

Human Tissue and Medical Research: Code of Conduct for responsible use (2011)

**English translation of the “Gedragscode 2011:
Verantwoord omgaan met lichaamsmateriaal ten behoeve van
wetenschappelijk onderzoek”**

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Code of Conduct for responsible use of
human tissue in the context of health research

Human Tissue and Medical
Research: Code of Conduct
for responsible use (2011)

Drawn up by the FEDERA
in cooperation with:
Patiëntenfederatie NPCF
Vereniging Samenwerkende Ouder- en Patiëntenorganisaties (VSOP)
Biobanking and biomolecular research infrastructure for the Netherlands (BBMRI-NL)

About the FEDERA

www.federa.org

Federa stands for the Federation of Dutch Medical Scientific Societies (FDMSS). The FDMSS aims to represent the various professional and scientific biomedical societies by promoting interdisciplinary communication and self-regulation. Self-regulation has become a major activity e.g. by means of Codes of Conduct. FDMSS represents more than 35 scientific biomedical societies with all together 13,000 members.

Within FEDERA the Committee for Guidelines in Research (COREON in Dutch) is responsible for development and publication of Code of Conducts. COREON consists of representatives from 26 research organisations, 7 scientific societies, and 2 university medical centers, thereby representing all important research organisation in medical and health research in The Netherlands.

Foreword

This second version of the Dutch Federa developed self-regulatory code of professional biomedical conduct regarding secondary use of tissue and cells and 'de novo' biobanking follows the footsteps of the first code developed during 1999-2001. www.federa.org

The Federa is a 50+ year old voluntary association of about 35 biomedical scientific societies of which about one third in clinical disciplines, including among others paediatricians, geriatricians, medical microbiologists, rheumatologists, pathologists, immunologists, hematologists and medical oncologists. From almost all of these societies, representatives have had input in this code, in addition to the valuable contribution of geneticists and especially epidemiologists who are very active in large cohort studies and collaborative studies. Patient representatives also had their input especially on difficult issues such as tracing back patients with unexpected research findings. Please read appendix 3 for the elaborate argumentation by Mr Evert-Ben van Veen, LLD, of MedLawconsult (The Hague) who drafted the texts largely.

This English translation, also replacing the previous one, not only allows for high integrity participation in international studies or show editors of scientific journals how Dutch biomedical scientists managed their human tissue & cellular research activities covered by the code (the 2001 version only gradually being replaced by the 2011 version)

This domain of increasingly translational medicine thus enjoyed a strict but light regulatory touch during the first decade of the 21st century within the Netherlands, certainly in those hospitals which implemented the 2001 version by amongst others informing newly diagnosed patients that letting their material being used for research is to be the default option for research use. Patients can always opt out from this default situation. Quite much of that scientific or evidence seeking activity has a quality of care purpose which all patients subscribe to anyway, i.e. consisting of validity checks of their disease definition.

We consider this Code of Conduct also as good practice to be included in any European collaborative translational research activity and thank all the participants and the research institutes which contributed financially through the COREON, a FEDERA subcommittee which discusses regulatory aspects of medical research.

Prof dr J.W.W. Coebergh
Chair FEDERA / COREON, 2011

Added foreword in 2015

This Code of Conduct has been distributed widely among academic medical centres, research organisations, hospitals, patient organisations as well as all medical ethical committees in the Netherlands.

On June 29, 2012, a congress was held on implementation of this Code of Conduct with over 1100 participants. In 2014 the Dutch initiative Biobanking and Biomolecular Research Infrastructure published a guidance on involvement of patients and their organisations in biobanks, using the Code of Conduct to link governance of biobanks with informed consent modalities. Currently, a new structure for medical ethical evaluation is being developed, taking as starting point the guidance presented in chapter 9 of this Code.

Given the rapid developments in the area of use of patient material for research, several issues have emerged that will need to be addressed in future updates of this Code, for example data linkage and privacy protection, and notification of patients of particular medical findings which may be important for their health. In order to facilitate this development, we have decided in 2015 to provide all Code of Conducts as “Open Access”. We sincerely hope this will contribute to responsible use of human tissue material in research.

Prof Dr L. Looijenga, chair FEDERA
Prof Dr A. Burdorf, chair COREON

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Reading Guide

This Code of Conduct for the responsible use of human tissue for medical research is an extensive document. The content is set out in three stages:

1. The Code of Conduct in outline
2. Elaboration
3. Basis for the choices made in this Code of Conduct and further explanations

At the back there is a glossary of the terms employed.

To become acquainted with the standardisation of the chain of handling human tissue for scientific research as intended in this Code of Conduct, the section 'The Code of Conduct in outline' is sufficient, together with the glossary.

Actual implementation also requires a study of part 2, Elaboration.

The background to the norms is described in the appendices. For an in-depth discussion about the Code of Conduct, these appendices need to be read. Those wishing to study the Code of Conduct from a policy or legal perspective could start the other way around, first with the appendices and then the Code of Conduct itself.

Appendix 7 describes the materialisation of the Code of Conduct. It shows that the Code of Conduct is based on a broad consensus of patients, researchers and others in the chain.

List of abbreviations

BBMRI-NL	Biobanking & Biomolecular Resources Research Infrastructure Nederland
BSN	National identity number (Burgerservicenummer)
BW	Civil code (Burgelijk Wetboek)
CBP	Data protection agency (College Bescherming Persoonsgegevens)
CCMO	Central Committee on Research involving Human Subjects (Centrale Commissie Mensgebonden Onderzoek)
COREON	Committee on Research Regulation (Commissie Regelgeving Onderzoek) (from the FEDERA and the VvE)
DNA	Desoxyribonucleic acid
ECHT	Ethics committee on human tissue
EHCR	Electronic health care record
FMWV	Federation of Medical Scientific Associations (Federatie van Medisch Wetenschappelijke Verenigingen)
GLP	Good laboratory practices
GWA	Genome wide association
ICT	Information and communication technology
IGZ	Health Inspectorate (Inspectie voor de Gezondheidszorg)
KNMG	Royal Dutch Society for the Advancement of Medicine (Koninklijke Nederlandsche Maatschappij tot Bevordering der Geneeskunde)
KWZi	Law on the Quality of Health Care Institutions (Kwaliteitswet zorginstellingen)
LIMS	Laboratory information management system
METC	Medical ethics committee (Medisch ethische toetsingscommissie)
MTA	Materials transfer agreement
NVVP	Dutch Association for Pathology (Nederlandse Vereniging voor Pathologie)
OECD	Organisation for Economic Co-operation and Development
PET	Privacy enhancing technology
RCT	Randomised clinical trial
TTP	Trusted third party
UMC	University (College) Hospital (Universitair Medisch Centrum)
VVE	Association for Epidemiology (Vereniging voor Epidemiologie)
VWS	Ministry of Health, Welfare and Sport (Ministerie van Volksgezondheid, Welzijn en Sport)
WBO	Public screening Act (Wet op het Bevolkingsonderzoek)
WBP	Data protection Act (Wet bescherming persoonsgegevens)
WCZ	Client rights in health care Act (Wet cliëntenrechten zorg)
WGBO	Medical treatment agreements Act (Wet op de geneeskundige behandelingsovereenkomst)
WMO	Medical scientific research with human subjects Act ()

Part 1
Code of Conduct in outline

Part 1

Code of Conduct in outline

1. The scope of application of the Code of Conduct

- The Code of Conduct applies to the use of human tissue for scientific research.
- This Code of Conduct does not apply to foetal tissue, embryos and germ cells, or to tissue from deceased persons, even if scientific research is done with it. In the Netherlands there is already specific legislation applying to the use of such material.
- The term ‘for scientific research’ implies that this Code of Conduct does not apply to forensic use of human tissue, use in the context of Public Health regulations or use of human tissue in another human being.¹
- The norms formulated here can also be applied to the use of human tissue for calibrating instruments or the use of tissue samples for educational purposes.

2. The character of the Code of Conduct

- The Code of Conduct reflects the consensus of all those in the Dutch health care system already involved with the chain of human tissue for scientific research: patients and donors, treating physicians, (controllers) of biobanks and scientific researchers.
- Norms are set out for the whole of this chain. The Code of Conduct is not solely directed at scientific researchers.
- The Code of Conduct not only deals with the handling of human tissue expressly taken for the purpose of scientific research, but also ‘further use’ of human tissue, that is to say human tissue that is removed from a patient during the normal course of treatment and is later made available for scientific research.
- The Code of Conduct indicates in the first place what needs to be achieved. In the elaboration, suggestions are made as to how this can be achieved.
- The Code of Conduct needs to be worked into the policies of health care institutions, biobanks and researchers. These groups can be held to the norms formulated here by relevant internal regulations, accreditation schemes, review procedures for research with human tissue.
- For some of the norms, the principle of ‘apply or explain’ is assumed. It will not always be possible to comply with all the norms at once. In that case, a timeline needs to be drawn up together with an explanation of how (near) compliance will be achieved.
- More consideration is necessary on how the norms can be translated into ‘best practices’. There is an open invitation to share these with the research community. The FEDERA aims to play a coordinating role here.
- In that sense, the Code of Conduct is a ‘living instrument’ whereby feedback from practical experience will prompt further fine-tuning. This is in line with the aim: based on the broad consensus of the immediate stakeholders.
- The Code of Conduct is based on a number of assumptions and deals extensively with normalising the chain within that scope. Pure ‘commercial use’ of human tissue for scientific research falls outside that scope. In the light of the definition of ‘commercial use’ for the Dutch chain of human tissue for scientific research, this subject is less relevant.² See norm 14 which explains why the valorisation of academic knowledge does not fall under ‘commercial use’.

¹ As dealt with in the Dutch Law on the Safety and Quality of Human Tissue, for example.

² It is possible that a future update will also cover pure commercial use.

