



Netherlands National Committee
for the protection of animals
used for scientific purposes

The Availability and Accessibility of Human Tissue for Biomedical Research and Teaching



Policy advice of the Netherlands National Committee for the
Protection of Animals Used for Scientific Purposes

For laboratory animals of today and innovations of tomorrow

Netherlands National Committee for the protection of animals used for scientific purposes

The NCad

The Netherlands National Committee for the Protection of Animals Used for Scientific Purposes (NCad) is an independent advisory body that protects the welfare of experimental animals. The Committee does this by publishing opinions upon request and on its own initiative, by encouraging innovation and knowledge development, and by uniting stakeholders. In doing so, the NCad achieves visible improvements that are related to the Replacement, Reduction and Refinement (3Rs) of animal procedures and animal-free innovation.



Members of NCad

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Summary

Human tissue is an extremely important research and teaching resource, and it can help to validate or replace animal experiments. The National Committee for the Protection of Animals Used for Scientific Purposes (NCad) has set itself the task of answering this question:

To what extent is human tissue available for scientific research and teaching, and how can its availability and use be promoted, including to replace or complement the use of laboratory animals?

The report starts by describing the many pieces of legislation and ethical codes of conduct and guidelines that regulate and standardise the use of human tissue for research. It goes on to give an overview of the various sources of human tissue for use in research and teaching. It also points out some problem areas, one of which is the number of different pieces of legislation regulating the use of human tissue for research. The Control over Human Biomaterials Bill (conceptwet zeggenschap lichaamsmateriaal, WzI) is intended to link up the various pieces of legislation. Biobanks are often difficult to find and access, and their financial stability is frequently a concern. This problem can be overcome by investing in the professionalisation of biobank management. More research is needed into the possibilities of using human tissue in research, in particular post-mortem tissue. There also needs to be better harmonisation of decision-making between ethical review committees. Proper coordination of the licensing system for animal experiments with the review and assessment systems for the use of human material is needed to promote the use of human tissue in research.

The following recommendations are based on this report:

To the Minister of Agriculture, Nature, and Food Quality



1. **The NCad recommends that you support the Health-RI initiative actively and on a long-term basis**, also after the funding by the National Growth Fund ends.
2. **The NCad recommends that you urge the Minister of Health, Welfare and Sport to prioritise the promulgation of the Control over Human Biomaterials Act.**
3. **The NCad recommends that you stress to the Minister of Health, Welfare and Sport the importance of the harmonisation and mutual acceptance and recognition of appropriate WMO (Medical Research involving Human Subjects Act) committees** and their decisions on biobank material, samples from pathology archives and post-mortem tissue.
4. **The NCad recommends that you ensure that the licensing system for animal experiments is linked up with the systems for using human material when the Control over Human Biomaterials Act is implemented.**

5. **The NCad recommends that you draw the attention of the Minister of Health, Welfare and Sport to the fact that companies need to be clear** about the origin of human tissue in every case and that there must be informed consent for its storage and use.
6. **The NCad recommends that you stress to the Minister of Health, Welfare and Sport the importance of professionalising biobank management.**
7. **The NCad recommends that you ask the Minister of Health, Welfare and Sport to commission guidelines on the use of material from deceased persons** for research, to complement the concept-Control over Human Biomaterials Act.

To the:

8. **Dutch Pathological Society: The NCad recommends that you investigate ways of developing a post-mortem database.**
9. **Life Sciences degree courses: The NCad recommends that you have the use of human material included in the curricula.**

Table of contents

Summary	3		
Introduction	6		
Definition	7		
Method	8		
History	8		
 1. Legislation, ethical codes of conduct and guidelines	10		
Legislation	10		
<i>The Medical Treatment Contracts Act</i>	10		
<i>The General Data Protection Regulation (GDPR) and the GDPR (Implementation) Act (UAVG)</i>	11		
<i>The Control over Human Biomaterials Bill</i>	11		
<i>The Medical Research involving Human Subjects Act (WMO) and non-WMO research</i>	12		
<i>The Burial and Cremation Act</i>	12		
<i>The Embryos Act</i>	12		
<i>The Foetal Tissue Act</i>	13		
<i>The Population Screening Act (Wbo)</i>	13		
Ethical codes of conduct and guidelines	13		
General analysis	15		
<i>The donors</i>	15		
<i>Legislation, guidelines and codes of conduct</i>	15		
<i>Basic principles concerning donated tissue</i>	15		
<i>Quality criteria</i>	16		
 2. Sources of human tissue	17		
Commercial companies	17		
Biobanks	18		
Pathology departments	20		
Post-mortem bodies donated for scientific research and teaching	20		
Organs rejected for organ donation	22		
Fresh tissue	22		
Embryos	23		
Foetal tissue	23		
3. Conclusion	24		
4. Recommendations	26		
5. Experts consulted	28		
6. Appendix 1	30		

Introduction

Human tissue is an extremely important research and teaching resource. The expectation is that the use of human tissue will improve the translation, and hence relevance, of research findings to humans.¹ Increased knowledge of human tissue will also make research using human material more attractive, as it will help to accumulate data with the aid of which researchers can interpret their findings – reference data that are not yet available in many cases. It will also make it increasingly clear how human tissue can be used to replace or validate animal experiments. The use of Phase 0 clinical trials (including microdosing) could possibly play a role in reducing the numbers of animal experiments.² Phase 0 research involves studying the biological mechanisms that play a role in a disease or that are important in validating clinical models or the mechanism of action of a new drug in humans. Microdosing can be used in Phase 0 studies to study the uptake of a molecule in the human body. The greater knowledge will thus make it increasingly attractive to use human material in research.

The question we have set out to answer is this:

To what extent is human tissue available for scientific research and teaching, and how can its availability and use be promoted, including to replace or complement the use of laboratory animals?

This report identifies the current opportunities for and barriers to using human tissue in scientific research and teaching, from a national and international perspective. It also gives an overview of the relevant statutory frameworks and ethical codes of conduct and guidelines in the Netherlands, and discusses the sources of human tissue and potential problems with obtaining and using it, including in relation to the Control over Human Biomaterials Bill. It concludes with recommendations on ways of optimising the availability and findability of human tissue for scientific research and teaching.

¹ K. Herrmann, F. Pistollato and M.L. Stephens, 2019. Beyond the 3Rs: Expanding the use of human-relevant replacement methods in biomedical research. *ALTEX*. 36(3):343-352. doi: 10.14573/altex.1907031. PMID: 31329258.

² T. Burt *et al.* 2018. Phase 0, including microdosing approaches: Applying the Three Rs and increasing the efficiency of human drug development. *Altern Lab Anim*. Dec;46(6):335-346. doi: 10.1177/026119291804600603. PMID: 30657329.

Definition

The term 'human tissue' as used in this report (also referred to as 'human material') covers (primary) cells, tissue, organs, entire bodies, body fluids (e.g., blood, cerebrospinal fluid, urine etc.), embryos and foetuses. Tissue can be used fresh or stored frozen or fixed after having been removed or obtained. 'Fresh tissue' means tissue that is used for research after having been taken from a patient (e.g. during an operation) or a person who has recently died, without prior processing.

A good deal of human tissue will already have been fixed and embedded in paraffin blocks for diagnostic purposes. This material is stored in e.g. pathology departments. A good deal of other patient data, e.g. medical records and images (from all sorts of medical scans: MRI, CT, X-ray, PET, digital photos of tissue slices taken for pathological diagnosis, etc.), are also available for use in research. This report discusses the ways of using human tissue in scientific research but not the other available patient data mentioned above.

Method

In order to compile this report, a literature survey was conducted, websites of appropriate organisations were studied, an international questionnaire was sent out³ and experts were interviewed. The interviews were transcribed verbatim, summarised and checked by the interviewees. A few experts only provided written input.

History

The question we set out to answer is not new: an informal network, the European Network of Research Tissue Banks (ENRTB), was launched around the millennium as an initiative of representatives of seven European countries, following on from ECVAM workshops 32 and 44.^{4,5} The aim was to exchange experience and improve such things as the availability and quality of human tissue for biomedical research and biomedical tests, e.g. by drawing up Standard Operating Procedures (SOPs) for tissue banks containing human tissue.

The ENRTB was only short-lived. It transpired that there were not enough human tissue biobanks yet, they catered mainly to local needs, and local biobank networks proved unsustainable. Internationally, the situation was even more problematic, partly because the relevant laws – where they existed – differed from one country to another, which made the international exchange of human tissue difficult. The SOPs were never drawn up.

Jan van der Valk, involved in the ENRTB at the time, commented: “The biggest problem at the time was probably that many tissue banks were local initiatives and too dependent on too many different people with differing interests: for example, nursing staff who need to obtain informed consent from patients, and surgeons

³ The questionnaire was only completed by four respondents, and not in full by any of them, and we were therefore not able to obtain much information from it.

