ANNEX 7

SUMMARY OF OTHER (POTENTIAL) APPLICABLE LEGISLATION

Introduction

1. Below we will provide an overview of the European and Dutch laws and regulations that apply to processing medical and genomics data, besides the GDPR. Parties that process such data must comply with the Dutch Medical Research Involving Human Subjects Act ("WMO").

2. The Medical Research Involving Human Subjects Act draws a distinction between the investigator[1] (the party actually carrying out the research) on the one hand, and the sponsor[2] (the party actually taking the initiative for the research and the organisation thereof).[3]

3. The Embryo Act, the Population Screening Act, and the Medical Treatment Contracts Act, which apply to medical data and research in general are also for the sake of completeness.

Medical Research Involving Human Subjects Act ("WMO")

4. The Medical Research Involving Human Subjects Act[4] ("WMO") concerns the protection of (potential) subjects in medical-scientific research.

Applicability WMO

5. Research falls under the WMO if the following criteria are met: 1) it concerns medical-scientific research and 2) participants are subject to procedures or are required to follow rules of behaviour.

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[1] Article 1(1)(g) WMO: the investigator: a physician or a person as referred to in section 3 (e) [*the trial is to be performed at suitable institutions and by or under the supervision of persons possessing research expertise, at least one of whom possesses expertise of direct relevance to the procedures involved in the trial in which the subject is to participate*] who is responsible for the conduct of the clinical trial at a specific trial site. If the clinical trial is actually conducted by an employee or other assistant, then the party making use of that person's services is deemed to be the investigator.
[2] Article 1(1)(f) WMO: the sponsor: an individual, company, institution or organisation responsible for the initiation, management and/or financing of the clinical trial.
[3] We have not analysed the position of HMF under the WMO.
[4] Act of 26 February 1998 governing regulations concerning medical scientific research with humans http://wetten.overheid.nl/BWBR0009408/2017-03-01 (in Dutch).

i. It concerns medical-scientific research

6. The WMO defines research as "medical research, part of which involves subjecting persons to actions or imposing certain behaviours upon them"[5] but does not contain a clear and specific definition of medical-scientific research. The explanatory memorandum also speaks of "*research with the goal of developing or improving diagnostic methods and curative treatments*".[6] The Central Committee on Research Involving Human Subjects[7] assists in this by offering the following definition:[8]

   "*Medical/scientific research is research which is carried out with the aim of finding answers to a question in the field of illness and health (etiology, pathogenesis, signs/symptoms, diagnosis, prevention, outcome or treatment of illness), by systematically collecting and analysing data. The research is carried out with the intention of contributing to medical knowledge which can also be applied to populations outside of the direct research population.*"[9]

7. Medical research, therefore, must lead to general knowledge that may eventually benefit patients in general, but not solely the individual participant in the study.

8. Research with a medicinal product is also categorised as medical-scientific research. And behavioural-scientific research can in certain cases also be deemed medical-scientific.[10] Furthermore, nursing, physiotherapy and psychology research can in some cases fall under the WMO. The kinds of studies that do not fall under the WMO are, for example, studies relating to quality analysis of two different laboratory instruments with the aim of researching the possibility of switching to a cheaper instrument or research on the improvement of existing techniques for new applications. An example is research on the configurations and conditions of MRI to visualize certain organs, or on fMRI to be able to measure brain activity during certain tasks. However, as soon as such research is aimed at improving diagnostic possibilities of (f)MRI, it does fall within the definition of medical-scientific research.

9. of all DNA "faults" in the tumour. These activities fall within the definition of medical-scientific research.

ii. Participants are subjected to procedures or are required to follow rules of behaviour

10. In general, research with human subjects only falls under the WMO if there is an infringement of the physical and/or psychological integrity of the subject. The subject himself/herself must be physically involved in the research for the research to fall under the WMO. Therefore

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[5] Article 1(1)(b) WMO.
[6] *Parliamentary Papers II* 1991/92. 22 588, no 3, p. 7
[7] http://www.ccmo.nl/en/, accessed on 9 April 2018.
[8] CCMO memorandum – Definition of medical research 25 November 2005.
[9] Non-official translation.
[10] CCMO note - behavioural research, http://www.ccmo.nl/en/your-research-does-it-fall-under-the-wmo, accessed on 27 March 2018.

retrospective research/file research does not fall under the WMO. In that case the data is already available and not collected specifically for a medical-scientific research. The subject does not have to do or abstain from something on behalf of the research.[11]
A blood sample being taken from the participant for the purpose of scientific research: this always falls under the WMO as the participant is subjected to a procedure. If additional blood is taken for the research as part of a planned vene puncture or from an existing line, then the research also falls under the WMO.

