Experimental treatment or medical research?

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If a doctor carries out an experimental treatment with only the individual patients’ interests in mind, that is to say there is no scientific aim to carrying out the treatment, then this does not fall under the scope of the Dutch Medical Research Involving Human Subjects Act (Dutch: Wet medisch-wetenschappelijk onderzoek met mensen (abbr: WMO)). Instead it falls under the Dutch Civil Code, under the Agreement on Medical Treatment Act (Dutch: Burgerlijk Wetboek inzake de geneeskundige behandelingsovereenkomst (WGBO)). If he or she deviates from the professional standard and the applicable protocols and guidelines then this must be accounted for. The WMO applies if a treatment is carried out within the context of a research protocol or when procedures are carried out such as randomization and the removal of extra tissue. In cases such as these, the statutory provisions with regards to medical ethical reviewing and written informed consent must be met.

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If a new surgical method or therapy is tested on patients then should this be considered a medical research or an experimental treatment? Most doctors who have ever offered a patient a new treatment will have asked themselves this question. And it is a justifiable one as the line between ‘pioneering in healthcare’, even with the best of intentions, and medical research is sometimes thin. With this in mind, should a plausible treatment method which has not yet been tested in a clinical trial be allowed? A new medicinal product for an illness or ailment which has not yet been studied and registered (also termed ‘off-label’ application) can be offered in
both contexts. This also applies to the application of new and promising surgical techniques which have not yet been sufficiently studied with regards to their effectiveness and safety. Yet who decides what is sufficient?

From a legal perspective the difference between medical research and patient care is extremely relevant as this determines whether the legislation covering medical research applies, namely the Dutch Medical Research Involving Human Subjects Act (Dutch: Wet medisch-wetenschappelijk onderzoek met mensen (abbr: WMO)). This law stipulates for example that a research protocol must be written which must then be approved by an accredited medical research ethics committee (MREC).

In this article we will explain the difference between an experimental treatment and a medical research by examining 3 cases which (could) arise on a daily basis.

DIFFERENT AIMS, DIFFERENT LAWS
Experimental treatment: medical care aim To differentiate between experimental medical procedures – with patients – and medical research – with research subjects – one must first and primarily examine the scope of the WMO. Article 1, section 2 of this law stipulates that procedures which are carried out with the sole aim of providing medical care to a patient do not fall under the scope of the WMO. These procedures are only subject to conditions as stated in the Dutch Civil Code under the Agreement on Medical Treatment Act (Dutch: Burgerlijk Wetboek neergelegde bepalingen inzake de geneeskundige behandelingsovereenkomst (abbr. WGBO)), which include the most important rights of the patient, such as those pertaining to information, consent, privacy and access.

Therefore, carrying out an experimental treatment in the capacity of healthcare professional does not fall within the scope of the WMO. However, in this situation the healthcare professional must adhere to stricter conditions with regards to informing patients than when providing regular care. For example, a patient must be informed that the outcome of the suggested treatment has not yet been scientifically proven and that there is insufficient evidence with regards to its effectiveness and risks. Implicit consent is insufficient. Explicit consent must be given by the patient, though this can be provided in a phased manner. Furthermore, a healthcare professional must at all times go about his/her work in a particularly careful and diligent manner to ensure complying with the judicial system and legislation covering the quality of the medical profession. If he or she deviates from the professional standard and the applicable protocols and guidelines, then this must be accounted for and if necessary be reviewed by a colleague. And finally, the Central Medical Disciplinary College (Dutch: Centraal Medisch Tuchtcollege) stated in 1992 that a physician must inform all fellow practitioners involved in the treatment of a patient of the experimental character of the suggested treatment.

Medical research: scientific aim If the aim of a new treatment offered to patients is not only therapeutic though also scientific in character, then this qualifies as medical research, as stipulated in the previously mentioned Article 1, section 2 of the Medical Research Involving Human Subjects Act (Dutch abbr: WMO). If a research protocol has been written and the new treatment is offered within the context of this protocol then the aim of the treatment is without a doubt scientific. However, even if there is no protocol present there may still be a research aim to the treatment and it could therefore also fall under the scope of medical research within the meaning of this law. These are often situations which involve carrying out extra procedures directly on patients alongside the new treatment (see Article 1, sub b of the WMO which determines that research falls under the law if ‘(…) participation involves being subjected to procedures or are required to follow rules of behavior’ (unofficial translation). This is the case if, for example, patients are to be randomized prior to the treatment, if extra measurements are to be taken, or extra blood or tissue is to be extracted than is necessary for the
treatment itself. If the WMO applies then written consent must be provided by the research subject for participation and the research protocol must be approved by an accredited MREC. The WMO and underlying legislation lists the criteria which must be met in order for an approval to be issued. One of these is the condition that there must be a reasonable assumption that the relevance of the research (new insights and knowledge) are proportional to the objections and risks for the research subjects involved, and that certain conditions must be met such as damage insurance coverage. A posterior analysis of research data or material gathered during a particular treatment falls outside the scope of the WMO as the patient is not directly involved in this procedure. This type of research was deliberately kept outside the scope of the WMO by the legislator as the stipulations covering it in the law were determined to be too strict. However, specific regulations do apply to this type of research and these are laid down in the Dutch Civil Code, under the Agreement on Medical Treatment Act (WGBO, see above) (on a legislative level), and in the behavior codes ‘Good Behavior’ (data) and ‘Good Practice’ (tissue) (on the level of self-regulation) of the Federation for Medical Associations.