⁴ S. Orr *et al.* 2002. The establishment of a network of European human research tissue banks. *Cell Tissue Bank.* 3(2):133-7. doi: 10.1023/A:1022811232250. PMID: 15256890.

⁵ R. Anderson *et al.* 2001. The Establishment of Human Research Tissue Banking in the UK and Several Western European Countries: The Report and Recommendations of ECVAM Workshop 441,2. *Alternatives to Laboratory Animals.* 29(2):125-134. doi: [10.1177/026119290102900204](https://doi.org/10.1177/026119290102900204)

who were often willing to collaborate but uncertain about the ethical and legal aspects and had no direct interest in the research. Another barrier was 'competition' between surgeons and pathologists as to who has control over the material. Fast, reliable transport was also not always available, and there was uncertainty about the regulations and the ownership of the tissue, about payments, about who has control over the supply of tissue, about how a tissue bank for frozen tissue should be managed, and so on."



1.

Legislation, ethical codes of conduct and guidelines

It is important for researchers using human material to obey the laws and be aware of people's right to self-determination and data protection. As acting ethically is one of the main prerequisites for using human material, we first give an overview of the applicable laws and codes of conduct; we then discuss the available sources of human material for research.

Legislation

A series of laws apply to the use of human tissue for scientific research and (to some extent) teaching, namely the Medical Treatment Contracts Act (WGBO), the General Data Protection Regulation (GDPR), the General Data Protection Regulation (Implementation) Act (UAVG), the Control over Human Biomaterials Bill (WzI), the Medical Research involving Human Subjects Act (WMO), the Burial and Cremation Act, the Embryos Act, the Foetal Tissue Act, and the Population Screening Act (Wbo). A few other pieces of legislation touch upon the use of human tissue for research, e.g. the Organ Donation Act (WOD), the Healthcare Quality, Complaints and Disputes Act (Wkkgz), the Individual Healthcare Professions Act (BIG), the Special Medical Procedures Act (Wbmv), and the Public Health Act (Wpg). These are not discussed below, as they relate more to medical care than to scientific research.

The Medical Treatment Contracts Act

The Medical Treatment Contracts Act (WGBO)⁶ is the statutory basis for medical care. If a researcher wishes to use patient data (not only from medical records but also from tissue) for scientific research, the patient must give consent. Under certain conditions, and with the consent of the person from whom the material originates (or the parents e.g., in the case of embryos, fetuses and children), researchers may use the tissue for scientific research or store it for later use. The conditions can be found, among other places, at <https://elsi.health-ri.nl/>. The Medical Treatment Contracts Act also lays down exceptions to the requirement of informed consent, namely: (1) if consent cannot reasonably be obtained, e.g., because the donor of the material has died or cannot be

⁶ Civil Code, Book 7, downloaded 1/7/2020 from https://wetten.overheid.nl/BWBR0005290/2020-07-01/#Boek7_Titeldeel7_Afdelings



contacted, and (2) if consent cannot reasonably be required, e.g. because the researcher is using a large population. In these cases an ‘opt-out’ system is often used, i.e. consent is assumed unless the donor objects.⁷ There are a few exceptions to this opt-out system, namely: (1) if the research is expected to produce results that could be clinically relevant to the donor, (2) if the body material is being used for cell lines, organoids or patient-derived xenotransplantation (PDX) models, and (3) if another law applies to research using the material, e.g. the Burial and Cremation Act, Embryos Act or Foetal Tissue Act.

The General Data Protection Regulation (GDPR) and the GDPR (Implementation) Act (UAVG)

The Medical Treatment Contracts Act (WGBO) lays down the main prerequisites for using human material in healthcare. General rules on data protection are laid down in the General Data Protection Regulation (GDPR),⁸ which requires fresh consent to be obtained from the person from whom the material originates for each new use of the material. This only applies to material that is traceable to that person. There are exceptions: (1) if it would not be reasonably possible to obtain consent, or (2) if disproportionate efforts would be required to trace and contact the person from whom the material originates.

The GDPR (Implementation) Act lays down that the use of personal data for scientific research is permitted as an exception, provided the research is in the public interest, express consent has been given for ‘one or more defined purposes’ (subject to the principles of reasonableness mentioned above), and the person’s private life is not disproportionately harmed by the use of the material. The Health Research Code of Conduct (Gedragscode gezondheidsonderzoek)⁹, the Dutch manual par excellence on

the responsible use of personal data and body material for health research, states that subsequent re-use of the material should be taken into account when requesting consent for research using body material. This enables a kind of general consent to be obtained, and provides scope for not requiring fresh consent for every sub-study, i.e., an ‘opt-out’ system. Care providers that regularly access patient data and/or body material for a variety of health research may ask the persons concerned for general consent for its supply and further use (e.g., for scientific research and teaching). This is already standard practice in various university hospitals and top clinical hospitals.

The above rules do not apply to anonymised material until such time as the Control over Human Biomaterials Act enters into force (see below). This applies e.g., to material used for teaching purposes. The persons concerned must however be informed about the use of the material and be given the opportunity to object easily. This is referred to as the ‘opt-out plus’ concept.

The Control over Human Biomaterials Bill

The Control over Human Biomaterials Bill (WzI), before the House of Representatives at the time of writing, complements the Medical Treatment Contracts Act and other pieces of legislation. In particular, it lays down who has control over the use of body material, e.g., for blood transfusions and pathology, complementing other statutory frameworks. The consent of the person from whom the material originates plays an important role in this Bill too. It also makes an ethical review prior to the supply of human material compulsory, and provides a framework for the storage and use of material that becomes available after death for scientific research and teaching. This is discussed in the section on the Burial and Cremation Act. Researchers have criticised the current Bill, in particular as regards the requirement of active consent instead of the current ‘opt-out plus’ system. They fear that this will result in less and more selective material being available, in addition to higher administrative costs that will bear down on their research budgets.¹⁰ When the Act will enter into force is unclear.

⁷ ELSI Servicedesk (n.d.). *Servicedesk voor Ethische, Juridische en Maatschappelijke Vraagstukken Over Personalized Medicine & Next Generation Sequencing* [Service Desk for Ethical, Legal and Social Issues relating to Personalized Medicine & Next Generation Sequencing]. Downloaded 11/10/2022 from <https://elsi.health-ri.nl/categorieen/toestemmings-en-bezwaarprocedures>

⁸ Algemene Verordening Gegevensbescherming, geraadpleegd op 13-2-2023, https://autoriteitpersoonsgegevens.nl/sites/default/files/atoms/files/verordening_2016_-_679_definitief.pdf

⁹ COREON, 2022. *Gedragscode gezondheidsonderzoek. Verantwoord omgaan met (persoons) gegevens en lichaamsmateriaal bij gezondheidsonderzoek* [Health Research Code of Conduct: The responsible handling of personal data and body material in health research]. <https://www.coreon.org/wp-content/uploads/2022/01/Gedragscode-Gezondheidsonderzoek-2022.pdf>

¹⁰ S. Rebers et al. 2012. Zeggenschap over nader gebruik van lichaamsmateriaal [Control over the further use of body material]. *Ned Tijdschr Geneeskd.* 2012;156:A4485. <https://www.ntvg.nl/artikelen/zeggenschap-over-nader-gebruik-van-lichaamsmateriaal>



The Medical Research involving Human Subjects Act (WMO) and non-WMO research

When material is obtained in clinical trials, the Medical Research involving Human Subjects Act (WMO)¹¹ applies, in addition to the GDPR and the GDPR (Implementation) Act. A review of a research proposal of this kind is requested from the local Medical Ethics Review Committee (MERC). In other words, the WMO does not deal with the supply of material from biobanks: in such cases, an ethical review by a local MERC or biobanks review committee should be requested when making the application. Such review committees do not exist everywhere yet, and they are currently not required. With the introduction of the GDPR and the GDPR (Implementation) Act, the setting-up of non-WMO committees is being speeded up, but reviews are not uniform or harmonised, and when material from multiple institutions is involved ('multi-centre research'), a fresh review is carried out for each institution.¹² The Control over Human Biomaterials Bill makes such reviews compulsory. The Health Research Code of Conduct also makes it clear that this is desirable, but clear guidelines on review criteria, the strictness of reviews, a better definition of what non-WMO research is, and the national harmonisation and recognition of reviews and their results are still badly needed.¹¹

The Burial and Cremation Act

The Burial and Cremation Act lays down what must and may be done with the body of a deceased person. People are generally buried or cremated after death. In some cases, an autopsy is carried out (an internal examination of a person who has died). There is not much legislation on autopsies, resulting in a good deal of uncertainty. Autopsy falls under the Burial and Cremation Act, which refers to it as 'sectie' (another term for autopsy). The Act distinguishes between complete and partial autopsies. A complete autopsy involves making the body available to science, in which case it need not be buried or cremated and it may be used in its entirety for scientific research, with the exception of reproductive cells. Only one consent is

required for this, which is given before the death of the donor by the donor themselves.