Research during which a participant must provide one urine sample once, generally does not fall under the WMO. However, research during which urine samples must be provided over the course of a three-week period does.

11. The collection of data from cancer patients is carried out in cooperation with affiliated hospitals. Before treatment, doctors will ask their patient if they are willing to undergo a biopsy, a procedure to extract tissue from a tumour, and give blood.[12] Participants are therefore subjected to a procedure.

Rules on research involving human subjects

Approval committee

12. Research that falls under the WMO must first be submitted to an accredited medical research ethics committee ("MREC") or the Central Committee on Research Involving Human Subjects ("CCMO"). The WMO draws a strict distinction between research that falls under the jurisdiction of the CCMO and that of the accredited MRECs. In practice the majority of research protocols are reviewed by the accredited MRECs.[13]

13. The reviewing committee reviews research protocols in accordance with the WMO. Without a positive decision from an independent committee of experts it is forbidden to carry out research which falls under the WMO.

14. The committee competent shall only be empowered to approve a research protocol provided that:[14]
    a. *it is reasonable to expect that the trial will lead to the advancement of medical science;*
    b. *it is reasonable to expect that the advancement referred to under a could not be achieved without the participation of human subjects or by less radical means;*
    c. *it is reasonable to expect that the anticipated benefit to individual subjects and other present or future patients will be proportionate to the risks and inconveniences for subjects;*

[11] CCMO, Your research: does it fall under the WMO, http://www.ccmo.nl/en/your-research-does-it-fall-under-the-wmo, accessed on 27 March 2018.
[12] https://www.hartwigmedicalfoundation.nl/en/what-we-do/how-it-works/, accessed on 30 March 2018.
[13] http://www.ccmo.nl/en/medical-scientific-research-and-the-wmo, accessed on 19 March 2018.
[14] Article 3 WMO.

d. the methodology of the trial is to be of the requisite standard;
e. the trial is to be performed at suitable institutions and by or under the supervision of persons possessing research expertise, at least one of whom possesses expertise of direct relevance to the procedures involved in the trial in which the subject is to participate;
f. it is reasonable to expect that any payment offered to the subject would not be of undue influence upon the decision as to whether consent should be given for the subject's participation in the trial;
g. any payments to be received by the investigator and the institution at which the trial takes place are reasonably commensurate with the nature, scale and purpose of the clinical trial;
h. the research protocol clearly indicates the extent of the potential benefits of the clinical trial to the subjects involved in it;
i. the research protocol includes suitable criteria for the recruitment of subjects;
j. the results of the research will be made public by the central committee, unless the investigator objects;
k. the trial satisfies all other criteria which may reasonably be set for it.

15. A committee may suspend or withdraw its approval for a research protocol if it has objective grounds for considering that continuation of the trial would lead to unacceptable risks for subjects.[15]

Excluded subjects

16. It is prohibited to conduct trials involving as subjects persons of less than sixteen years of age or who cannot be deemed capable of reasonable assessing their interests in this respect. It is also prohibited to conduct trials involving as subjects persons whose actual or legal relationship with the sponsor or investigator or with the party recruiting the subjects is such that this relationship may reasonably be expected to be prejudicial to the principle of free participation.