3. Basic assumptions for establishing the norms

- Scientific research with human tissue encompasses very important promises for health care, from the prevention of mild conditions to the treatment of serious illnesses and everything in-between.
- This research needs to be carried out responsibly. When that is the case, there are, contrary to clinical medicine research, no inherent risks for the donor.³
- The interests of the donors need to be safeguarded with this kind of research. Optimal privacy protection applies here, as does dealing responsibly with the ‘findings’ (see point 4) and a balanced system of consent, that is to say a system that gives donors adequate influence without unnecessarily burdening the availability of human tissue for scientific research and the consequent scientific research with that tissue.
- The consent modality needs to be embedded in a system of norms that encompass the whole chain of scientific research. That is to say: from the taking of the tissue from a donor to its ultimate use for scientific research (look in the glossary for these terms and a description of the chain). In this way, utmost care is guaranteed and possible risks are avoided.
- There should be optimal transparency regarding scientific research with human tissue. The public in general and certainly patients and potential donors should be easily able to find information about this kind of research and the chain involved.

The latter two groups should have information provided to them directly.

- Donors and/or patient organisations should be involved as far as possible with the governance over and the research with human tissue.
- The use of human tissue for scientific research primarily boils down to dealing responsibly with data, namely dealing with the already available data which can be linked to the tissue and with the new data which is derived from the analysis of the tissue – often in conjunction with the pre-existing data.
- This scientific research with human tissue and data should preferably take place with coded-anonymous tissue and data. The chain should be set up to work with such coded-anonymous use for scientific research.
- There is only room for research with non-anonymous material if circumstances dictate as such. For example, the treating physician is also the researcher.
- Research with material which is totally anonymous throughout the chain (thus not coded-anonymous) is, for scientific reasons, largely less meaningful and sometimes even pointless.
- The aim of scientific research is that it eventually benefits health care through improved possibilities for prevention or treatment. Hereby is the Dutch (or West European) system of health care taken as a reference point. It guarantees in large part solidarity between the sick and the healthy and those with and without resources. Validated results which offer cost-efficient added-value above the existing opportunities become, on principle, available to everyone who requires them on the basis of medical criteria. Furthermore, results of scientific research may not be used outside health care to deny access to important societal services.
- Thus it is acceptable in the system of consent to work on the basis of a certain measure of solidarity between those being treated with the current possibilities and those who, in the future, could profit from the results of scientific research.

³ Apart from the minimal risk that is sometimes attached to the extraction of tissue for scientific research. See Appendix 1 for a discussion of the risks.

4. 'Findings'

- 'Findings' are the results of scientific research with human tissue which are considered to be of immediate importance for the future health of the individual donor.
- Such findings are rare. The results of scientific research with human tissue generally lead to new hypotheses for which the clinical implications are unclear or which need to be validated by clinical research.
- The use of human tissue for scientific research is not medical screening and should not be represented as such. There is from several angles a fundamental distinction between the world of treatment and the world of research.
- The feedback of 'findings' to individual donors, together with the results relevant to that donor, can only occur when, due to a specific duty of care by the researcher, the donor should reasonably be informed.
- Such feedback should fundamentally only be considered if the following conditions are met:
 - It concerns a serious medical condition.
 - Actual information, recognised by professional standards, can be offered to the donor, primarily in the form of a treatment option or further follow-up.
 - It is uncertain if the findings are conclusively included in the current treatment of the donor; for example, whether the condition is manifested. If, for example, the findings are visible through a test normally applied as standard for certain complaints and is still in time, there is no point in warning the donor earlier.
- The researcher alone will not be able to determine if such circumstances occur. This needs to be discussed in a commission. The research protocol should contain a procedure regarding possible 'findings'.
- The following also needs to be considered. Scientific research is aimed at discovering statistical connections and does not generally take place under GLP or comparable conditions. Should findings come to light fulfilling the conditions mentioned above, the analysis needs to be repeated under GLP conditions with special attention to ensuring that no mixing of samples or cross-contamination has occurred.
- Since such mixing or contamination would most likely have occurred since the release of the samples for research, this repeat analysis should not be carried out by the researcher himself.
- The possible feedback should not be done by the researcher but by the treating physician or specialist.⁴ They will then consider if this should be communicated to their patient or not.
- The basis described here applies, as with the majority of the norms, to research with coded-anonymous human tissue whereby the researcher is remote from the treating physician. In the event that the researcher and the treating physician are one and the same, his role as 'good caregiver' must predominate. The research will be running parallel to the treatment and not coded-anonymous. In that case, other considerations play a role, partly depending on what has been agreed with the patient.

⁴ In any case, the researcher is fundamentally unable to do the feedback since the researcher does not know the identity of the patient

5. Consent to 'further use'

- For 'further use' in scientific research of coded-anonymous human tissue, an augmented system of 'opt-out' is deemed acceptable unless there are special circumstances.
- To that end, general information should be provided in various locations in the facility where the tissue is extracted, on:
 - How coded-anonymous human tissue is used for scientific research.
 - That health care benefits are the ultimate aim of this research but that it is a question of small steps.
 - That this research is often a question of collaboration with others, also abroad, and that the human tissue might possibly be analysed there, still (coded) anonymously.
 - That the research can sometimes lead to new discoveries and commercial applications.
 - That the results of scientific research are often exploratory and in the first instance do not involve feedback to the donor but, if they prove of value for health care, they are incorporated in the care of all patients.
- Alongside sufficient information, such a system of 'opt-out' should have:
 - If requested, a consultation should be available. There should be one or more points of contact with sufficient knowledge to be able to answer supplementary questions;
 - There is an easily accessible opportunity for objecting to 'further use', also at a later date;
 - The possible objection naturally follows the chain of tissue and data up to the custodian;
 - The complaints procedure of the facility also applies to the 'further use' chain.
- The special circumstances referred to above whereby even with coded-anonymous human tissue it cannot be assumed that a patient did not opt-out are:
 - The guarantee of optimal privacy protection ('your data is anonymous in the research) cannot be fulfilled. Such situations must be discussed with the patients involved and the donor will need to have given consent for such use.
 - Due to the nature of the research, 'findings' are certainly expected and feedback deemed desirable. This needs to be discussed with potential donors along with the nature of the feedback desired by the donor and how it should take place.
 - For a certain group of patients there is an on-going or proposed project with human tissue specially reserved for it. This group needs to be specifically informed. However, following this specific information a system of 'no objection' can be used. The information must, however, be more specific.
 - It concerns a medicine trial according to the applicable national legislation and there is an investigation into clinical markers using human tissue from the research subjects to explain the reaction to the medicine. The patient here is not a donor but a research subject and participates on the basis of detailed informed consent. The consequent 'biomarker' research needs to be included in this consent. This can even lead to a possible adjustment to the treatment protocol during the research.
 - It does not concern research into the origin of illnesses, or their treatment, for which a public consensus can be assumed. The basis is that the patient participates for the benefit of other patients. That basis does not apply when matters are investigated which have nothing to do with the improvement of prevention of illness or with its treatment after onset of the illness. For example, research into biomarkers which could explain delinquent behaviour cannot take place on the basis of a 'no objection' system.
 - It is a project specifically aimed at finding a commercial application or the human tissue is turned over to a commercial undertaking where by the 'controller' loses custody. The potential donor is required to give consent for this.

- For 'further use' in scientific research of human tissue where the donor is identifiable by the researcher (even if this has been coded internally, see the definitions), the donor is first required to give consent.

6. Consent to tissue specifically extracted for scientific research

- This concerns both where human tissue is extracted exclusively for scientific research and situations where procedures are being carried out for diagnostic purposes anyway and extra tissue for scientific research is taken.
- It should be clear to the potential donor what the extra minimal risks are (other risks are not acceptable, see below) and what the extra burden is associated with the procedure.
- It should be clear to the potential donor what the purpose is for the tissue extraction. In other words, what the ultimate benefits are to health care. The project can be described in general terms.
- It should be clear to the donor in general what the chain of human tissue entails; from the extraction and storage, to the making available for research and the partners involved. The privacy guarantees should be described.
- It should be clear to the donor what he or she can expect or be offered further in the context of the project in addition to the provision of human tissue, such as a medical exam at the start of the project or the filling in of possibly regular questionnaires.
- It should be clear to the donor how he or she will be informed about the progress of the project and that in principle no feedback about 'findings' will take place. A general explanation of the governance' of the biobank (see point 10) should be given and the way in which donors or patient organisations are represented.
- It should be clear to the donor how he or she can withdraw from the project and what the consequences would be for the tissue already taken and the already available data.
- Within this context, broad consent is acceptable.
- However, if the special circumstances arise as dealt with by 'further use' above, the further conditions mentioned there will apply accordingly. In those cases, specific consent is required for any or all of the aspects concerned.
- The tissue is made available by the donor without remuneration. The donor can receive expenses for attending the clinic for the extraction procedure and the like.
- Should additional personal data about the donor be integrated from other sources than simply the questionnaires the donor fills in in the context of the project, specific consent is required.
- The project should provide for a complaints procedure. It should be clear to the donor to whom he or she can direct questions or complaints.

7. Supplementary information

- It should not remain with the actively offered, more global information referred to above. If required, the (potential) donor should be able to find additional information on all the above points. This can be in the form of supplementary brochures, links to websites and the like.

8. Minors and those unable to give informed consent

- Human tissue from minors (age depending on national legislation) and those unable to give informed consent may only be used for scientific research if there are scientific reasons for specifically requiring human tissue from this group and the scientific research could not be done with human tissue from adults able to give consent. This applies as much to 'further use' as specially extracted material.
- For the purposes of consent and objecting, respectively, these groups are represented by their legal guardians. The exact ages applicable will be determined by national legislation on the subject.
- It may be that minors are also required to give consent, from an age laid down by national legislation, for the removal of human tissue for scientific research. Any resistance by young children or those unable to give informed consent must be taken into account.
- Where human tissue from children is used for scientific research which has been taken at an early age and the children are monitored in their development over a long period, they will need to give consent themselves when they reach the age of competence laid down by national legislation.
- When, for the purposes of a one-off (coded-anonymous) scientific research project, material from a certain group of children needs to be fallen back on, this group does not need to be approached with the question of whether they object to research now they have reached the age of majority (as defined by national legislation).