A partial or 'medical' autopsy is carried out by a medical pathologist, and the material taken to answer the medical questions may also be used and stored for research. The Medical Treatment Contracts Act has a lot to say about body material taken during a person's lifetime, but there is no statutory regulation of the use of material from deceased persons for research, not even in the Burial and Cremation Act. The Control over Human Biomaterials Bill lays down that material that becomes available from autopsies may be stored and used for scientific research and teaching. This will not always require consent from an authorised person, as the same exceptions apply as to material taken during a person's lifetime (i.e., if it is impossible to obtain consent or that would require disproportionate efforts). If material is taken specifically for scientific research or teaching, the Bill lays down that informed consent must be obtained from the authorised person. Foetuses older than 24 weeks that die in the womb fall under the Burial and Cremation Act (those less than 24 weeks old are covered by the Foetal Tissue Act¹³). Until such time as the Control over Human Biomaterials Act enters into force, it is unclear to what extent material taken from a partial autopsy may be used for scientific research, as there are no codes of conduct or guidelines on this at present. The ethical aspects in particular are making many pathologists reluctant to collaborate.

The Embryos Act

Research using embryos is regulated in the Netherlands by the Embryos Act¹⁴ of 2002, which lays down that only embryos donated following in vitro fertilisation (IVF) treatment may be used for research, up to day 14 of their development, provided the Central Committee on Research involving Human Subjects (CCMO) grants consent. The Embryos Act¹⁵ also covers the use of reproductive cells, which requires a review by

¹¹ Wet medisch-wetenschappelijk onderzoek met mensen [Medical Research involving Human Subjects Act], 1998. Downloaded 1-1-2020 from <https://wetten.overheid.nl/BWBR0009408/2020-01-01>

¹² M. Boeckhout et al. 2020. Niet-WMO-plichtig onderzoek en ethische toetsing [Non-WMO research and ethical review]. <https://elsi.health-ri.nl/sites/elsi/files/2020-07/Verkenning%20nWMO-onderzoek%20DEF.pdf>

¹³ Wet foetaal weefsel [Foetal Tissue Act], 2001. Downloaded 19/3/2020 from <https://wetten.overheid.nl/BWBR0012987/2020-03-19>

¹⁴ Embryowet [Embryos Act], 2002. Downloaded 1-10-2020 from <https://wetten.overheid.nl/BWBR0013797/2020-10-01>

¹⁵ Embryowet [Embryos Act], 2002. Downloaded 1-10-2020 from <https://wetten.overheid.nl/BWBR0013797/2020-10-01>



the CCMO. The third evaluation of the Embryos Act in 2020¹⁶ resulted in a number of recommendations to expand and clarify it. One was that creating embryos for medical research should be permitted, and research using embryo-like structures (ELs) involving mainly human DNA and with the aim of simulating the organised development of an intact human embryo should be regulated by that Act. It was also recommended that the acceptability of raising the 14-day limit to 28 days be examined. What is being done with these recommendations is unclear as yet.

The Foetal Tissue Act

The Foetal Tissue Act in the Netherlands lays down that tissue from foetuses (from spontaneous or induced abortions) prior to week 24 of pregnancy that have lived outside the mother for a maximum of 24 hours may be used for 'medical purposes, medical and biological research or medical and biological teaching'. This requires the mother's express written consent. The biological father may object to the use of the tissue, in which case it cannot be used. The conditions and rules laid down by the institution where the foetus is born must also be met.

Model regulations for the use of institutions have been drawn up for this purpose,¹⁷ dealing with such things as:

- when the use of tissue is or is not permitted,
- review by a medical ethics committee,
- the mother's informed consent,
- the role of the biological father, and
- the traceability of the material. The use of tissue from foetuses born prior to 24 weeks pregnancy is not subject to the WMO or to CCMO approval.

¹⁶ W.J. Dondorp *et al.* 2021. Derde evaluatie embryowet [Third evaluation of the Embryos Act]. Commissioned by the Netherlands Organisation for Health Research and Development (ZonMw), 15/03/2021/Jeugd, ISBN 9789057631610. <https://open.overheid.nl/repository/ronl-dgab9cfa-7361-4500-90c0-f2cb91f1be3d/1/pdf/derde-evaluatie-embryowet.pdf>

¹⁷ A.P. Drogtróp *et al.* 2012, revised version 2018. Leidraad terbeschikkingstelling van foetaal weefsel [Guide to the provision of foetal tissue]. Ministerie van Volksgezondheid, Welzijn en Sport in collaboration with Nederlands Genootschap van Abortusartsen and Nederlandse Vereniging voor Obstetrie en Gynaecologie. <https://www.nvog.nl/wp-content/uploads/2019/05/Leidraad-Terbeschikkingstelling-van-foetaal-weefsel-2.0-2018.pdf>

The Population Screening Act (Wbo)

The Population Screening Act¹⁸ lays down the frameworks within which screening programmes can be carried out, e.g., for various types of cancer (including breast, bowel and cervical) and severe metabolic diseases (the heel prick test on newborns). It does not say anything about what should happen to the material thus collected, however: there are separate frameworks for this, e.g., for the cervical cancer screening programme¹⁹ and on the antenatal and neonatal screening programmes website.²⁰ In many cases a prerequisite is that the material must be used for research in the context of the disorder being screened for.

Ethical codes of conduct and guidelines

There are various national and international ethical codes of conduct and guidelines on the use of human tissue: a list can be found in Table 1. National legislation lays down to what extent a standard can be applied in the particular country. In many countries, including the Netherlands, this is not yet regulated.

¹⁸ Wet op het bevolkingsonderzoek [Population Screening Act], 1992. Downloaded 1/7/2021 from <https://wetten.overheid.nl/BWBR0005699/2021-07-01>

¹⁹ RIVM Centrum voor Bevolkingsonderzoek, 2019. Kaderdocument lichaamsmateriaal bevolkingsonderzoek baarmoederhalskanker [Framework document on body material from the cervical cancer screening programme]. <https://www.rivm.nl/sites/default/files/2019-01/Kaderdocument%20lichaamsmateriaal%20obvo%20bmk.pdf>

²⁰ RIVM (n.d.). Pre- en neonatale screening (PNS) [Antenatal and neonatal screening programmes]. <https://www.pns.nl/hiepriik/professionals/opvragen-data-en-bloed>



Table 1. List of relevant legislation and guidelines in the Netherlands

Act/guideline	application	geographical scope
Medical Treatment Contracts Act (WGBO)	The basis for medical care on living persons.	The Netherlands
General Data Protection Regulation (GDPR) + GDPR (Implementation) Act (UAVG)	General rules on data protection for living persons.	The Netherlands
Medical Research involving Human Subjects Act (WMO)	Material taken in the course of clinical trials, not in a care context.	The Netherlands
Burial and Cremation Act	Deceased persons, including dead fetuses born prior to 24 weeks.	The Netherlands
Embryos Act	The use for research of reproductive cells and embryos before day 14 of development.	The Netherlands
Foetal Tissue Act	The use of tissue from fetuses born prior to 24 weeks pregnancy that have lived for a maximum of 24 hours.	The Netherlands
Population Screening Act (Wbo)	The frameworks within which screening programmes can be carried out.	The Netherlands
Control over Human Biomaterials Bill (Wzl)	Who has control over the use of body material, complementing other statutory frameworks. The extension of active informed consent for the use of body material for research. Compulsory ethical review prior to the supply of human material. Frameworks for the storage and use of material that becomes available after death for scientific research and teaching. The benchmark in the Netherlands.	The Netherlands

Act/guideline	application	geographical scope
Health Research Code of Conduct ²¹	Fleshed out the general open-ended standards laid down in legislation. Applicable to all research designed to answer questions relating to disease, health and healthcare: research as defined in the Medical Research involving Human Subjects Act (WMO) (WMO research) + questionnaire surveys and biobank research and further use. Commands broad support and is used as the benchmark in Dutch research and teaching.	The Netherlands
Brain banking Code of Conduct ²²	Brain tissue in brain biobanks. Used as a guidance document for brain banks.	The Netherlands and international, worldwide
Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0) ²³	Generally applicable to cells and tissues used to create cultures. Used, but is not the general benchmark for research as yet.	Within the EU, international, worldwide
ISBER Best Practices: Recommendations for Repositories ²⁴	Biobanks and tissue banks/storage of human material. Not in general use in the Netherlands.	International, worldwide

²¹ COREON, 2022. Gedragscode gezondheidsonderzoek. Verantwoord omgaan met (persoons) gegevens en lichaamsmateriaal bij gezondheidsonderzoek [Health Research Code of Conduct: The responsible handling of personal data and body material in health research]. <https://www.coreon.org/wp-content/uploads/2022/01/Gedragscode-Gezondheidsonderzoek-2022.pdf>

²² N.M. Klioueva *et al.* 2015. BrainNet Europe's Code of Conduct for brain banking. *J Neural Transm* (Vienna). Jul;122(7):937-40. doi: 10.1007/s00702-014-1353-5. PMID: 25578485; PMCID: PMC4498226.