17. This prohibition does not apply to scientific research that may be of benefit to the subjects involved and to scientific research that cannot be carried out with the assistance of subjects from the category to which the test subject belongs.[16]

Consent and information

18. It is forbidden to conduct trials:[17]
    a. if the subject has reached the age of sixteen years and if subsection (c) is not applicable: without the subject's written consent;
    b. if the subject is a minor of at least twelve years of age and if subsection (c) is not applicable: without the written consent of the subject and the subject's parents (if they exercise parental responsibility) or legal guardian;

[15] Article 3a(1) WMO.
[16] Article 4 and 5 WMO.
[17] Article 6 WMO.

c. *if the subject is at least twelve years of age but cannot be deemed capable of giving informed consent: without the written consent of the subject's parents (if they exercise parental responsibility), or legal guardian, or (if the subject is not a minor) his or her legal representative, or (if no legal representative has been appointed) the person authorised in writing by the subject to act on his or her behalf, or (if no such person is available) the subject's spouse, registered partner or other companion in life;*
d. *if the subject is a minor of under twelve years of age: without the written consent of the subject's parents (if they exercise parental responsibility) or legal guardian.*

19. If the subject is unable to write, consent may be given orally in the presence of at least one witness.[18] The substitute consent of the of the persons referred to in subsection c and d above must represent the presumed will of the subject.[19] If the clinical trial can be conducted only in medical emergencies in which the consent required cannot be given and if inclusion in the trial may benefit the person in urgent need of medical treatment, procedures to implement the trial may be undertaken without such consent for as long as circumstances continue to prevent the giving of consent.[20]

20. Before consent is sought, the investigator shall ensure that the person whose consent is required has been informed in writing and, if so desired, in a prior interview, of:[21]
    a. *the objectives, nature and duration of the trial;*
    b. *the risks which the trial would present to the health of the subject;*
    c. *the risks which premature termination of the trial would present to the health of the subject;*
    d. *the inconveniences which the trial might cause to the subject.*

21. The information shall be given in such a way that it is reasonably certain that the recipient has understood its implications. The recipient shall be given sufficient time for reflection to permit him or her to reach a considered decision on the request for consent on the basis of the information provided.[22] The investigator shall ensure that, where subjects are less than twelve years of age or are incapable of giving informed consent, information about the trial is provided by an appropriately trained person in a manner befitting their ability to understand.[23] The research protocol shall specify how the foregoing is to be implemented.[24]

[18] Article 6(2) WMO.
[19] Article 6(3) WMO.
[20] Article 6(4) WMO.
[21] Article 6(5) WMO.
[22] Article 6(6) WMO.
[23] Article 6(7) WMO.
[24] Article 6(8) WMO

22. The subject or, if that person is incapable of giving informed consent, the person who is competent to give substitute consent, may revoke consent at any time without giving reasons.[25]

23. The investigator is responsible for ensuring that the subject is informed in good time and is kept informed about the progress of the research. Additional information shall be provided upon request. The investigator shall be responsible for similarly informing any other person whose consent is required.[26] The investigator shall be responsible for ensuring that the privacy of the subject is respected as far as possible.[27]

24. The investigator shall be responsible for ensuring that before the trial commences those whose professional assistance is required for the conduct of the trial are informed of its nature and aim.[28]

Insurance

25. The trial may not be conducted unless at the time of its commencement a contract of insurance has been entered into covering losses due to death or injury resulting from the trial. Such insurance need not cover injury which is inevitable or almost inevitable, given the nature of the trial.[29]