9. The management of the 'further use' biobank

- A 'further use' biobank has two aims:
 - Careful custody for the purposes of the original and, normally the follow-up diagnostics for the patient;
 - The storage and possible release of material for scientific research.
- The second aim must not occlude the first. As long as the material is still required for the treatment of the patient, this aim is paramount.
- The function of 'controller' of the biobank must be created. In short, the 'controller' is the intermediary between the patient and the treating physicians that extracted the tissue on the one side, and the researchers on the other. This 'controller' does not need to be a natural person, it can also be a commission, collaboration, etc. It is, however, a distinct function which can, of course, be combined with other functions. Specifically, the following functions need to be catered for:
 - Agreeing with treating physicians about their making human tissue available for research;
 - Storing human tissue in such a way that it can indeed be of use for scientific research;
 - Storing and making available for scientific research in such a way that comply with the donors' consent.
 - Drawing up fair and transparent procedures for making human tissue available to researchers;
 - The release of human tissue to researchers according to the decisions already taken.
- By larger 'further use' banks or collaboration projects, it can happen that these functions are divided between different responsible people. For example, the storage by one functionary, the decision-taking on the release by a commission, and the procedures laid down in regulations or the collaboration agreement.
- The release of human tissue for scientific research should take place on the basis of an MTA. This MTA should guarantee that further down the chain the human tissue will be used for the proposed purpose, that the consent modalities will be complied with and the anonymity of the donors will be safeguarded.

- The tissue and the related data fall under the confidentiality of the treating physician that extracted the material or had it extracted.⁵ The tissue and data cannot – in principle⁶ – be used for forensic purposes unless directed by a court order.
- Furthermore, the following are recommendations for ‘further use’ biobanks which regularly make human tissue available for scientific research:
 - Regulations for the biobank in which the above points are applied;
 - An LIMS enabling human tissue to be issued coded-anonymous for scientific research;
 - A general annual report covering the availability, storage and release;
 - Discussion of this report in the appropriate representative advisory board or patient council (depending on national legislation);
 - If the biobank also releases human tissue for researchers outside the institution, this should be published on a suitable website, indicating what human tissue is available for scientific research and under which conditions.
 - Charges can be levied for the release of material to cover the whole of the proceeding process. A differentiated regime is possible whereby internal researchers are not charged.

10. The ‘de novo’ biobank

- This bank is part of a broader plan to make human tissue available for scientific research. The comments here also partly apply to that plan as a whole.
- The scientific and societal aims of the plan have to be determined. The methods to reach these goals need to be scientifically underpinned, but also sufficiently flexible should new insights lead to reaching these aims better using different methods.
- A procedure needs to be drawn up for the recruitment of donors, the informed consent procedure and subsequent contact with them. These donors are participants and stakeholders in the plan.
- A procedure must be drawn up to allow donors to withdraw and indicating what will happen to the material and data already gathered.
- There needs to be a clear separation of functions between collection, control and the actual scientific research. For control, the norms mentioned above for ‘further use’ apply accordingly. In the context of the plan, agreements will already have been made.
- A procedure must be drawn up for the release of material for research in the context of the plan.
- Correspondingly, a procedure for ‘tissuesharing’ and ‘datasharing’ needs to be drawn up.
- If human tissue is to be made available to third parties, this needs to be done on the basis of an MTA. The MTA should guarantee the chain of human tissue in accordance with the norms in this Code of Conduct and the intentions of the parties involved in the research project. The MTA could contain elements of the collaboration agreement in respect of the intended research, or form an appendix of it. The chain of data also needs to be guaranteed.
- The duration of the plan should be determined and the term for keeping the human tissue made available.
- A long-term perspective should be drawn up for the financing and arrangements about what to do with the collection should financing become precarious.
- All of this should be bedded in a ‘governance structure’ which offers room for the review of the ethical and societal aspects of the project and any possible course corrections (in addition to changing societal opinions) and whereby donors and/or patient organisations are involved.

⁵ Even if the tissue is solely intended for scientific research, the Law on Medical Treatment Agreements (Dutch situation) applies. There is always an appraisal of the health of the potential donor.

⁶ Sometimes an exception can be made on the grounds of a ‘conflict of duties’.

11. The health care facility where procedures for the extraction of human tissue take place

The facility needs to create the pre-conditions to enable the Code of Conduct to be complied with. That implies the following, amongst other things:

- Providing a good no-objection system at entry, both for scientific research with human tissue (anonymous or coded-anonymous) and for non-anonymous scientific research with data (as may be allowed for by national legislation)
- Providing staff who can respond adequately to possible questions from patients on scientific research.
- Providing a low-threshold opportunity to register objection.
- Include processing personal data for scientific research as one of the aims of processing personal data in the care facility.
- Provide for a hospital information system, electronic patient file or the like capable of registering both forms of objection referred to in the first point above, and follow this through the progress of data and human tissue through the facility.
- In addition, especially for University Hospitals and top clinical hospitals, the following is recommended:
 - Design the electronic patient file system in such a way that pseudonisation processes can easily take place with the personal data contained in it.
 - Ground the functions of the ‘controller’ of the biobank(s) in the facility as intermediary between the donors and treating physicians on the one side and the researchers on the other. For the distinct ‘further use’ biobanks, several ‘controllers’ could function within the facility’s defined boundaries.
 - Provide sufficient means for the biobank to be able to comply with the norms and recommendations described here.

12. The carers involved in the tissue extraction

1. Where extraction is exclusively carried out in the context of the treatment of the patient, the normal informed consent naturally applies. In the context of possible ‘further use’, the following will additionally apply:
 - The carer has an advisory role for additional questions from the patient about ‘further use’ for scientific research.
 - Any possible objection should be noted in the files. The carer is confident that this objection remains noted in future logistics.
 - The carer has an advisory role for the ‘controller’ of the biobank, and conversely the ‘controller’ can advise the carer on the optimal transmission of material of material so that it can be conserved for scientific research. The carer takes this into account as long as it is consistent with the interests of the patient, which always come first.
2. Where the extraction is exclusively carried out for scientific research or where, during the treatment, further tissue is extracted for this, the following applies:
 - The carer assures himself that informed consent has been given for this (extra) extraction;
 - The risks involved in extraction are minimal and the burden, acceptable. This has already been reviewed in abstracto in the protocol. Each and every donor should be asked if they can and want this procedure to be done.

13. The researchers

- The research should be carried out in accordance with a research protocol. This research protocol should explicitly state:
 - What insights are hoped for.
 - What material is necessary.
 - What data is necessary.
 - A methodological foundation for this combination.
 - Whether ‘findings’ are expected and how they will be dealt with.
 - How the chain of human tissue and data is set up (what analyses will be done and where, how and where the results will be pooled, etc.).
 - For how long the data and human tissue will be used.
 - What will happen to the material at the conclusion of the research and how notification from the ‘controller’ will be dealt with that a donor has withdrawn from the research.
 - How the privacy of the donor is guaranteed and how possible indirect reidentification in the chain can be prevented, such as the use of PET and further anonymisation procedures in the chain where collaboration with other researchers is involved.
- The research should be carried out according to the protocol.
- (Relevant) Patient organisations are recommended to be involved as far as possible in the research agenda.
- Agreements need to be made with the ‘controller’ about how to deal with possible patentable or other possible commercial discoveries resulting from the research.
- The research should be carried out according to the relevant MTA and other possible agreements with suppliers of data.
- It should be reasonably possible to audit that the chain is working as described.
- The research should be aimed to result in one or more openly accessible publications. Even if the MTA does not provide for this, the ‘controller’ should receive a copy of same.
- ‘Datasharing’ should be promoted within reasonable conditions.

14. ‘Commercial use’

- Knowledge valorisation is one of the subsidiary aims of academic or ‘investigator initiated’ scientific research. Even more so since the proceeds partly return to the institution, thus strengthening the position of academic research. Should it result in such knowledge valorisation, this is not in itself commercial use of human tissue.
- Collaboration with commercial enterprises equally does not imply commercial use, for example when certain analyses on human tissue are carried out or a collaborated research. For the latter, the same is implied for the commercial partner as in the previous point on researchers, up to and including ‘datasharing’. In other words, research in collaboration with a commercial partner doesn’t make it ‘commercial’ if the results are made public. In the MTA agreements are made on the intended use of the material. Ownership of the human tissue does not transfer to the commercial partner.
- Should the conditions mentioned in the previous point not apply with collaboration with a commercial enterprise, then that would constitute commercial use. Commercial use does not need to be discouraged. For the development of new medicines or the refinement of indications on existing ones, commercial enterprises are necessary. However, it does have consequences for the system of consent. If it is a question of commercial use, ‘further use’ cannot be based on a no-objection system. Also in the case of the ‘de novo’ bank, the donor will need to give explicit consent.

15. Review

- Both the process of obtaining human tissue for a ‘de novo’ bank and the scientific research with human tissue should be reviewed and approved by a specialised Medical Ethics Committee (ECHT).
- The review focuses on two points: the risks and burden of the extraction if the tissue is extracted specially for scientific research and the safeguards for the storage of the tissue and its release for scientific research in the light of the consent modalities and the privacy protection of the donors.
- The composition of such a Committee should reflect the task of reviewing this kind of research. The expertise required is not entirely the same as for reviewing clinical research.
- The review should focus on the adherence to the norms in this Code of Conduct.
- The Committee reviews proposed ‘further use’ on the basis of ‘no objection’ or whether the special circumstances referred to above would apply.
- Seeing whether the protocol justifies the use of the – in principle scarce – human tissue is not one of the grounds for review. The ‘controller’ of the biobank decides this, possibly after consultation of a scientific advice commission. Agreement can be reached with the Ethics Committee so that not each individual protocol needs to be reviewed. If the chain in which it takes place remains the same and the privacy guarantees within it have been reviewed, further related investigations and analyses can fall under one general approval.

16. Introduction of the Code

This Code of Conduct follows closely the ‘best practices’ in the field, especially those of University Hospitals. It will not be possible to comply everywhere in 2011 with the norms of the Code of Conduct. The intention is that the norms from the Code of Conduct are implemented and can be shown as such.