²³ D. Pamies *et al.* 2022. Guidance document on Good Cell and Tissue Culture Practice 2.0 (GCCP 2.0). *ALTEX*. 39:30-70. doi: 10.14573/altex.2111011. PMID: 34882777.

²⁴ L.D. Campbell *et al.* 2018. ISBER Best Practices: Recommendations for Repositories, 4th edition. International Society for Biological and Environmental Repositories (ISBER). https://cdn.ymaws.com/www.isber.org/resource/resmgr/best_practices_4th_edition/isber_best_practices_recomm.pdf



Act/guideline	application	geographical scope
American Association of Tissue Banks (AATB) Standards for Tissue Banking ²⁵	Tissue banks. Widely accepted and used as the standard e.g., by commercial organ donation companies, also in the Netherlands. No indications on the processing, storage and supply of body material.	Used as the standard for tissue banks in the USA and worldwide

General analysis

The donors

Many people are in favour of donating tissue for scientific research and the development of new medical treatments, especially if it is for their particular disorder or that of someone they know. The donors, usually represented by patients' organisations, are increasingly playing a role in identifying and prioritising research topics, in research advisory groups and steering groups, the implementation of research projects and the reporting and communicating of research findings. Patients are thus increasingly becoming partners in medical and biomedical research, consistent with the trend towards patient-focused healthcare in which patients themselves take responsibility for managing their care and health. Patients' knowledge and experience are very valuable to researchers; conversely, patients are keen to know what happens to their tissue. It makes sense, therefore, to involve patients in ethical reviews of applications for research that requires their tissue, laying down the rights of patients regarding their donations, access to existing samples on the part of research groups in other countries, the further use of existing samples, and the closure of biobanks. Donors also have concerns about such things as confidentiality, their own and other people's access to the material and the results obtained from it, and how that information is to be used.²⁶ These aspects are to some extent regulated by legislation, guidelines and codes of conduct.

²⁵ J.C. Osborne *et al.* 2017. American Association of Tissue Banks Standards for Tissue Banking, 14th edition. <https://static.squarespace.com/static/5f2dc76b6a743f2147b29a37/t/5f3334d9of2540201689051c/1597191396553/AATB+Standards+for+Tissue+Banking+-+14th+Edition-+-+Posted+8-3-16-.pdf>

²⁶ D. Mitchell *et al.* 2015. Biobanking from the patient perspective. *Res Involv Engagem* 1, 4. <https://doi.org/10.1186/s40900-015-0001-z>

Legislation, guidelines and codes of conduct

All the legislation, guidelines and codes of conduct combined are clear about the ethical aspects of using human tissue for scientific research and teaching. First, there must generally be informed consent from the donor, and it must be clear that the donor knows e.g., that the tissue may be used both in the Netherlands and elsewhere, and that it may be used by both non-profit and for-profit organisations. There are exceptions to this in the Netherlands in the case of untraceable (anonymous) material, or where consent cannot reasonably be obtained, or it would involve disproportionate efforts on the part of the researcher to obtain consent. Donors can lay down restrictions, and these must be respected. In the case of tissue from deceased persons, the wishes of the surviving relatives must also be treated with respect, and they must be allowed to grieve.

Basic principles concerning donated tissue

The general basis for the guidelines and codes is that it must be clear who owns the donated tissue and any patents resulting from the research. The donated human tissue must be regarded as a gift to humanity and treated as such. The donor must not gain from it financially, for instance, and the organisation that manages it must not make a profit. This is not something we can take for granted, as companies fulfil a market need for the supply of human body material e.g., for medical training. Body donation itself must never provide money to the donor or the deceased donor's family, as there must not be a financial incentive to donate body material. A company can easily make a profit by making human material available e.g., for a medical training course at higher than cost price: one reason for this is that the amount of material required for training courses can often not be supplied by University Medical Centres (UMCs). Also, those courses in themselves provide a lot of money for the departments organising them, which makes it difficult for universities to supply human material (from donated bodies) for this purpose. These organising departments therefore have both the money and the need to use material from commercial companies. The cost of this is passed on to society indirectly. It is undesirable, therefore, for body donation to be available to companies that profit from it.²⁷ It goes without saying, however, that the use of tissue by researchers must provide enough

²⁷ T.H. Champney *et al.* 2019. BODIES R US: Ethical Views on the Commercialization of the Dead in Medical Education and Research. *Anat Sci Educ.* May;12(3):317-325. doi: 10.1002/ase.1809. PMID: 30240149.



money to cover their running costs. A researcher must sign a document setting out the conditions for the use of the tissue and of the data obtained from it that could result in the identification of a person, for example a 'conditions for consent' form or Material Transfer Agreement (MTA) document.

Quality criteria

It is clear from the legislation, guidelines, codes and recommendations that the storage, management and use of tissue must meet certain standards. It is also important for information to be available on the origin of the tissue or cells (including cell lines, primary cells and organoids) in order to guarantee the reproducibility of the research. The following need to be known as a minimum: sex; age at the time of removal; whether it is an organ, a tissue or a biopsy; and whether it was taken from a living or a deceased donor. Precisely what basic criteria are needed will differ from one application to another, also depending on the amount of material available. In the case of a deceased donor, it is important to know the cause of death, if possible, and the time that elapsed between death, removal of the tissue and its processing (the ischemia time). The tissue (or the patient) also needs to have been tested for viral infections (at least HIV and hepatitis B and C), and all the special properties of the donor cohort must be known. If any additional medical (or other) data are appropriate and relevant, these must be obtained from the medical record, provided the donor gives or has given consent for this. It is also important to know what procedures the tissue or cells have undergone and how they have been preserved and stored (e.g., the freezing method and the method for the isolation of cells from tissues before freezing them).



2.

Sources of human tissue

Human material can be obtained for research and teaching from various sources. Researchers using human material often use material that is easy to remove and therefore easy (or easier) to obtain, e.g., biofluids, primary cells²⁸ and organoids. Company researchers generally have less easy access to human material than those at academic institutions and research institutes. The impression is that this is an ethically sensitive issue, as companies could allow commercial interests to prevail over societal interests. Donors themselves, however, do not always regard this as a problem; on the contrary, they want new medication to be developed (for a disorder that they are familiar with), for instance, and are keen to contribute.²⁹ The findability, availability and accessibility of tissues are often barriers to their use on a larger scale. Also, priority is often given to supplying smaller quantities of material to multiple researchers rather than larger quantities to a single researcher.

We list and discuss available sources below.

Making quality standards compulsory for human material and having support from suppliers provides better assurance of the quality of the material available, and this contributes to the translatability and replicability of data obtained from the material.

Commercial companies

A relatively easy way of obtaining human tissue is to buy cells, cell lines or pieces of tissue, as these provide relevant information, provided they retain their properties. The Cellosaurus database gives an impression of the availability of cell lines³⁰. Body fluids are

²⁸ J. Edwards *et al.* 2015. Human tissue models for a human disease: what are the barriers? *Thorax*. Jul;70(7):695-7. doi: 10.1136/thoraxjnl-2014-206648. PMID: 25631322; PMCID: PMC4483787.

²⁹ C.A.M. Krul *et al.* 2021. Adviesrapport ten aanzien van de haalbaarheid van VitalTissue [Advisory report on the feasibility of VitalTissue]. https://www.vitaltissue.nl/_files/ugd/9131f5_b1ee5d578d-d841958716e4a68aa38b.pdf

³⁰ Cellosaurus – a knowledge resource on cell lines, 2022. www.cellosaurus.org



also available commercially, including to researchers on request.³¹ Donors can register with companies of this kind voluntarily. The supplier deals with all the paperwork, provides information to the researchers on protocols and methods, and will often support them if there are problems e.g., with culturing cells. In order to ensure ethical standards and the quality of the material obtained, it is important for researchers to have information available on the origin of the tissue, proof of informed consent, how the material has been processed, and additional information such as the donor's sex, age and any medical irregularities, and to check it. It is also important to know what quality control tests have been carried out.