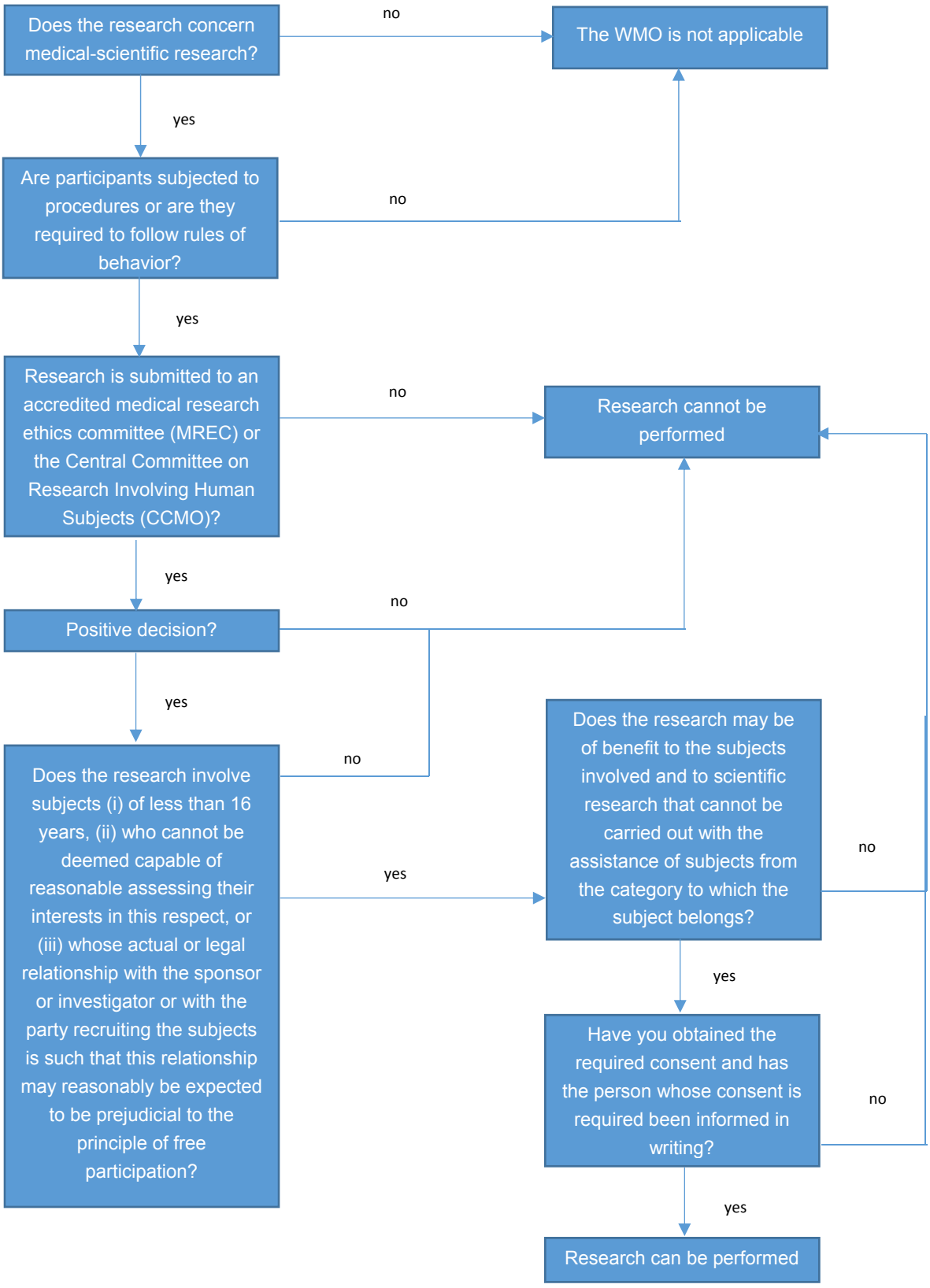
Supplementary rules for clinical trials involving medicinal products