3 PRACTICAL CASES

The 3 cases given below demonstrate how the above mentioned can arise in actual practical situations.

Case 1 An internist oncologist treats a few patients who have been diagnosed with a rare form of carcinoma, for which there is no specific treatment available, with a product that has been registered for use in treating not this but other malignant conditions, with the hope that the product will have a positive effect on the course of the illness. The doctor ensures the treatment results are carefully registered, primarily to evaluate his own work. If analysis of this evaluation shows that the results are positive, then he considers testing the product in a wider patient group.

Case 2 An ENT (ear, nose and throat) specialist has access to a new instrument which allows for an easier method of operating on difficult to reach tumors than the presently available standard method. This new instrument would strongly reduce the burden of surgery for the patients and would allow for a much quicker recovery period. He expects that the new instrument would achieve at the least similarly positive surgical results, though he cannot determine this with certainty. The doctor and some his colleagues therefore decide to split the patients who are eligible for a tumor resection in a random manner into two groups. The one group will receive the regular surgical procedure and the other the experimental treatment. The results of the two treatments are compared afterwards by examining the patient files.

Case 3 After determining that regular sleep medication does not seem to have any effect on a patient, the patient’s general practitioner (GP) prescribes a product which was not registered for this particular complaint though which is known to have a side-effect of drowsiness. The chosen experimental treatment turns out to be a huge success and therefore the GP decides to prescribe the same product for a larger group of patients who suffer from the same complaint, in the hope that the result was not just a coincidental finding in one patient, but that it will demonstrate a wider effect in patients with similar problems.

COMMENTS ON THE PRACTICAL CASES

How should the actions of the doctors in the above cases be viewed? In cases 1 and 3 the doctors have only the medical interests of their individual patients in mind when they decide to expose these patients to experimental procedures. As said earlier, in these cases they are theoretically not medical research in the sense of the WMO. Further to the example of the oncological treatment of the first case, another could be an experimental surgical procedure performed on a patient who would have otherwise died. The fact that a doctor reflects on his/her actions afterwards on the basis of documented information or blood extracted, that they possibly analyze these to be able to find answers to a question, and then perhaps publish the results of this analysis in a scientific journal, does not affect the conclusion.
Case 3 presents a special scenario. In this case a medicinal product which has not yet been tested with regards to its risks and possible side effects is offered to a larger group of patients after it was used successfully in the treatment of one patient. The question arises whether this is lawful within the context of an experimental treatment. The legislator made the following remarks on this during the parliamentary discussion of the what was then still a bill, the Medical Research Involving Human Subjects Act, in 1996: ‘If (...) [a doctor] has carried out a [new] procedure a number of times and is of the impression that this new procedure could be of benefit to other patients, then a clinical trial is undertaken to form a scientific basis for this assumption. A certain procedure and/or methodology is chosen for this. The interests of the individual patient being treated is not leading in the choice of which procedure/methodology is applied, as there is also the general aim of gaining knowledge into the improvement of the treatment of patients with a particular medical complaint. There is now evidently an entirely different main aim, namely increasing medical knowledge.’ The general practitioner from case 3 is therefore not allowed to prescribe the new ‘sleeping’ medication to a larger group of patients as an experimental treatment. He or she must first follow the official route of a clinical trial to gather the necessary evidence on the safety and effectiveness of the product concerned.

In case 2, from the outset the secondary aim of the application of a new surgical method was to gather and analyze information on the efficiency and effectiveness. Although there was no research protocol, there was the intention to split the patients who were eligible for the experimental treatment into various groups. As the WMO was applicable in this case, a research protocol must be written and submitted to an accredited MREC for approval.

**CONCLUSION**

Experimental treatment that is offered by doctors to a few patients without the pursuit of a scientific aim does not fall under the scope of the WMO. In this situation the doctor is only driven by the aim to try something new with purely the individual patient’s interests in mind, as existing therapies have demonstrated not to be effective (any more). However, as said before, despite ‘only’ the applicable regulations of the medical care profession (WGBO and quality legislation) apply in this case; these regulations do impose more rigorous stipulations for the actions of doctors with regards to a treatment which has not yet been tested.

The WMO and the conditions stated in it, such as those for written informed consent and review by an accredited MREC, are applicable when an experimental treatment is offered with the additional aim of gathering knowledge. If a research protocol has been put together then this is always the case, though it may also apply when planned research procedures are to be carried out.

Conflict of interest: none reported.
Financial assistance: none reported.
Accepted on 11 November 2009
For citations: Ned Tijdschr Geneeskd. 2010;154:A1197

**LITERATURE**


This article is a translated version of the paper ‘Experimentele behandeling van medisch-wetenschappelijk onderzoek?’ with minor modifications with permission from the publisher. The original paper was published in the Dutch medical journal NTvG 2010; 154:A1197.