The quality of material can vary between providers. To check cell lines (whether they actually are the cells that the researcher thinks they are), use can therefore be made e.g., of short tandem repeat (STR) profiling, which looks at DNA patterns that are unique to cells from the original unique donor.³² A great deal of importance is also attached to particular accreditations and standards, although they are not statutorily required for companies providing human material for research and teaching. Standards used include ISO 9001:2015, AATB and ISBER. The last two are not officially recognised everywhere: AATB is a recognised seal of approval in the USA but not elsewhere. The ISBER guidelines relate to biobanks worldwide, but they are not officially accredited. ISO 9001:2015 is a general seal of approval for quality management that has official worldwide accreditation. It lays down standards for management and customer satisfaction, but it is not specific to biobanks or the quality assurance of tissues and materials, although customer satisfaction does of course go hand in hand with the quality assurance of 'products'.

³¹ Tissue Solutions. A BioIVT Company – website 2020. <https://www.tissue-solutions.com/donate-samples/#1574939775777-bdec902-7d12>

³² C. Corral-Vázquez et al. 2017. Cell lines authentication and mycoplasma detection as minimum quality control of cell lines in biobanking. *Cell Tissue Bank* 18, 271–280. <https://doi.org/10.1007/s10561-017-9617-6>

Good support from companies, including experience and expertise, helps to improve the quality of the research conducted using the cells. Researchers themselves are responsible for confirming these properties before using the cells in experiments.³³

Biobanks

Researchers can make use of material from a biobank relatively easily. Only one application needs to be made; if the donor is still alive, this needs to be approved by the local MERC or ERC of the hospital in charge of the biobank. There are currently no clear rules on material from deceased persons, which is why this material is sometimes not (or no longer) provided for research. Once the Control over Human Biomaterials Act enters into force, a non-WMO committee will be required to give consent for research using material of this kind. This will provide greater clarity for researchers and may result in more material being provided for research.

The findability and accessibility of biobanks is often still a barrier to researchers. Health-RI is developing a central infrastructure for the Netherlands.

Biobanks provide material for scientific and clinical purposes (e.g. blood for transfusions, material such as corneas and bones for transplantation). This dual function makes it more difficult to identify relevant samples, for biobanks to collaborate, and to harmonise the legislation,³⁴ as material intended for clinical purposes needs to meet different requirements from material intended for research. A great deal of work has already been done to improve the biobank infrastructure, in particular in the area of standardising the description of samples and clinical data, the quality of samples and laying down how consent for use is to be obtained.³⁵ These efforts have helped among other things to improve the findability of suitable samples, but researchers still have difficulty finding

³³ ZenBio Advanced Cell-based Solutions & Services (n.d.). Primary Cells white paper. https://www.zen-bio.com/pdf/PrimaryCells_whitepaper_ZenBio.pdf

³⁴ K. Beier and C. Len, 2015. Biobanking strategies and regulative approaches in the EU: recent perspectives. *Journal of Biorepository Science for Applied Medicine* 2015;3. <http://dx.doi.org/10.2147/BSAM.S64578>

³⁵ M. Castellanos-Urbe et al. 2020. Biobanking Education. *Biopreserv Biobank*. Feb;18(1):1-3. doi: 10.1089/bio.2019.29062.mjc. PMID: 31971815.



suitable human material in biobanks for their research. This is partly due to the accessibility of biobanks: in the case of some of them access is regulated worldwide, but access to other banks is limited to the researcher's research department or university. Strenuous efforts have been made in the past ten years to professionalise biobanks. Many European and national³⁶ initiatives are trying to make it easier to search for the right samples and avoid duplicate collections with the creation of online directories, portals and discovery platforms. On top of this, more and more countries are developing (or already have developed) a central infrastructure, making the human material available in a particular country easier to find and more accessible to researchers. In many cases there is a single point of contact for the submission of applications, which improves findability and accessibility and provides clarity about the legislation and regulations in force. In the Netherlands, Health-RI is setting up a Dutch health data infrastructure for research and innovation,³⁷ covering biofluids (e.g., blood, cerebrospinal fluid and urine) and images as well as body materials. Health-RI's aspiration is ultimately to include all Dutch biobank and health data initiatives (it already includes e.g. the BBMRI and Parelsnoer biobanks), in order to provide a single point of contact for researchers where all the information is pooled.

Investing in the professionalisation of biobanks will make it easier to ensure both their financial stability and the quality of materials.

Most biobanks in Europe are population or disease biobanks. Dutch examples of population biobanks include the Maastricht Study,³⁸ ERGO³⁹ and Lifelines.⁴⁰ Examples of disease biobanks are the Parelsnoer biobank,⁴¹ which comprises many smaller disease-

³⁶ E.g., in the United Kingdom: UK Tissue directory and coordination centre, UK clinical research collaboration. <https://directory.biobankinguk.org/>. In the Netherlands: BBMRI.nl catalogue (n.d.), <https://www.bbmri.nl/services/samples-images-data/catalogue>, etc.

³⁷ Health-RI: enabling data driven health, 2022. <https://www.health-ri.nl>

³⁸ De Maastricht studie [The Maastricht Study], 2022. <https://www.demaastrichtstudie.nl>

³⁹ Erasmus Rotterdam Gezondheid Onderzoek (ERGO) [The Rotterdam Study], 2019. <https://www.ergo-onderzoek.nl>

⁴⁰ Lifelines Biobank (n.d.). <https://www.lifelines.nl>

⁴¹ Health-RI: enabling data driven health, 2022. Multicenter klinische biobanken [Multi-centre clinical biobanks]. <https://www.health-ri.nl/parelsnoer>

specific biobanks, local tumour banks such as those of the Dutch Cancer Institute,⁴² the Netherlands Brain Bank,⁴³ and the biobank for foetal and embryonic tissue.⁴⁴ A special biobank is HUB Organoids:⁴⁵ this contains a collection of frozen organoids from epithelial tissue (e.g. lung, breast and bowel). The collection is as diverse as possible, containing organoids from many different donors, both sick and healthy. The material is collected through collaboration between HUB Organoids, ten hospitals throughout the Netherlands and a few hospitals abroad.

There are many organisational differences between these biobanks. To avoid fragmentation, there are various networks in the Netherlands and the EU, e.g., the Biobanking and Biomolecular Resources Research Infrastructure –European Research Infrastructure Consortium (BBMRI-ERIC),⁴⁶ which also has a Dutch branch, BBMRI⁴⁷.

There is a need for both healthy and abnormal tissue in biomedical research. For example, abnormal tissue can be used instead of animal models for particular diseases. Healthy tissue is used to study normal physiology. Projects such as Lifelines⁴⁸ and Generation R Next⁴⁹ provide biological material from healthy subjects.

One of the major concerns regarding biobanks is their financial stability. Characterising and cataloguing samples and donors is usually expensive, often making the long-term financial situation of biobanks uncertain. They need to be professionalised, including education on biobank management,⁵⁰ as developments in connection with biobanks are rapid, including in terms of technical capabilities, e.g., refined gene and protein

⁴² Netherlands Cancer Institute Antoni van Leeuwenhoek (n.d.). Core facility molecular pathology & biobanking. <https://www.nki.nl/topmenu/molecular-pathology-biobanking-core-facility/>

⁴³ Nederlandse Hersenbank, Nederlands Herseninstituut (n.d.). <https://www.hersenbank.nl>

⁴⁴ Amsterdam UMC, de Bakker group – Imaging Human Development (n.d.). <https://medischebiologie.nl/de-bakker-group/>

⁴⁵ HUB Organoids – A patient in the lab (n.d.). <https://www.huborganoids.nl>

⁴⁶ BBMRI-ERIC (n.d.). <https://www.bbmri-eric.eu>

⁴⁷ BBMRI.nl, 2019. Biobanking Netherlands – makes biosamples, images and data findable, accessible and usable for health research. <https://www.bbmri.nl>

⁴⁸ Lifelines Biobank (n.d.). <https://www.lifelines.nl>

⁴⁹ Generation R Next, 2022. <https://generationr.nl/next/>

⁵⁰ M. Castellanos-Urbe et al. 2020. Biobanking Education. Biopreserv Biobank. Feb;18(1):1-3. doi: 10.1089/bio.2019.29062.mjc. PMID: 31971815.



expression techniques, and those do not come cheap. BBMRI.nl has published an analysis of good practices for biobanks and a list of recommendations to contribute to their financial stability and sustainability in other respects.⁵¹ This shows that market analysis prior to the setting-up of a biobank is essential, and a quality management system helps with the continual optimisation of both supply and demand and quality. Biobank accreditation can also help to improve quality and stability. Accreditation is currently not compulsory for biobanks. NEN-EN-ISO 20387 *General requirements for biobanking*⁵² has been in existence since 2020, but it does not appear to be generally known and used as yet. NFS 96-900 certification⁵³ is another accreditation system specifically for biobanks, but it is only an officially recognised standard in France.