A large number of the other norms in the Code of Conduct are already directly applicable. These encompass the consent modalities for donation and the applicable conditions. If, for example, it cannot be reasonably guaranteed that material reaches the researchers (coded)anonymous, the research cannot take place on the basis of no-objection. This applies also when the no-objection system within the institution hasn’t been properly organised.

Part 2
Elaboration

CHAPTER 1

AIM OF THIS CODE OF CONDUCT

1. Introduction

For the 'further use' of human tissue for scientific research, the FEDERA, in collaboration with patient organisations and the KNMG, instigated a Code of Conduct (FEDERA 2002). This was implemented in virtually all University Hospitals and a large number of other hospitals.⁷ The accreditation of laboratories by the Stichting CCKL was also based on the Code of Conduct from 2002.

A lot has happened in the meantime. The Code of Conduct from 2002 was perhaps ahead of its time. Scientific research with human tissue has become a hot topic and is seen as one of the most important promises for further progress in clinical and preventative health care.

Time, therefore, for an update. The scope of this Code of Conduct has been broadened. The former Code of Conduct dealt exclusively with 'further use' of human tissue for scientific research. That is to say human tissue extracted for a specific purpose (usually diagnostic) which can then be used for scientific research. This Code of Conduct also deals with human tissue specifically extracted and stored for scientific research. In addition, this update places more emphasis than the previous one on the chain of human tissue from extraction to use in scientific research. Only by viewing the whole chain and all the elements in it in context can a responsible standardisation be drawn up.

Just as with the previous Code of Conduct, this Code of Conduct has been drawn up together with the relevant patient organisations.

2. Scope of the Code of Conduct

The Code of Conduct covers the use of human tissue for scientific research. As a result of the definition of human tissue, this Code of Conduct does not apply to foetal tissue, embryos, germ cells or tissue from deceased persons. Separate national legislation usually applies here.

This Code of Conduct equally does not apply in other situations where separate legislation applies. This concerns namely use for forensic purposes and in the context of Public Health. In any case, this is not a question of scientific research.

3. Structure of the Code of Conduct

This Code of Conduct contains substantive chapters and a large number of appendices. In the appendices, a number of elements and principles from the Code of Conduct are expanded on. In appendix 1, for example, the perceived 'dangers' of scientific research with human tissue are gone into. The compilers of this Code of Conduct regard these dangers to be far less serious when the chain is sufficiently guaranteed. This Code of Conduct provides guidelines for this.

The substantive chapters first deal with several general themes. Following that, the roles and responsibilities of each player in the chain are set out in individual chapters.

⁷ In Dutch medical law there was also criticism (olsthoorn 2003, dute 2008, Ploem 2010). these were partly based on misunderstandings which are covered in the text. see also Appendix 4.

4. The legal character of this Code of Conduct

This Code of Conduct is a form of self-regulation of the relevant professional practitioners together with those most closely involved with this subject, the patient-interest movement. Those who do not adhere to this Code of Conduct will be called to account by their colleagues and professional organisation. Sanctions might be taken by the professional organisation as a result. What is more important is that the Code of Conduct is translated in the policies of the organisations where the chain is handled. In that way, through the internal rules of the organisation, individuals are directly bound by it. That is what happened with the Code of Conduct from 2002. The Code of Conduct can then also be regarded as 'sector norms' in the eyes of relevant national legislation and assist in accreditation processes.

The Code of Conduct will also play a role in the review of research proposals. Chapter 8 deals further with review possibilities by an ethics committee.

In this regard, it is important that this Code of Conduct contains two kinds of norms. There are hard and fast norms which nobody should contravene. Alongside these are recommendations according to the 'comply or explain' principle. It is possible to deviate from a certain norm, for example if the scale of a 'biobank' is too small to completely implement that norm, but that does need to be explained.

This Code of Conduct does not deviate from existing legislation in the Netherlands. See appendix 4. There is not a wealth of such legislation in the Netherlands. The Code of Conduct fills in the voids in a responsible way, according to the opinion of the parties involved. In certain areas, this Code of Conduct is less strict in the normalisation than a number of non-binding international declarations. Appendix 4 also explains why less weight is attributed to these than the relevant parties determined.

5. Securing the norms in this Code of Conduct

This Code of Conduct sets out norms for the whole chain involved in the use of human tissue for scientific research. Scientists among themselves, the organisations to which they belong, funders of research and ethics committees will in the first instance see to it that these norms are adhered to. There is also a role for patient organisations to address researchers and biobank initiators on their responsibilities as described in this Code of Conduct. In addition, the norms in this Code can play a role in health inspectorate supervision, accreditation or determining liability in complaints procedures.

Should (further) legislation be drawn up in respect of the use of human tissue for scientific research, this Code of Conduct offers clear guidelines. Even then the securing of the norms will not take place any differently. Those involved in the sector need to implement the norms first. Thereafter come review and supervision.

The question is whether more needs to happen. how can it be guaranteed that those involved in the chain actually do what they are supposed to.

Technical and procedural guarantees will need to be implemented throughout the whole chain. ICT-tools already exist for the PET with which anonymization can be achieved, but databases in the research world more often than not do not allow logging to reveal who did what with which data. This does not mean there are indications at the moment that unusual, undesirable things happen with data. However, it is not possible to substantiate that. The securing we are talking about here concerns this level: to be able to demonstrate that what is said to be done is being done. As discussed in paragraph 2.3 of chapter 8, the instruments for this still (largely) need to be developed.

This is a work in progress. A middle path must be found between the possible risks and the means which would be devoted to this securing. The risks involved in this kind of observational research are of a different order to those in intervention-research, such as medicinal research (cf Editorial 2010). The appendix on the risks in handling data (which accompany the human tissue during research or which can be deduced from the human tissue) deals in more detail on the risks associated with research with human tissue. On the path of progression to more guarantees, the principle of 'apply or explain' is applicable. For practical recommendations which can be implemented in the short term, see also Van Veen 2011.

This is not the whole story. Transparency is one of the golden threads running through this Code of Conduct. It must be possible to show where, when and for what purpose human tissue for scientific research is being used. Chapter 6 deals with this further.

6. Planned introduction

A number of the required norms are new for some of those involved in the chain. In particular, not every 'controller' of a 'further use' biobank will be able to comply with the applicable norms. In addition, setting up the means to involve donor and patient organisations will require further work. The transparency surrounding 'further use', as additional support for the information provided by the facility, also needs to be improved. The FEDERA intends to set up a website for this purpose. The norms regarding guarantees in the entire chain, in the sense that it can be demonstrated that people are only doing what they have promised to do, have already been dealt with above. Also here it will not be possible to comply across the whole board.

Nevertheless, the norms need to be complied with where possible or where necessary in connection with consent from the donor.

Therefore there are two 'transitional periods', each with its own consequences:

- The first concerns the implementation in all facilities of the consent models as set out in this Code of Conduct.
- The second concerns the additional norms intended to achieve greater transparency, clearer procedures and more responsibility.

With the first type of norms it will be clear whether they are being complied with or not. If not, it will mean an intervening period during which human tissue will not be available for scientific research unless an alternative, and at least equivalent consent model has been implemented. In other words, if the no-objection system has not been well organised in the facility, human tissue cannot be used on the basis of no-objection. Where the no-objection system has been implemented, it must be guaranteed that human tissue from people who have raised objections will not be available for 'further use' scientific research. Where no objection has been raised, the material will still not be able to be used unless it can reasonably be guaranteed that the material reaches the researcher (coded-) anonymous. Etc.

The second type of transitional period is much less determined. It concerns (in order of processing in the chain):

- The realisation of all the functions set out for the control of the biobank.
- The greater involvement of donor and patient organisations in the governance of specially set-up biobanks or the resulting research.
- The instigation of systems in the researchers' databases such that it can be demonstrated that data and human tissue is being used exclusively according to the protocol (see previous paragraph).

Providers of subsidies however can already take these norms into account and require 'apply or explain' when financing a project. Applicants for subsidies would be wise not only to apply for funds for the research itself but also to enable compliance with the norms. This would help make a progressive transition possible.

CHAPTER 2

THE THEMES IN THE CODE OF CONDUCT

1. The chain of tissue in healthcare

The use of human tissue for scientific research cannot take place without a chain of events. In this chain, the following functions can be distinguished:

- a. The making available of human tissue.
- b. The acquisition of human tissue.
- c. The storage and release of human tissue for scientific research.
- d. The installation and maintenance of the infrastructure required for a-c and often e-g.
- e. The use of human tissue and the associated data for scientific research.
- f. The propagation of knowledge through research, in the form of publications, patents and the like.
- g. The review of the above-mentioned elements in the chain.
- h. The effect of the results in health care.

Distinguishing the functions does not imply that the persons connected with those functions need to be separate. Along with the distinct functions however come distinct responsibilities, and in the case of a. also distinct rights. Subfunctions are not distinguished. Most scientific research is not possible without collaboration, very often at an international level. That is not dealt with here. the Code of Conduct deals with what is necessary for the normalisation of each function – not with what is required for the practical implementation. For example, this Code of Conduct does not go into technical normalisation (such as at which temperature tissue needs to be kept and so on).

All the functions are dealt with separately, with the exception of function h. It is not possible for the FEDERA (or equivalent organisation) together with patients to draw up norms for that. However, that effect in health care is the ultimate aim. Research takes place to achieve better health care in the future, in the form of better treatment or better prevention. This Code of Conduct does not apply to other applications of research with human tissue. For other possible applications outside of health care, the norms suggested, for example on consent systems, do not apply.

2. A number of basic assumptions

The normalisation in the Code of Conduct is based on a number of basic assumptions. These are expanded on further down. Below is a summary of the assumptions which form the framework for what follows.

