors and incapacitated subjects.

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Websites
The Central Committee on Research Involving Human Subjects http://www.ccmo.nl/en

E-learning on legislation and procedures of medical research involving human subjects in the Netherlands http://www.pauljanssenfuturelab.eu/

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