Researchers who need fresh material can collaborate with surgeons or pathologists. Tissue can be collected and stored during an operation in a way agreed by the doctor and the researcher, who receives the tissue directly from the operating theatre soon after it has been removed. Biobanks can also mediate between doctors and researchers, thus ensuring that the tissue required is made available to researchers soon after it has been removed. Consent for this must however always be obtained from the MERC first, along with informed consent from the donor.

Pathology departments

Pathology departments are a treasure trove for researchers wishing to use human tissue. They hold many kinds of human tissue taken for diagnostic or medical research, usually fixed in formalin and embedded in paraffin. All samples taken in the Netherlands since 1971 (over 77 million) are recorded and findable in Palga (www.Palga.nl), with nationwide coverage since 1991. They can be obtained for scientific research, and the Palga organisation helps with selecting and writing applications for tissue.

⁵¹ BBMRI.nl, 2019. Sustainable biobanking. <https://www.bbmri.nl/services/knowledge/sustainable-biobanking>, R. van der Stijl et al. 2020. Randvoorwaarden voor sustainable biobanking in Nederland [Preconditions for sustainable biobanking in the Netherlands]. BBMRI.nl. https://www.bbmri.nl/sites/bbmri/files/BBMRI-NL_Aanbevelingen%20orandvoorwaarden%20voor%20sustainable%20biobanking_stakeholders_2020_04_30.pdf

⁵² NEN, Stichting Koninklijk Nederlands Normalisatie Instituut, NEN-EN-ISO 20387:2020. <https://www.nen.nl/nen-en-iso-20387-2020-en-276001>

⁵³ Euro-quality system - Organisme de certification, 2022. NF S96-900 Biological resource centers. <https://www.euroqualitysystem.com/en/our-offers/nf-s96-900/>

Formalin-fixed and paraffin-embedded (FFPE) tissue is stored in 'blocks'. Their quality is stable, especially since 2000, when a switch was made to buffered formalin for tissue fixation. Current techniques also enable the blocks to be used for molecular analysis (proteins, DNA). The standard stains for each type of tissue can be obtained on request, and digital photos are available in many cases. The international initiative BIGPICTURE is working to make these digital images widely findable and accessible.⁵⁴

Direct collaboration with a pathology department can be useful to researchers. Many pathology departments (in university or research centres) have staff who are keen to collaborate and brainstorm with researchers on the design of their studies and what is needed before material can be provided. Researchers' special wishes can often be met as well. Collaboration of this kind is a protocol-regulated but easy-access route for researchers to obtain human tissue.⁵⁵

Post-mortem bodies donated for scientific research and teaching

Some people decide during their lifetime to register with a university medical centre (specifically the anatomy department) or company (e.g. RISE Labs⁵⁶) to donate their body after death for scientific research and teaching. Several hospital anatomy departments are finding that the number of people registering as donors exceeds their needs (approx. 120-150 per year) and have therefore imposed a halt on registration.

Since about 2005, companies in the United States have been offering people the opportunity to donate their body after death for research and teaching purposes. These companies focus mainly on the need for human tissue in medical training and to develop medical aids. For several years now, the for-profit organisation RISE Labs has been operating in the Netherlands, along with the non-profit organisation

⁵⁴ Bigpicture, 2022. <https://bigpicture.eu/what-bigpicture-about>

⁵⁵ Verbal communication with various pathologists

⁵⁶ RISE Labs lichaamsdonatie [RISE Labs body donation] – Research, Innovation, Surgical Education (n.d.). <https://www.riselabs.eu/lichaamdoneren>



United Tissue Network Germany in that country.⁵⁷ The expectation is that the number of companies in Europe to which people can donate their body after death will increase in the years ahead, given the increasing demand for human tissue resulting from the development of new medical technology.

Anatomy departments conserve (embalm) bodies and freeze organs or parts of organs. Some of the bodies are used to train medical students and surgeons. Embalmed bodies can be stored and used for years, demonstration specimens indefinitely, and frozen tissue – especially from the chest/abdomen/pelvis area – can be thawed out twice at most, after which it is cremated. Anatomy departments also carry out research using the material. Material can also be removed fresh⁵⁸ and processed at the request of researchers. It does not make sense for anatomy departments to become souped-up biobanks, as they have research and teaching responsibilities. Partnerships involving researchers from other departments using the dissection rooms, the available bodies and the techniques and expertise of staff of anatomy departments have more potential.

RISE Labs has greater capacity and operates in conditions different from those at university anatomy departments. The latter accept bodies within 24 hours of death, RISE Labs currently from 36 hours after death, because of Section 69(1) of the Burial and Cremation Act.⁵⁹ Anatomy departments enjoy an exemption. In future, RISE Labs may also apply for an exemption to the 36-hour rule if a requesting researcher has a specific need.

Human tissue from bodies made available to science after death may be used to develop new equipment or aids and for training and education, which could reduce the use of laboratory animals for these purposes.

RISE Labs freezes all the tissue, meeting the quality requirements and standards laid down by the American Association of Tissue Banks: the tissue is carefully handled, packaged and provided with multiple identity labels. Companies that specialise in supplying human materials for medical education or medical/biomedical research, including RISE Labs, mainly supply tissue to companies and universities to develop new equipment or aids (e.g. new knee prostheses) and to educate and train doctors to use them correctly on patients. The blood supply can be restored after death, enabling training to be given for particular operations.⁶⁰ The use of human material may reduce the use of laboratory animals for these purposes.

Some professionals involved in body donation have the idea that the full potential of the bodies donated to science is not being utilised. The possible uses of these bodies depend on the physiological changes that take place after death. What influence post-mortem processes have on the condition of the various tissues is not always known, hence it is unclear as yet what tissues could be used for purposes that would otherwise require animal experiments.

How long organs remain suitable for transplantation is known: the heart and lungs, for example, must be removed within four to six hours after death, the liver within 12 hours, and the kidneys within 24 hours.⁶¹ This suggests that donated bodies could also provide fresh tissue suitable for physiologically relevant research. A list or database of all the possible uses of this type of human tissue could be useful but does not exist as yet.

⁵⁷ United Tissue Network, 2022. Human tissue bank & anatomical tissue Germany. <https://unitedtissue.org/human-tissue-bank-germany/#!/about>

⁵⁸ Pathology departments within 24 hours after death, companies only from 36 hours after death.

⁵⁹ "Dissection shall not commence prior to 36 hours after death."

⁶⁰ Justia, patents – anatomy, physiology, therapeutic treatment, or surgery relating to human being. US Patent for post mortem reconstitution of circulation patent (patent #6,824,389), 2004. <https://patents.justia.com/patent/6824389>

⁶¹ Nederlandse Transplantatie Stichting (NTS) (n.d.). Orgaandonatie: Hoe gaat dat? [Organ donation: how does it work?] <https://www.transplantatiestichting.nl/donatie-transplantatie/hoe-gaat-orgaandonatie>



Organs rejected for organ donation

Not all organs removed for donation are actually transplanted in the end, for various reasons. They are usually rejected because they are not of sufficient quality for transplantation. Some of the rejected organs are used for research relevant to organ donation, and the remainder are destroyed. Organs and tissues rejected for organ donation could provide a worthwhile source of human tissue for researchers.

Around 2011, there was a marked increase in requests for tissue removal from donors for use in scientific research. The national removal teams committee (landelijk overleg uitnameteams), part of the Nederlandse Transplantatie Vereniging (Dutch Transplantation Society) that concerns itself with substantive issues regarding organ removal from post-mortem donors, had to decide whether the removal teams could collect the tissues requested. The first requests were mainly for organs rejected for transplantation; subsequent requests were more wide-ranging, for a whole range of tissues.

As only verbal consent is required for organ donation, requesting consent – compulsory written consent – for removing tissue for research could arouse suspicion, hence this is no longer being done.

Until about 2011, a blind eye was turned to the removal of tissues provided the documentation requirements were met, but the increased demand led to a need for better regulation. With the implementation of the Good Practice Code, explicit written consent was required for the removal of additional tissue for research, whereas verbal consent is sufficient for organ donation. This aroused suspicion among families of the deceased, and there was a risk that trust in organ donation procedures could be affected. In light of the shortage of organ donors, it was then decided to close the door firmly to the removal of other tissues for research. As a result of that decision, there has been no unrest about organ donation for the past five or six years. Research could possibly be done using residual tissue left after the removal of organs for transplantation, however: there would then have to be clear-cut agreements on the use of this tissue, and the family would have to give consent.