- a. Optimal privacy protection of the donors, that is to say of those that make their human tissue available. The use of human tissue in scientific research should in principle exclusively take place coded anonymously.
- b. A consent system for donors which on the one hand does justice to the expectations of the donors and on the other can be realistically integrated in the chain, thus contributing to what the patient movement expects, namely that the promises on scientific research with human tissue can be made true.
- c. A cautious and scientifically responsible handling of findings⁸ from the research with human tissue.
- d. Thus, so-called 'micromanagement' by the donor concerning the handling of the human tissue made available and the possible feedback of 'findings' have not been the basis for this normalisation. This is not the desire of patients and it would increase the costs of research enormously.
- e. The possible commercial application of the results of scientific research with human tissue should be dealt with in perspective. University hospitals are also required to 'valorise' their knowledge. This can strengthen their position as research institute and make more valuable research possible. The limit for the system set out here is reached when human tissue is made directly available to an industrial concern. Here, the sight would be lost of how the results are applied and uncertainty arise as to whether 'shareholder value' wasn't more important than the contribution to research and health care.
- f. The Code treats genetic data no differently from other data which give an indication as to the future health of a person. In other words, no 'genetic exceptionalism'. Aside from the exceptions of relatively rare, but also quite serious, monogenetic conditions, the results of research with human tissue reveal a likelihood, which has to be considered in conjunction with family history, lifestyle, and other – genetic or not – factors.
- g. Clarity about who is responsible for what, for example, about who the donor can turn to in a problem situation or who the researcher can apply to obtain human tissue for scientific research.
- h. Transparency by researchers on scientific research with human tissue.
- i. A clear administrative structure for collections of human tissue (biobanks) applicable to the scale and origin of the collections but nevertheless such that careful administration and fair release procedures for scientific research are guaranteed.
- j. Such governance of larger projects so as to allow the voice of donors or the patient movement to be heard one way or another.
- k. An important role for the 'support facility' (in other words, those that fulfil function d from the previous paragraph) to implement the consent system 'at the front door' and provide the means to achieve the above, and in particular f to i.

⁸ In appendix 3, the corresponding paragraph 4 from the Code in outline are expanded on and substantiated.

And last but not least, the following principle that, as it were, buttresses all the others:

- I. An inbedding of the chain of scientific research with human tissue in the solidarity-based health care legislation of the country concerned. This is not gone into here but implies, in short, the following. The validated results are employed within health care for the benefit of everyone who has a right to that health care based on need. The results are not used to disadvantage groups of patients in their quest for care. In this sense, the Dutch or European legislation differs considerably from that of the United States, and is important when evaluating much of the literature on 'biobanking' from the U.S. Naturally, opinions can vary as to whether a country like the Netherlands has sufficient or possibly too much or too little solidarity. It is possible to argue both ways. But equal access to health care and important social facilities is, despite these arguments, paramount. This is an important principle for donors and researchers alike. Donors make human tissue available in the light of solidarity with other patients. Researchers must have the expectation that the results of research actually contribute to that solidarity.

3. Biobanks and the chain

Much of the present discussion involves 'biobanks'. That is the modern term for a collection of human tissue which can be used for scientific research. A biobank is however an aid to research and not an end itself. It is a link in the chain. There are many different sorts of biobank. For the normalisation, only one distinction is of importance, namely:

- Has the human tissue become available because it is left over after being acquired during the course of treating the patient?
- Has the human tissue become available after being acquired specifically for scientific research?

Incidentally, both types of material can be stored in the same biobank. In that sense, the difference is one of degree. The difference is apparent from the consent system, which then forms the basis for which the material can be used for scientific research.

CHAPTER 3

THE FIRST STEP IN THE CHAIN OF EVENTS: CONSENT TO RESEARCH

1. Foreword

This is about the whole chain. Everything said later on about the other elements in the chain have a reflexive working on this step. To put it another way, the normalisation of this step is dependent on the normalisation of the subsequent steps, as suggested in this Code of Conduct. If the follow-up normalisation is not carried out, then the contents of this chapter do not apply.

2. In the context of 'further use'

A detailed no-objection system for coded anonymous use offers in principle sufficient say by the donor. The conditions in this stage are as follows:

- a. There is optimal transparency regarding 'further use'. Patients and potential donors need to know.
- b. The information should describe in general terms the way of working from storage to research.
- c. If required, a consultation should take place. there should be contact-people who have sufficient knowledge to be able to answer supplementary questions
- d. There is a low-threshold possibility to object to 'further use', also at a later stage.
- e. There are no foreseeable circumstances which exclude 'further use' without express consent as described in appendix 2.

Both those who extract human tissue (for the purposes of therapy or diagnosis for which the patient has given informed consent) and the support facility need to be directly involved in achieving these conditions. Others have an indirect role. That will be dealt with later in this Code of Conduct.

This is about consent to possible coded-anonymous use. The researcher cannot discover the identity of the donor. That is known elsewhere. The researcher will not be able to receive any additional personal data from the donor. The researcher could possibly receive via pseudonimisation procedures additional anonymous data about the donor, possibly from other sources.

3. The taking of samples for scientific research

This covers both the extraction of human tissue specifically to obtain human tissue for scientific research and extraction already being done in the context of patient treatment and whereby extra material is extracted for scientific research. Broad consent is sufficient to give permission for this extraction. The aim of the project can be described in general terms. As far as the extraction itself is concerned, the information must be specific concerning the possible risks and burden.

The additional conditions are:

- a. The risks of the extraction are minimal and the burden commensurate with the aim of the research for which specifically this kind of tissue needs to be available. Extraction posing an extra burden should only be considered if the biomarkers sought cannot be found in other human tissue which could be extracted through a less burdensome procedure.
- b. The 'governance' of the project should be explained in general terms, and specifically if, and if so, in what way participants or the patient movement are represented.
- c. The pseudonimisation process should be explained. If it is foreseeable that additional information will be requested from other sources (the dossier, cancer registry, etc.), this should also be explained. Should the researcher receive personal data, express permission must be requested.
- d. It should clear how consent, once given, can be withdrawn and what the consequences would be (see also the next paragraph).
- e. It should be clear where and how further information can be found on the studies (researches) emanating from this project. Referring to a website is sufficient, but depending on the project, a newsletter should also be considered.

4. More on the information provided to donors

A distinction can be made here between (a) the information given directly to the donor and (b) the supplementary information the potential donors can obtain elsewhere if required. The assumption here is the 'further use' situation. It equally applies to the situation where human tissue is specifically extracted.

Ad a:

- In general how human tissue coded anonymous is used for scientific research.
- In general that a contribution to health care is the ultimate aim, although this is a process of small steps.
- In general that this research is often a question of collaboration with others, also abroad, and that the human tissue could be analysed abroad too, still (coded) anonymously.
- In general that the research can lead to new discoveries and inventions which may provide funding for the facility.
- That the results of scientific research more often than not are speculative or provisional, and thus in principle are not fed back to the donor but, once they appear valuable for health care, will be incorporated into the care of all patients.

Ad b:

- The possible donor that wants to know more should be able to obtain further information on all of the above. The carers involved should be able to give this and furthermore a website should be available where details are given and possibly specific projects are explained.
- The general brochure on self-regulation and biobanks coupled to this Code of Conduct offers much valuable information. Parts of this Code of Conduct could be made available and, of course, for the avid reader, a link to the Code itself.
- Links to general sites on scientific research and 'genomics', such as the Dutch site www.allesoverdna.nl.

5. Raising objections or withdrawing permission

A donor can always change an already-taken decision. The question is what the consequences are of this new decision (whether the raising of an objection or the withdrawal of permission) for the already existing human tissue. Although this question could be dealt with in the chapter on storage, this is the more logical place for it. It concerns the primary scope of the consent. Naturally this material cannot be used for new research. immediate destruction of the material is, in general, one step too far. It depends on the circumstances. The following aspects need to be distinguished:

- The material is located (a) still in the biobank or (b) the material (or a portion thereof) is already with the researcher.

Ad a:

- In the case of a 'further use' biobank, where the material is stored not only for research but also for diagnostic purposes, only the coding in the Lims needs to be amended. The material will then be preserved purely for the latter purpose.
- In all other cases the material should be destroyed.

Ad b:

- The researcher is informed by the provider (= 'controller' of the biobank, see below) of the withdrawal of consent. The material may not be used for new research.
- The results obtained from the research in which this material has been used do not need to be deleted. The withdrawal affects future research with human tissue and related data.
- The data already obtained through the research can be kept.
- For the validation of published results it is sometimes necessary to fall back on old material. If by the withdrawal of the sample, the ability to reproduce the data would be corrupted, the sample may be kept. This will exclusively concern a very small series of samples. In the majority of cases, the withdrawal of one sample will not compromise the statistical relevance of the research and the sample should be destroyed.
- The researcher should inform the provider of the destruction of the sample, or, in exceptional cases, the conservation of the sample for validation purposes. in that case, the researcher should indicate when the sample will ultimately be destroyed.
- On receipt of this information, the provider should destroy the link between the sample issued and the identity of the donor. The data from the researcher are then completely anonymous and exist as a purely independent file in a closed research. the possibly left-over sample still present with the researcher is equally anonymous and will be destroyed as soon as it is no longer required for validation.

CHAPTER 4

NORMS FOR MINORS AND THOSE UNABLE TO GIVE INFORMED CONSENT

1. Foreword

Minors form a specially vulnerable group. For the use of human tissue from these donors, extra conditions need to apply.

2. General assumption

Human tissue from children under the age of 16 and patients unable to give informed consent should only be extracted (if that is required for the research), stored or used for scientific research if the research question and methodology make human tissue from this specific group a necessity. If the research could be conducted with human tissue from donors older than 16 and able to give informed consent, it should not be done with human tissue from minors or those unable to give informed consent.

Examples of research where their human tissue is a specific necessity is research into cancer in children, or the onset of early ageing in people with down's syndrome. This norm was also set out in the previous Code of Conduct.

3. Representation

a. *'further use'*

For the cases where human tissue can be used for scientific research, the minor in a 'further use' situation is represented by the legal guardian as laid down by law.