26. The WMO provides additional provisions that apply to clinical trials involving medicinal products.[30]

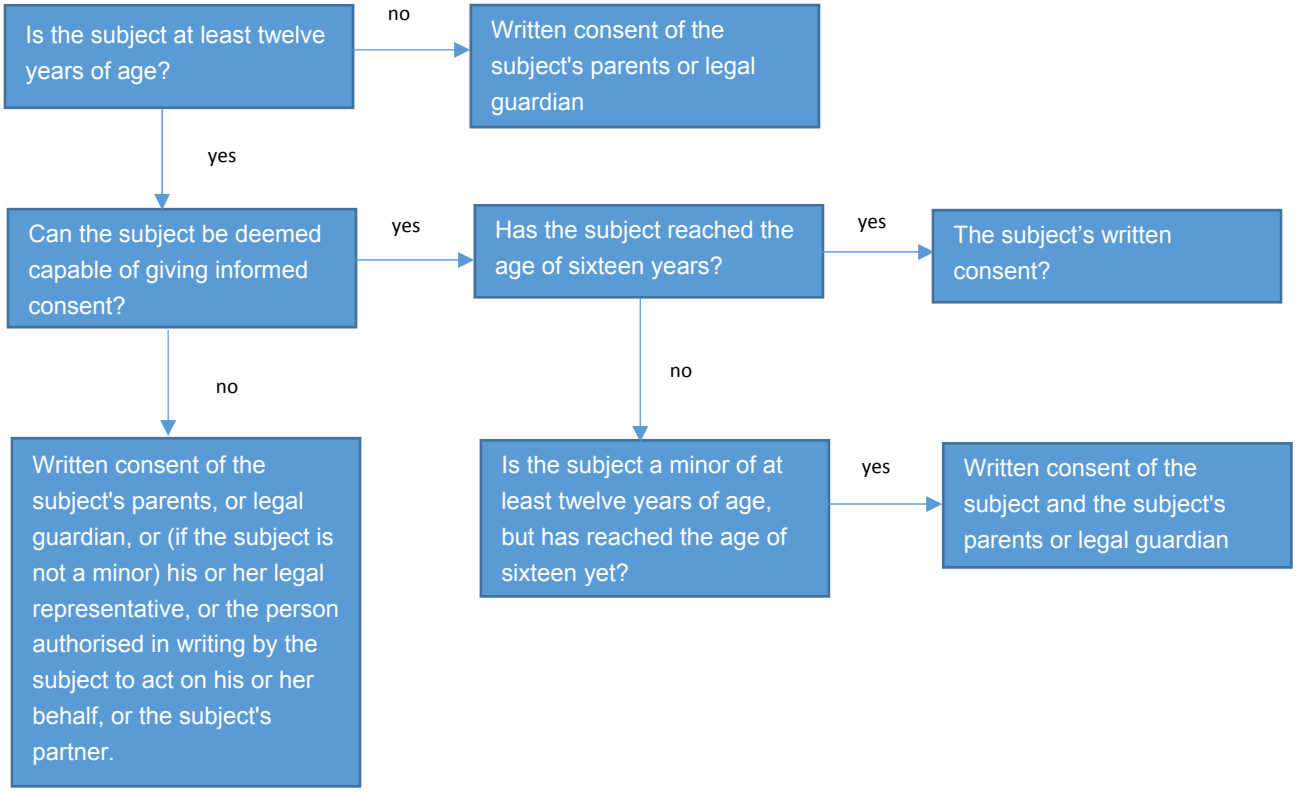
[25] Article 6(9) WMO.
[26] Article 11 WMO.
[27] Article 12 WMO.
[28] Article 13 WMO.
[29] Article 7 WMO.
[30] Article 13a-13r WMO.

WMO overview

i. Does the WMO apply to my research?



ii. Consent


Is the subject at least twelve years of age?
no
Written consent of the subject's parents or legal guardian
yes
Can the subject be deemed capable of giving informed consent?
yes
Has the subject reached the age of sixteen years?
yes
The subject's written consent?
no
Written consent of the subject's parents, or legal guardian, or (if the subject is not a minor) his or her legal representative, or the person authorised in writing by the subject to act on his or her behalf, or the subject's partner.
no
Is the subject a minor of at least twelve years of age, but has reached the age of sixteen yet?
yes
Written consent of the subject and the subject's parents or legal guardian

Embryo Act

27. The Embryo Act contains rules relating to the use of human gametes and embryos.[31] According to the Embryo Act the managing board of an establishment where embryos are created outside the human body, or other procedures involving embryos are carried out, shall draw up a protocol regarding the use of gametes and embryos after receiving recommendations from the committee which, pursuant to the WMO, is charged with the assessment of research proposals for medical research in the establishment. Any changes and additions to the protocol shall likewise require prior recommendations from the aforementioned committee.[32] Since HMF does not use human gametes and embryos, the Embryo Act does not apply to HMF.

Population Screening Act

28. The WMO does not apply to clinical trials whose conduct requires authorisation under the terms of the Population Screening Act[33] and, in so far as these relate to clinical trials where the research protocol, pursuant to the Embryo Act, has been approved by the CCMO.[34]

29. The definition of population screening, as laid down in the Population Screening Act, is: "*medical research in persons carried out on an entire population or a category thereof aimed at the detection of certain types of disease or certain risk indicators for the benefit of the participating subjects".*[35] This definition contains a number of elements:
    - It must concern a medical research within the population screening.
    - The research must be carried out in the entire population, or a category thereof, that is it concerns screening. The investigator must be presented to the population or the population group through, for example, individual consultations, advertisements or other general communication, such as in the waiting room of the practice of the investigator.
    - The screening should partly take place for the benefit of the participants, so that the individual results of the research can be offered to every participant as a health care benefit. With 'partly' is meant that the research can possibly also be a 'trial population research' and may have a medical/scientific character.
    - The term 'disease' is defined in the wider sense to include disorders, pain, injuries, deficiencies, or other physical or psychological conditions.