Researchers can obtain fresh tissue through direct collaboration with doctors or mediation through an organisation, if they have VitalTissue or a biobank in mind.

Fresh tissue

'Fresh tissue' means tissue containing living cells that is used for research after being taken from a patient (e.g. during an operation) or a person who has recently died, without prior processing. A pilot was launched a few years ago in the Netherlands with support from the transition to animal-free innovation (Transitie Proefdiervrije Innovatie, TPI) platform, known as 'VitalTissue'. The aim is to set up a supply chain between hospitals and researchers for the exchange of fresh residual tissue from operations. It is currently being examined how VitalTissue could be launched as a non-profit organisation. Pathology departments and biobanks can also mediate regarding fresh residual tissue, but often such mediation is dependent on personal contacts within the organisation concerned and therefore vulnerable.

The big advantage of using this tissue is that the patient themselves can give consent. Patients are very willing to donate tissue, and many doctors are open to collaborating with researchers. The statutory procedures required must be clear, however. Direct consultation between the doctor and the researcher can help to ensure that the tissue is of the required quality. In practice, however, researchers often have difficulty gaining access to fresh human tissue. Research market research by VitalTissue⁶² shows that the need for fresh tissue for scientific research in the Netherlands has increased. VitalTissue aims to focus on improving the exchange of residual tissue from surgery. The idea is that VitalTissue staff will help hospitals to supply the right material and organise a process whereby researchers receive material that is not traceable to the donor and that meets all the statutory requirements, including informed consent.

It is important for fresh tissue to be available for research. This is underscored by the fact that companies that adopt a similar approach to that of VitalTissue (e.g. Tissue Solutions⁶³) are already operating in this area, but with worldwide coverage. We are not aware of any experience with this company.

⁶² VitalTissue - Vitaal Weefsel. Iedereen heeft het in zich [Vital Tissue: everyone has it in them] (n.d.). <https://www.vitaltissue.nl/>

⁶³ Tissue Solutions, a BioIVT Company, 2020. Prospective collections. <https://www.tissue-solutions.com/services/prospective-collections/#1525083034191-794d07dc-efa>



Embryos

In the Netherlands, embryos are only created for the purpose of pregnancy. In vitro fertilisation (IVF) procedures, however, often yield embryos in addition to those replaced in the mother. The remaining embryos can be used for scientific research with the consent of the Central Committee on Research involving Human Subjects (CCMO). Embryos are used mainly for research designed to increase the IVF success rate, i.e. into the early development of the embryo, the placenta, causes of miscarriages, the development of defects and possible gene therapy to repair them. This latter type of research is not yet taking place in the Netherlands. In other countries, embryos are also already being used to harvest stem cells to treat particular degenerative diseases and genetic disorders. In 2016, scientists succeeded for the first time in keeping a human embryo in culture for more than seven days while preserving the right properties. After that it is currently still difficult to carry out reliable research using this tissue, as the cells change in culture.

Creating embryos and modifying them for research is banned in the Netherlands, hence it is not possible to study the effects of genetic changes on development using human embryos effectively. Human embryos consequently play a limited role in replacing animal models at present. If the Embryos Act were to provide more scope for creating embryos specifically for research, there would be more scope for studying the effects of genetic changes on development directly in human embryos, which would reduce the use of mice in particular for this type of research. Embryo-like structures (ELs) that are cultured from human stem cells but lack typical structures required for further development (e.g. the placenta) and cannot therefore grow into a human being⁶⁴ could meet a need here. They do develop a primitive streak, for example, thus enabling research into its formation. Effects of genetic changes on the early development of an embryo could also be studied using ELs, for instance, and they could be used for toxicology tests.

⁶⁴ D. Cyranoski, 2019. Embryo-like structures created from human stem cells. Nature. doi: 10.1038/d41586-019-02654-w. PMID: 32908288.

The statutory frameworks do not currently make it clear to what extent their use is permitted for research. There is plenty of material, as parents often do not consent to the destruction of the embryos but are open to the possibility of making them available for research. Because of the strict regulations, however, there are few licence applications, and few embryos are used for scientific research.⁶⁵

Foetal tissue is used for a wide range of research. It is immature tissue, however, hence caution is called for when extrapolating results to adult human tissue.

Foetal tissue

Foetal tissue that can be used for research in the Netherlands comes mainly from the eight abortion clinics in the country. Abortion is permitted in the Netherlands up to 24 weeks pregnancy. Most abortions (59%) take place during the first eight weeks, and 25% between the eighth and twelfth week.⁶⁶ This tissue falls under the Foetal Tissue Act and can only be used with the consent of the mother and the local MERC. The biological father can object to the use of the tissue, in which case it cannot be used.

Foetal tissue is used for a whole range of scientific research, including toxicology, regenerative medicine, virology, and research into organ development. It is also used for vaccine production and transplantation. Research requires more donated fetuses born after 24 weeks pregnancy, e.g. to study normal and abnormal development, but these fall under the Burial and Cremation Act and body donation.

⁶⁵ Verbal communication with Prof. Susana Chuva de Sousa Lopes of the Department of Anatomy and Embryology, Leiden University Medical Center.

⁶⁶ Rutgers (n.d.). Feiten en cijfers abortussen in Nederland [Abortion facts and figures in the Netherlands]. <https://rutgers.nl/themas/abortus/feiten-over-abortussen-in-nederland/>

3.

Conclusion

We conclude that there are many ways for researchers to use human tissue. Research using human tissue and animal experiments complement each other, and combining them could improve the quality of research. It is not possible to indicate precisely, based on the present analysis, to what extent research using human tissue could replace animal experiments: there are as yet no hard figures on the effect that using human tissue has on the use of laboratory animals. It is likely, however, that improving the opportunities for research using human tissues could make certain types of animal experiments unnecessary, as using human parts will improve the translatability of results to humans. In future, we expect animal experiments to be increasingly targeted, following in vitro research using human material. The use of Phase 0 clinical trials (including microdosing) could also be an alternative to animal experiments in some cases.⁶⁷ This is beyond the scope of this report, however, and requires further exploration.

Human tissue can be obtained in various ways. There are commercial companies from which researchers can order tissue or cells. Pathology departments store all tissues taken for medical research, and these are available to researchers. Researchers can collaborate directly with pathologists and doctors to obtain tissue for research purposes. There are also companies and organisations that mediate between researchers and doctors, e.g., biobanks and – possibly in future – VitalTissue. Human tissue from bodies made available to science (both universities and companies) after death may be used to develop new equipment or aids and for training and education. Foetal tissue is used for a whole range of research. The use of human embryos for research is restricted in the Netherlands, but there may be more scope for this with the use of embryo-like structures (ELs).

Some problem areas have been pointed out, however: first, there are many different pieces of legislation in the Netherlands regulating the use of human tissue for research. There are also gaps in the current legislation that will not all be regulated by the Control over Human Biomaterials Bill (Wzl). A guideline on the use of post-mortem tissue could provide clarity

⁶⁷ T. Burt et al. 2018. Phase 0, including microdosing approaches: Applying the Three Rs and increasing the efficiency of human drug development. *Altern Lab Anim.* Dec;46(6):335-346. doi: 10.1177/026119291804600603. PMID: 30657329.

regarding the use of this material. Not all of the possible uses of tissue from donated bodies in scientific research are in fact known as yet: this is an area of research that could potentially prove fruitful.

Research using embryos is highly regulated, which makes it difficult for researchers to obtain consent for it. Written consent is required for research using tissue from organ donors. As only verbal consent is required for organ donation, requiring written consent for research using other tissue could arouse suspicion, hence this is no longer being done. As the organ donation process is trusted and is not giving rise to unrest, it is thought undesirable in transplantation medicine circles to embark on yet another debate about the provision of tissue for research and teaching.

More general, broad-based consent for research using human tissue could also help to make it more accessible for research. Proper coordination of the licensing system for animal experiments with the review and assessment systems for the use of human material could help to draw the possibility of using human tissue to the attention of a wider group of researchers. In addition, it could make the process leading up to consent for the use of human material easier and help to avoid duplicate paperwork.

Non-WMO committees – which will be required if the Control over Human Biomaterials Bill becomes law – review everything that does not fall under the Medical Research involving Human Subjects Act (WMO) and does not require a review by a Medical Ethics Review Committee (MERC). Decision-making by non-WMO committees needs to be harmonised in the Netherlands, as different decisions are currently being made by ethical review committees in various organisations in this country. Moreover, decisions by ethical review committees are not mutually recognised and accepted, which makes it more complicated for researchers to use human tissue. Health-RI could play a major role in collaboration with the Central Committee on Research involving Human Subjects (CCMO) – possibly at a later stage – in the harmonisation and uniformity of decision-making by MERCs and non-WMO committees concerning non-WMO research. There also needs to be a better link-up with animal experiments.