According to the relevant national legislation, this can imply:

- A minimum age before which a legal guardian has total say;
- An intermediate age limit when the minor and guardian jointly take decisions. A child or young person already has their 'own' right to privacy. It is however appropriate to apply the right to object, in the context of 'further use', both to the guardian and to the child. In other words, if one of them objects, that would already be sufficient;
- An adolescent of 16 years or older can decide independently not to object (the default situation) or to give consent.

b. *Age limits for the extraction specifically for scientific research*

There are examples, e.g. in the Netherlands, where the minimum age for legally taking part in a scientific research project differs from that referred to above. In that case, the legal age limit must be observed.

c. *No extraction following resistance*

Relevant national legislation, such as in the Netherlands, can specify what should and should not happen upon resistance from the minor or patient unable to give informed consent in the case of non-therapeutic research.

4. Renewed permission or opportunity for objection upon reaching the age of competence

In literature it is suggested that when a guardian has given consent, the young person should themselves give consent upon reaching the age of competence. In the same way, they should also be given the opportunity to raise an objection. It should be noted that this recommendation is commonly based on broad 'population based' biobanks. From paragraph 2 it follows that material from children does not in principle belong in such biobanks.

We are talking here more about specially set-up projects concerning certain medical conditions or children with certain characteristics, such as twins. These are then much more than simply donors, but members of a cohort. It follows that (re)confirmation should be obtained when the child reaches the age of competence and is still involved in the project.

It is going too far to impose this condition across the board. There are conceivable situations where human tissue is stored which years later assumes importance for a certain project. The costs involved in re-contacting would be high and the added value in terms of consent, small. The guarantees lie in the careful execution and privacy protection and individual feedback is not an issue. In other words, when children are followed over a prolonged period, they should be asked when they reach the age of competence if the human tissue may still be used for scientific research. If, much later, a research question comes up in a single research which requires the use of human tissue from these children, and they have in the meantime reached and passed the age of competence, they do not need to be contacted to ascertain if they, like their guardians at the time, have no objection to such research.

CHAPTER 5

THE RESPONSIBILITY OF THE HEALTH CARE PROFESSIONALS INVOLVED WITH THE EXTRACTION

Also here, the distinction is important between (a) the 'further use' situations and (b) situations where human tissue is specifically extracted for scientific research.

Ad a:

- The extraction of course takes place against the background of informed consent to the procedure itself. That is not gone into here. That is the normal health care and patient rights which apply here.
- The carer has an advisory role to patients who, after reading the informational material, have questions about 'further use' for scientific research.
- Any objection should be entered clearly in the dossier and remain noted in the logistics of the material and data.
- The carer has an advisory role to the 'controller' of the biobank on whether material from certain patients can be made available for scientific research, bearing in mind the original aim of the treatment of the patient.
- If the material does not need to be stored for diagnostic purposes, the carer can agree with the 'controller' of the biobank as to how the material be delivered so that it can be optimally available for scientific research.

Ad b:

- Agreements have previously been made about the chain. these agreements should be followed, subject to the following:
- The carer needs to be certain that the donor is aware of the fact that (extra) human tissue for scientific research is being extracted and that informed consent has been given.
- The risks from the extraction should be minimal and the burden acceptable, bearing in mind the scientific aim. This has already been described in abstracto in the research protocol and approved by an ethics committee (ECHT). each individual donor needs to be appraised separately to see if they can and want to undergo the procedure if, apart from material required for diagnosis purposes, extra material for scientific research is extracted.

CHAPTER 6

RESPONSIBLE CUSTODY OF A COLLECTION OF HUMAN TISSUE (BIOBANK)

1. Foreword

Control of a biobank is a function within an organisation (for example, the care institution, the university hospital, the foundation running the research project), namely that of responsible storage, custody and release of the human tissue. This function needs to be based somewhere. The entity where this function is based is hereafter referred to as the 'controller'. It should be stressed that this does not need to be a natural person, but can refer to a committee or suchlike. naturally, 'controller' can be combined with other responsibilities within an organisation, for example – if it is indeed a natural person – a head of department. In addition, the distinct functions can be spread over several persons or organisations. Here they are distinguished in order to anchor them and for ease of use collectively referred to as 'controller'.

It goes without saying that the function is carried out within the broader framework laid down by the board of the organisation.

A distinction also needs to be made here between the 'further use' biobank and the 'de novo' biobank.

2. The 'further use' biobank

2.1 *In general*

Within a care institution there could be several biobanks, for example from pathology, microbiology/infectious diseases, clinical chemistry. The primary requirement is careful storage for the original purpose. The applicable professional standards vary per type of biobank (clinical chemistry, pathology, etc.). These are not dealt with here of course. The 'controller' of such a biobank must be seen as the 'custodian' of the material for possible scientific research with it (Yassin 2010). This custodianship needs to be elaborated in a clear policy regarding the handling of the material.

- A 'further use' biobank has, as it were, two aims.
 - The first aim is the storage and whatever is associated with the original purpose, generally follow-up diagnostics for the benefit of the patient.
 - The second aim is the storage and release of the material for the purposes of scientific research.
- The relation between the two aims is not dependent on how the material is stored, namely whether:
 - There is a separated collection from the original for 'further use' human tissue.
 - The material for the original purpose and possible 'further use' material are combined.

The first situation is exclusively when there is so much of that material that it is possible to create two separate collections: one for the original purpose and one for the use for scientific research, without that being at the expense of the original purpose. such a separate 'further use' biobank does occasionally exist. But generally it works differently. A series of samples from the same patient can be employed for both purposes. The second dimension is an additional layer of norms regarding the use of one and the same samples or series of samples. For the second purpose, scientific – technical aspects apply (a) and administrative (b).

Ad a:

This concerns the storage and release of human tissue under such conditions that meaningful scientific research can be done with it. Also this will vary per type of biobank, see amongst others Riegman 2008, Riegman 2011 for tumour material. The possibility of further use needs to be taken into account in the handling of the material following extraction for the purposes of patient treatment. It is an illusion to think that all that material is equally suitable for scientific research, especially in international researches where material has to meet carefully drawn-up standards of quality. The standards cannot be dealt with here.

Ad b:

This concerns the responsibilities of the 'controller' towards:

- The care givers and the primary purpose; availability for further diagnosis.
- The donors where 'further use' is concerned.
- The researchers that want to use the material for scientific research.
- Society as a whole.

The above responsibilities should preferably be set out in a set of regulations. Since virtually every collection of human tissue for the purposes of patient treatment is a candidate for 'further use', almost every such collection should have such a set of regulations. From this side it is recommended. It is however still too early to require every 'further use' biobank to do so. Where no such regulations exist, that needs to be justified. For example, because 'further use' virtually never occurs, and if it does, the material is used exclusively by doctors within the institution for scientific research with their own patients. The no-objection system for such 'further use', as already seen, does not apply. The material is identifiable for the (treating) doctor-researcher and the research discussed with the patient and only carried out with their explicit consent.

For the majority of 'further use' biobanks, such regulations will be appropriate. A norm of this kind is indeed a form of regulation that did not exist before. It is however today of great importance to guarantee the responsible handling of material.

The regulations should deal with:

- How can it be guaranteed that the release of human tissue for scientific research does not take place at the expense of the primary purpose of the storage.
- How can it be guaranteed that consent – given earlier or expressed to the care giver – is complied with. thus, how possible objection is honoured and how no material on the basis of this system is released if the general conditions mentioned in chapter 4 for the no-objection system cannot be complied with.
- What procedure is followed for the release of human tissue for scientific research.
See below at 2.2 for more on this procedure.
- The privacy guarantees by the coding of the material when it is released to researchers.
See for this section 2.3.
- The contact person for the 'controller'.
- The accountability for the handling in the context of 'further use'.
- The method of release once a decision has been taken.

Accountability means an 'annual report'. Such a report can be brief. It is about showing in general which material has been released to which projects and how the system of the regulations has worked in practice. The annual report should be available to the public, for example, on a website, and sent to the regular users of the material. It should also be sent to the relevant patient organisations and to the patient councils where applicable. In this way, transparency regarding research with human tissue is promoted and patients actively involved in the chain.

2.2 *The procedure for the release of human tissue for scientific research*

This is about a fair and transparent procedure. Researchers need to know what they can count on or not. There are in general three steps:

- a. The scientific: is this a scientifically meaningful project to employ (usually) scarce human tissue for. Is it possible with the human tissue present in the bank and the data that can be linked to it?
- b. The ethical: have the conditions for consent been complied with?
- c. The consideration: even if a and b are positive, the 'controller' can decide to reserve the material for other research, on the grounds of criteria in the regulations.

With regard to these three steps, the following is recommended:

For a, a scientific committee should be called upon.

Step b can be reviewed by an ECHT. Also there the importance of the regulations 70 is apparent. On the basis of that the researcher can show that the material to be released complies with the conditions.

Step c is the most awkward. It is conceivable that a 'controller' sets priorities in regards to research for which human tissue is released. If the regulations clearly state that, and how those priorities are arrived at, the 'controller' should have that freedom. For example, that priority should be given to projects from within their 'own' institution or alternatively international projects they have pledged support to. The researcher will de facto want to know this first before dealing with steps a and b. There will need to be talks before a request is submitted and also about how a request should be submitted. A points-system is conceivable for the scientific review and prioritising. Depending on the number of points, the human tissue is either released for research or not.

The release of material to researchers outside the institution will be done in the form of an MTA. This can include elements of a collaboration agreement. Generally speaking, this is not simply about the release of human tissue but about a project whereby also data from the patients involved is concerned, which have to be disclosed up (not forgetting privacy considerations) and interpreted. Very often, the original carers and the 'controller' are involved here.

2.3 *The privacy guarantees*

The release of material to researchers will, apart from exceptions, take place coded-anonymous. This is a fixed norm. If the material is traceable for the researcher, it can only be released on the basis of explicit permission from the donor. This does not necessarily mean that the material in a 'further use' biobank has to be stored anonymously. This applies also to a 'further use' biobank where the material is specifically reserved for scientific research. There is often some form of quality control necessary there making it necessary to go back to the original patient data. The 'controller' of the 'further use' biobanks does not operate as an extension of the research arm but of the doctors that provide the material. the 'controller' is an intermediary towards the researchers.

Recommendation

Coded-anonymous use by scientific research is the primary rule. Within the same consent system, the material can also be released completely anonymous. However, completely anonymous considerably decreases the scientific value of the material.