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[31] Act of 20 June 2002, containing rules relating to the use of gametes and embryos (Embryo Act), http://wetten.overheid.nl/BWBR0013797/2013-09-27 (in Dutch).
[32] Article 2(1) Embryo Act.
[33] Population Screening Act of 29 October 1992, http://wetten.overheid.nl/BWBR0005699/2014-02-15 (in Dutch).
[34] Article 1(3) WMO.
[35] Non-official translation.

- Risk indicators are seen to be 'information on an individual containing details concerning the level of risk to that individual defined within a set time period and clinical manifestation. These increase the chance of contracting certain diseases.'

30. There are three categories of population research for which a license is required:
    i. population screening whereby ionising radiation is used;
    ii. population cancer screening;
    iii. population screening of serious diseases or defects for which there is no treatment and prevention is not possible.

31. A license must be obtained from the Ministry of Health, Welfare and Sport for population research.

32. Research can be both population research (as covered by the Population Screening Act) and medical/scientific research (within the sense of the WMO): the definitions of both legislations overlap. However, only one of the laws apply: in the case of research for which a license is needed the Population Screening Act Applies, and otherwise the WMO. Since HMF does not perform research carried out on an entire population or a category thereof, the Population Screening Act does not apply to HMF.

33. Research subjects who participate in population screening for which a license is required are also protected. The Population Screening Act has its own protection regime. In the case of screening for which a license is required, the Health Council is asked to give advice prior to the Minister reviewing the screening and issuing a license. The standards for execution of screenings are laid down in the Population Screening Act and the Population Screening Decree.[36]

Medical Treatment Contracts Act

34. The Medical Treatment Contracts Act[37] (in Dutch: *Wet op de geneeskundige behandelovereenkomst*) regulates the relationship between the patient and healthcare provider, and is therefore not applicable to HMF.

35. Retrospective research/patient file research does not fall under the WMO as the research subject is not physically involved in the research. The data being researched are also not being gathered for the sake of the research. Such research is only subject to the Agreement

[36] Population Screening Decree of 1 August 1995, http://wetten.overheid.nl/BWBR0007499/1996-07-01 (in Dutch).
[37] Medical Treatment Contracts Act of 17 November 1994, http://wetten.overheid.nl/BWBR0005290/2018-02-01#Boek7_Titeldeel7_Afdeling5 (in Dutch).

on Medical Treatment Act and, in certain cases, the General Data Protection Regulation (GDPR).

Final remarks

36. A legal framework is currently not available for the (further) use of human tissue for medical/scientific research. The regulation regarding the medical treatment contract does however contain a stipulation on the use of anonymous human tissue. Section 7:467 of the Dutch Civil Code (in Dutch: *Burgerlijk Wetboek*) states:

    '*Anonymous tissues and parts which have been separated from the body can be used for medical statistics or other medical/scientific research as long as the patient, from who the human tissue originates, has no objections against such research and the research is carried out with the necessary care*'.[38]

37. The second paragraph of section 7:467 of the Dutch Civil Code states that the human tissue used in the study, and any data generated from this, may not be traced back to the person. It also states that general information (issued prior to the treatment) and the possibility for the patient to object is sufficient for further use of non-traceable human tissue. Information and consent is repeatedly needed for human tissue which can be traced back to an individual (directly identifying or via a code).

38. The Dutch Federation of Biomedical Scientific Societies set up the Code of Conduct for Responsible Use.[39] This is a manual on responsible use of human tissue with regards to medical research.

[38] Non-official translation.
[39] Human Tissue and Medical Research: Code of conduct for responsible use (2011), https://www.federa.org/sites/default/files/digital_version_first_part_code_of_conduct_in_uk_2011_12092012.pdf.