Another concern that may be an obstacle to the wider use of human tissue is the fact that biobanks are often difficult to find and access. There is a clear-cut quality standard that they ought to meet, NEN-EN-ISO 20387:2020, which includes quality standards for the tissue available, but it does not appear to be generally known and used as yet. This hampers the replicability and translatability of the data. The financial stability of biobanks is also a concern. These obstacles could be addressed by investing in the national infrastructure that Health-RI is working on and professionalising biobanks, both by training their managers and requiring biobank certification.

The situation in Europe and worldwide is similar to that outlined in the Netherlands.⁶⁸

⁶⁸ Physicians Committee for Responsible Medicine, 2018. Human Tissue Roundtable: increase the availability and quality of human tissue in science – Roundtable flash report. <https://www.pcrm.org/sites/default/files/2019-02/Human%20Tissue%20Roundtable%20Summary%20Report%20Final.pdf>

4.

Recommendations

To the Minister of Agriculture, Nature and Food Quality:

1. **The NCad recommends that you support the Health-RI initiative actively and on a long-term basis**, also after the funding by the National Growth Fund ends. The infrastructure that Health-RI is working on will improve the findability and accessibility of human material and the results obtained using it, and will promote the harmonisation of rules and guidelines, by providing a single point of contact for all the information required. This is in line with the aims of the transition to animal-free innovation (Transitie Proefdiervrije Innovatie, TPI) platform. If support were also provided from the Ministry of Agriculture, Nature and Food Quality – e.g. through TPI –, there could be a link-up with researchers using laboratory animals.
2. **The NCad recommends that you urge the Minister of Health, Welfare and Sport to prioritise the promulgation of the Control over Human Biomaterials Act.** This Act will create clarity regarding the further use of body material for research and teaching, and a framework for the use of post-mortem tissue. It also makes an ethical review compulsory before material is supplied, which could overcome potential ethical and moral objections e.g. on the part of doctors assisting with the collection of material.
3. **The NCad recommends that you stress to the Minister of Health, Welfare and Sport the importance of the harmonisation and mutual acceptance and recognition of appropriate WMO (Medical Research involving Human Subjects Act) committees** and their decisions on biobank material, samples from pathology archives and post-mortem tissue. This will promote access to human tissue obtained from clinical trials and collaboration between doctors and biomedical researchers, and the combined use of material available from various sources at various institutes.
4. **The NCad recommends that you ensure that the licensing system for animal experiments is linked up with the systems for using human material when the Control over Human Biomaterials Act is implemented.** If work takes place to optimise exchange and cross pollination between the licensing system for animal experiments and the review and assessment systems for the use of human material at the implementation stage of the Control over Human Biomaterials Act, this will draw the possibility of using human tissue to the attention of a wider group of

researchers. The Central Authority for Scientific Procedures on Animals (CCD) and representatives of researchers should ideally be involved here, as this will improve review committees' awareness of ways of answering research questions without animal experiments.

5. **The NCad recommends that you draw the attention of the Minister of Health, Welfare and Sport to the fact that companies need to be clear** about the origin of human tissue in every case and that there must be informed consent for its storage and use. We recommend that you consider the possibility of banning the commercial exploitation of human body material, as this would make the system transparent, reduce the cost of using human material for research and teaching, and could avoid public suspicion.
6. **The NCad recommends that you stress to the Minister of Health, Welfare and Sport the importance of professionalising biobank management.** This can be achieved by:
 - a. investing in a solid knowledge base for the professional management of biobanks in the Netherlands.
 - b. requiring official accreditation (e.g., NEN-EN-ISO 20387:2020) for biobanks, pathology archives and companies trading in human material.
 - c. coordinating national standards internationally to increase the geographical availability of human tissue for research.
 - d. providing a point of contact for researchers to obtain assistance with deciding on their study design, selecting the right material and carrying out analyses, e.g., as part of Health-RI.
7. **The Ncad recommends that you ask the Minister of Health, Welfare and Sport to commission guidelines on the use of material from deceased persons** for research, to complement the concept-Control over Human Biomaterials Act. A good deal of potential is currently going unused, because the rules on the use of material from deceased persons are too unclear and too open-ended. Existing guidelines and codes of conduct (Brain Research, AATB, etc.) could be used to develop a guideline.

To the:

8. **Dutch Pathological Society: The NCad recommends that you examine the possibilities of developing a post-mortem database** to collect information on the purposes for which tissues can be used post-mortem, in order to make the potential of post-mortem tissue for scientific research clearer.
9. **Life Sciences degree courses: The NCad recommends that you include the use of human materials in life sciences curricula** in order to increase awareness of this research field and develop it.

5.

Experts consulted

In preparing its recommendations, the NCad makes grateful use of the services of experts in the Netherlands and elsewhere. Stakeholders and supply chain partners are also consulted. The experts consulted are not co-authors of this NCad report, and their views on certain matters may differ from those presented in it by the NCad.

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6.

Appendix 1

Appendix List of sources of human tissue referred to in this report

Below is a list of links to organisations, biobanks and human tissue projects that Dutch researchers can make use of. It is not exhaustive, but in our opinion, it provides sufficient jumping-off points for researchers to locate human tissue relevant to their research.

Infrastructures

Health-RI: a national and international integrated health data infrastructure (including human tissue, biomaterials, imaging data) based on the FAIR principles: [Data Driven Health: Connect, Share and Reuse | Health-RI](#)

ELSI Service Desk for Ethical, Legal and Social Issues relating e.g. to the use of human material in research and teaching [ELSI Servicedesk | Elsi Servicedesk \(health-ri.nl\)](#)

BBMRI-NL: a searchable database containing information on over 200 biocollections and data collections in the Netherlands: <https://www.bbmri.nl/services/samples-images-data/catalogue>

European research infrastructure for biobanks, for research using human tissue and biomaterial: [Home - BBMRI-ERIC: Making New Treatments Possible](#)

Bigpicture: a European platform for pathology images and AI algorithms: [What is Bigpicture about? | Bigpicture](#)

Population biobanks

[Homepage | De Maastricht studie](#) The Maastricht Study is a unique survey of the population of South Limburg into the incidence, causes and treatment of type 2 diabetes, cardiovascular disease and other chronic disorders.

[The ERGO study \(ergo-onderzoek.nl\)](#) a Rotterdam survey into healthy ageing

[The Lifelines Biobank](#) health data on thousands of people for research into healthy ageing.

[Generation R Next - Generation R](#) – monitors the growth and development of a new

generation of Rotterdam children (starting with prospective parents before pregnancy, in the womb, and after birth).

Data and blood from antenatal and neonatal screening programmes: [Opvragen data en bloed | Prenatale en neonatale screeningen \(pns.nl\)](#)

Cell lines

Cellosaurus – a knowledge resource on cell lines. www.cellosaurus.org

Fresh tissue (healthy)

VitalTissue (not yet operational): fresh human tissue for scientific research (Netherlands) [HOME | Vitaltissue](#)

Through collaboration with surgeons and/or pathology departments.

Diseased + Healthy tissue

Tissue Solutions: for human tissue and biomaterials (Worldwide) [Tissue Solutions | Virtual Biobank | Provider of Human Tissue & Biomaterials \(tissue-solutions.com\)](#)

Embryonic and foetal material: [de Bakker group – Medical Biology – AMC \(medischebiologie.nl\)](#)

Organoids from a wide range of epithelial tissues: [HUB Organoids: Patient in the lab](#)

Disease or organ-centred

[Multicenter klinische biobanken | Health-RI](#) Multi-centre clinical biobanks: material collected for particular diseases

Netherlands Cancer Institute (NKI) biobank for blood, DNA, RNA, histology samples, biopsy material from NKI patients. [Core Facility Molecular Pathology & Biobanking \(CFMPB\) | Netherlands Cancer Institute](#)

Netherlands Brain Bank: fresh brain tissue: [Welkom bij de Nederlandse Hersenbank \(NHB\)](#)

Local central biobank of UMC Groningen: [UMCG Cohort and Biobank Coordination](#)

[Hub \(umcgresearch.org\)](http://umcgresearch.org)

Post-mortem human tissue: Body donation

RISE Labs: body donation – post-mortem human tissue for research and teaching ([RISE Labs](#))

United Tissue Network: body donation organisation in Germany – for post-mortem human tissue for research and teaching: [Human Tissue Bank Germany | Anatomical Tissue - United Tissue Network](#)

Body donation through Dutch universities: <https://www.lichaamsdonatie.info>. Researchers can gain access to tissue through anatomy departments.

Contact

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February 2023 | Publication-nr. 23400365