The 'further use' biobank begins in a laboratory for clinical research. Every laboratory is advised to take into account from the beginning the release of human tissue for coded-anonymous scientific research.

The 'laboratory information management system' (LIMS) which codes the samples must make provision for this. The more advanced systems already ensure that the sample number does not contain the patient number or national identity number. In the long term, in order to be able to function as an important 'further use' biobank, such biobanks will need to invest in such a LIMS.

Next, the ICT systems are of importance to be able to provide additional coded-anonymous patient data. the complexity of the project determines how far this has to go. The privacy guarantees included in the project are also of importance. If human tissue from several biobanks is being pooled in order to provide sufficient statistical power (and that is often the case), then a further coding step is required to be able to analyse the pooled data. That second coding step will take place at the researcher that receives the material. they will, however, need to provide clarity on this beforehand.

2.4 Cost

The actual cost of releasing (a) and providing (b) the material may be passed on to the researcher. This does not have to be the case and will depend on the internal procedures of the facility the biobank is attached to.

A refers to the fact that the preceding process whereby human tissue for research can be released can be included in the cost. This can entail the extra investment in the LIMS or the quality measures for the storage for scientific research to the cost of assessing the request. Aspect b is self-evident. Very often only b is considered, but a can also be included. The line is drawn at making a profit. This is about the actual costs. how these should be calculated is another matter. The biobank that is too lavish, for example, by also trying to farm out the cost of their primary function (patient treatment) will soon price themselves out of the market. It is acceptable if internal researchers are not charged at all or at the most different prices than for external researchers. These internal researchers pay in quite a different way, as it were, through the institute's research budget.

2.5 *Should a 'further use' biobank also publish what human tissue is available for scientific research?*

Collaboration, often internationally, is essential for scientific research with human tissue. Making collections visible is the first step. This is highly recommended. In the U.S. and in Europe there are already a number of websites showing what human tissue is available.

3. The 'de novo' bank

This situation differs quite radically for the 'controller' from a 'further use' biobank. Although 'de novo' biobanks vary widely, there is one common feature. first comes the plan to collect material, specifically for scientific research, and then comes the collection. For the 'further use' biobank it is the other way around, as it were: first comes the collection for the purpose of patient treatment, and then the possible opening-up for a different purpose, namely scientific research. The control of 'de novo' biobanks is thus part of the 'plan' to collect human tissue in the first place. This plan encompasses a rationale for the collection, a strategy for the collecting and the guarantee of careful storage, and release of the material according to the rationale. To guarantee this in practice, the 'de novo' biobank needs to have a 'governance structure'.

This covers more than the regulations discussed in the previous paragraph. Custody and release of material is just one of the aspects of a 'de novo' biobank. In addition to the elements already mentioned, the following additionally apply to the governance of such a bank as a whole:

- Determining the scientific and societal aims for the collection.
- The recruiting of donors and ensuing contacts. Although micromanagement is not encouraged, participants should be able to approach the biobank with their possible questions and concerns.
- Furthermore, the bank or the plan it is part of should provide a complaints procedure (with a 'further use' biobank, this is already part of the complaints procedure of the care institution).
- Arrangements certainly need to be set out as to how participants can withdraw and what happens to the material already collected and the data available from earlier analyses. See what has been written about this in paragraph 5 of chapter 3. The bank must draw up a procedure for this.
- The transparency surrounding the project (see below).
- Release for research in the light of the rationale behind the setting-up of the biobank and possible adaptations should changing scientific or societal views warrant it.
- A procedure for 'tissue sharing' and 'data sharing' of results if the instigators of the bank and the researchers are closely linked.
- A clear separation of functions between collecting, custody and research.
- A long-term perspective and a procedure for dealing with the collection if the bank is dependent on subsidies and these are withdrawn. It would go too far in this Code of Conduct to describe the governance model in detail. A supervisory board is recommended. One of the members should preferably be a representative of the donors or relevant patient group. See also the following paragraph.

4. The involvement of donors and patients

The micromanagement by donors about which specific research and which 'findings' is not seen by the FEDERA as the solution for their necessary involvement. Nevertheless, a project could implement such micromanagement. Implementing it across the board however would mean the end of scientific research with human tissue in this country. The desired balance between the personal interests of donors and the general interest of furthering health care through biobanking would be upset.

In the context of the UK-tissuebank, it should be noted that the system for involvement (without micromanagement) and the governance structure have struck the right balance between personal involvement and the general interests of the participants and the public interest for which the project is intended (Campbell 2007). That is also the FEDERA's vision.

Many projects do not offer that balance at the moment. 'Further use' banks in particular are a twilight zone. Above has been set out how they could operate more transparently. By discussing the annual report in the patient councils of the care institutions, the necessary dialogue with the patients most involved is cultivated. A larger 'further use' bank could consider including a patient representative in the committee that deals with the requests for release of material. For a bank where this only comes up a few times a year, and then exclusively for internal researchers, this would quickly go too far. Even a smaller 'further use' biobank should aim at maximum transparency.

With 'de novo' banks, this balance should be built into the governance from the outset. How partly depends on the scale and nature of the bank. A limited local project differs from a large, population-based biobank. A disease-orientated bank differs from a bank with participants from the whole population. Involving the relevant participants or the population in general can take the form of an advisory council, a seat on the board when it involves a foundation, right of consultation by the relevant patient organisation with certain decisions (without the need to attend all the meetings), etc. The costs incurred by the participants or patients during this involvement need to be reimbursed and budgeted for from the outset. The 'de novo' biobank should certainly have a good website in which more can be found on the background to the project, the governance structure, the complaints procedure, withdrawal procedure and the current researches and possible results. A single model cannot be imposed from above. Each 'de novo' biobank needs to be transparent on its governance and make clear how the representation of donors and patient organisations is guaranteed.

CHAPTER 7

THE RESPONSIBILITIES OF THE INSTITUTIONS WHERE PROCEDURES TO OBTAIN SPECIMENS OF HUMAN TISSUE FOR HEALTH RESEARCH TAKE PLACE

The acquisition of all 'further use' human tissue takes place within care institutions. Often with 'de novo' biobanks the acquisition takes place in the care institution as well. These biobanks are often part of a department in the institution.

Aside from the possible financial contribution to the actual scientific research with human tissue, the institution is also important in creating the right conditions in the preceding chain of acquisition and storage.

The following recommendations deal with this. Norms which always apply, irrespective of the question whether the procedures are specifically for the purpose of scientific research or not, such as the general quality policy and the like, are not gone into here.

The following clear basic assumptions apply:

1. Provide a good no-objection system 'at the door', both for scientific research with (coded) anonymous human tissue and for non-anonymous data as might be permissible.
2. Provide staff with the ability to adequately answer questions from patients, including the basic rules for the possible feedback of 'findings'.
3. Provide a low-threshold possibility for raising objections.
4. Include the contribution to scientific research as one of the aims of processing personal data in the institution.
5. Provide a EHCR system capable of registering both forms of possible objection in 1 above and accompanying the passage of data and human tissue through the institution.

In addition, the following recommendations apply, in particular in university hospitals:

6. Programme the EHCR system in such a way that pseudonimisation steps can be carried out with the personal data.
7. Recognise the function of 'controller(s)' of the biobank(s) in the institution as intermediaries between the donors and carers on the one hand and the researchers on the other.
8. Provide sufficient means for the biobank(s) so that they can comply with the recommended administrative provisions and employ a LIMS enabling the release of coded-anonymous human tissue to researchers.
9. Involve the way the biobanks function in the institution as an aspect of the way the institution contributes to the advance of medicine, also in the contacts with the patient council.

CHAPTER 8

RESPONSIBILITIES OF THE RESEARCHERS

1. Introduction

Researchers sit at the end of the chain. This also applies to 'de novo' biobanks, even where the researchers took the initiative to set up the biobank and the bank is closely tied to the aims of their research. There needs to be a clear separation of function. This is necessary for two reasons:

- To honour the claim to privacy protection.
- To honour the promise that the material is indeed used for the purpose the donors were told about.

The separation of function means that it is wise to have 'someone' in-between to oversee both elements. As will come up later, that is not the role of an ECHT. This needs to be organised by themselves first. Then an ECHT can review whether this has been sufficiently taken care of.

2. The research protocol

2.1. *Aims of the research protocol*

In order to obtain or use material, a researcher will need to draw up a research protocol. It follows from the previous paragraph that this also applies when the researchers themselves initiated the biobank. The comments in the previous Code of Conduct on such a protocol are, apart from the odd nuancing, still up to date at this moment. The research protocol still has a number of aims:

- For the researcher to set out why and with which material he conceives to contribute to which advance in medical science (and thus patient care).
- To set out how the privacy protection of the donors is guaranteed and the responsible handling of
- Material and the possible resultant ‘findings’.⁹
- To provide the project team with guidelines on carrying out the project.
- To provide the ‘controller’ and third parties, such as an ECHT, insight into the responsible handling of the material and the interests of the donors.

2.2. *Hypothesis driven versus broad searches*

This is an important matter the Code of Conduct from 2002 was insufficiently explicit on. In the meantime, much more is known about research with human tissue. In that light, the following. Distinctions which can be made:

- What insight is hoped to be gained.
- Through which methodology that insight is hoped to be gained.
- What specific tests will be carried out on the human tissue.

The research protocol should be very clear and specific on the first two points.

The third point only needs to be described in general terms.

- This is closely related to the cautious attitude to micromanagement. Of importance to the donor are the aims of the research and whether his interests are sufficiently protected. This is part of the methodology, for example, the privacy protection when linking databases. It is not important for the donor to know exactly how this happens.

2.3. *Security*

This is a difficult matter. The claim by researchers is that the research protocol has been complied with. But contrary to patient-orientated research, this type of research just as with almost all epidemiological research, is for outsiders a kind of ‘black box’. Data and human tissue are put in. All being well, publications emerge. In contrast to this observational research, in clinical scientific research it can be seen what happens with the research subject, there are case record forms, there is an external monitor, etc.

The question is whether there should not be more laid down for observational research on clarity over the guarantee of certain critical aspects during the research. Those critical aspects are most of all:

- The interests of the donor (the claim of privacy protection is honoured, the material is used for the intended aim).
- The interests of the ‘controller’ and the supplier of the material (that the material is indeed used in a meaningful way).
- The first point applies especially to larger research projects in which material is used over a long period and links with other databases take place.

⁹ Not explicitly mentioned in the Code of Conduct in 2002. from the description of the contents of the protocol

It was apparent that it was clearly one of the aims of the protocol.

- The following recommendations apply.
- As indicated in paragraph 4 of chapter 1, a formal audit of all procedures is as yet a step too far. Certainly for larger projects with many links of data, the privacy protection needs to be taken care of as well as possible, and an ECHT should be able to request reasonable evidence that the procedures indeed work.
- Ideally, it should be clear in one way or another who did what with which data (browsed, analysed, added further data, processed). To properly enable this, a logging system comparable to what the dutch nen-norm 7510 and following norms demand for handling patient data. Virtually all the systems in which research data are processed are not set up for this.
- Such software still has to be developed. Naturally research databases are password-protected and there are procedures to determine who can access which data and what can be done with it. At the present time it is sufficient to set out these procedures and the risk of loss of data or unauthorised processing (including unauthorised additions) in a quality and security document (for further details, see Van Veen 2011). This would include attention to the weak points and what is being done to guarantee the security of the databases. In the future however, progress will have to be made towards systems which can show that what was intended has in fact been done. This means that an audit trail of the data has to be possible. In the new version of the Code of Conduct for health Research with Data, to be published in 2012, further comments on this will be made.

2.4. *The further processing of the human tissue and data*

- The research should be carried out according to the protocol.
- The human tissue should be used and stored as described in the protocol and possible MTA.
- Data obtained for the research (either accompanying the human tissue or from other sources) should be handled not only according to the protocol but also according to the Code of Conduct for Health
- Research¹⁰ and possible agreements with the suppliers of the data.
- Provide for procedures to remove human tissue from the research and destroy it should a notification be received from the ‘controller’ that the donor has withdrawn consent or has raised an objection.
- There should be a policy on dealing with ‘findings’, as described in appendix 3. See Bovenberg 2009 for more on this policy.
- The chain is often longer than described in chapter 2, paragraph 1. There is collaboration with other researchers or with third parties, commercial or not, for example to sequence the material. The chain needs to be finite, however, so that the human tissue and data cannot be lost sight of. MTAs should clearly specify what can be done with the material by the third party. These MTAs should specify that data may not be published or links established in such a way that the donor could be identified elsewhere in the chain without undue time and effort. In certain cases, such a third party could be required to provide an audit certificate clearly showing that they have only processed the material and resultant data according to the terms of the MTA (Riegman 2011).

2.5. *Transparency*

Particularly for larger research projects, it is recommended that a website be opened, possibly in conjunction with the ‘controller’ of the biobank, where information on the research can be published.

¹⁰ The present version does not explicitly deal with handling coded-anonymous data. The ban on (re)identification applies without exception.

3. Datasharing

All large international projects are already a form of 'datasharing' and 'tissuesharing'. This particularly refers here to the fact that researchers wish to share raw data from the research, as carried out within the research group, under fair conditions, with other researchers outside the research group. What those conditions are falls outside the scope of this Code of Conduct. For an initial suggestion, see RGO 2008, and in particular, appendix 1. The norm set out in this Code of Conduct is that researchers are prepared to cooperate on datasharing whereby the conditions for the release of raw data can be mutually agreed. such 'datasharing' prevents unnecessary research and use of scarce human tissue. In this way a contribution is made to the quicker attainment of potentially important results for health care, which is the ultimate aim of the research.

CHAPTER 9

THE (ETHICAL) REVIEW OF RESEARCH WITH HUMAN TISSUE

1. Introduction: the review criteria

The chain of use of human tissue for scientific research should be reviewed by an ethics committee. This is referred to here as an ECHT (ethics committee human tissue). This could be part of a medical ethics committee or an independent committee.

Such an ECHT requires a different composition from a typical medical ethics committee which reviews clinical trials.

A medical ethics committee, and in this case an ECHT, needs to see that scientific research whereby the interests of people are involved is carried out in such a way that the interests of these people are not unreasonably infringed. Legislation generally lays down how these interests should be weighed, in other words, what does and does not count as an interest.

That has been done here in this Code of Conduct. There are other opinions possible on the (ethical) conditions under which human tissue can be used for scientific research. The conditions set out here are acceptable and reflect the consensus in the Netherlands of most of those involved (doctors, researchers, jurists and ethicists and patients).

From the conditions dealt with here, the following review criteria emerge:

1. Does the acquisition of the material entail minimal risk and commensurate burden?
2. Is the acquisition and intended use for scientific research in agreement with the consent system in this Code of Conduct?
3. Is the privacy protection sufficiently organised in the chain from acquisition to scientific research?

The way of using these criteria in the review is expanded on in paragraph 3. If the review is being carried out under legislation dealing with scientific medical research with humans, the following is of enormous importance:

- Whether the research is sufficiently safe for the research subject (bearing in mind the aim of the research and the condition of the research subject).
- Whether the methodology of the research is adequately set up to answer the research questions.
- Whether the research forms an unreasonable burden for the test subject.

These aspects have a different meaning by scientific research with human tissue. There is no research subject at risk from this research (see also appendix 1) other than already dealt with above. It is therefore not necessary for the ECHT to evaluate the scientific 'sense' of the research with human tissue and whether this research is a responsible use of the (possibly) scarcity of human tissue against the contribution to scientific knowledge through the use of human tissue in this specific protocol. Such an evaluation does not contribute to the protection of the donor.

The ECHT would end up sitting on the chair of the 'controller' of the biobank and the researcher. Incidentally, the term 'meaningful use', as far as the term is known at all, is apparently not used abroad either in reviewing scientific research with human tissue.

Indirectly, the aim and methodology of the research reappear in the evaluation of the second criterium: is the proposed research in agreement with the consent system. The foundation of the consent system is that donors in this way contribute eventually to better health care. Research which cannot contribute in any way to this falls outside the consent system whereby no objection to 'further use' of coded-anonymous material and 'broad consent' for specifically acquired material are, as it were, the 'default options'.

2. Distinction in review moments

A distinction must be made between the review of the acquisition when human tissue for scientific research is extracted (a) and the review of the proposed research with human tissue before the acquired and stored material is made available for scientific research (b).

The review norms vary in expression depending on the type of research, namely whether concerns material from a 'further use' biobank or is it about a 'de novo' biobank for which material is specifically acquired.

The following table can be drawn up
(the numbers refer to the criteria mentioned in the previous paragraph):

	Review moment a	Review moment b
'further use' biobank		2,3
'de novo' biobank	1,2	2,3

The practical implications and the prevention of too many review moments are dealt with in paragraph 4.

3. The criteria examined further

3.1. For the taking of human tissue samples as such

This concerns exclusively the 'de novo' biobanks.

The extraction must meet two conditions:

- The risk from the procedure must be minimal.
- The burden of the extraction procedure must be in proportion to the interest in obtaining new scientific insights through this type of human tissue.

The element of minimal risk is self-explanatory.

About proportionate burden, the following. This refers to the physical and emotional burden, the time taken up by the procedure and the possible residual pain.

In principle, the burden should also be minimal. Sometimes it is not easy to acquire the human tissue necessary for research. A lumbar puncture for example is not a minimal burden. Yet there are situations where the possible biomarkers can only be found in lumbar fluid. It must be possible, with informed consent from the donor and as long as it is safe for the donor, and if it is the only definitive possibility for the proposed research. incidentally, this is already the practice in certain researches.

3.2. *Review of the consent modalities*

By the 'de novo' biobank, this concerns the information for the donor prior to the extraction. Does this give the information the donor needs to make the choice as to whether to allow extraction or not. Review then arises when the material is actually used for a research protocol. Is this in accordance with the information given, especially if no broad consent was applied.

By 'further use' biobanks, this review occurs upon request of human tissue on the basis of a submitted protocol for release from the biobank. then the trail is followed back to the beginning, as it were. Was there an comprehensive no-objection system for coded-anonymous material? Has it been set up so that indeed no human tissue is involved in the research from patients who have objected.

In both cases, the following will also be evaluated:

- Does the supplementary information include the elements referred to in chapter 3.
- Does the system adequately enable later objections (or withdrawal as donor) to be processed by the 'controller' and, if the material has already arrived at the researcher, that it is no longer used in the research.

If no coded material is being used but material identifiable for the researcher, the trail back means, of course, (broad) consent.

3.3. *Privacy protection*

The researcher will need to show reasonably that the material and the data reach him coded-anonymous (on the basis of the default situation). For this, a global insight into the pseudonimisation procedures must be given. Since this is about a chain of data, in particular here from the 'controller' to the researcher, that insight will need to come partly from the 'controller' or with his cooperation.

The researcher will need to offer a global insight in the chain of collaboration with other partners, such as when the material is sequenced in a laboratory elsewhere.

See chapter 7, paragraph 2.4. The ECHT must reasonably be able to draw the conclusion that the chain has been set up in such a way that the identity of the donor elsewhere cannot be traced without unreasonable time and effort.

4. **The practical consequences**

4.1. *Balanced approach to review moments*

From the above it would follow that each protocol needs to be reviewed. For smaller protocols from the same researcher, this would entail an unnecessary repetition. It is conceivable for example that the privacy protection in the chain and the broader research aims within which the protocols fall are reviewed once. Also with a 'further use' biobank, normally speaking, a single review of the basic no-objection system and the privacy procedures at the 'controller' would suffice.

Furthermore, agreements could be made with controllers of both 'further use' and 'de novo' biobanks as to which protocols with a further defined objective are acceptable and require no further review.

In general, the maxim applies that the review is so carried out to contain the administrative burden while leaving the ECHT with a clear view of whether human tissue is being handled responsibly in accordance with the Code of Conduct and the possible agreements with the ECHT.

4.2. Composition of the ECHT when reviewing scientific research with human tissue

The composition of recognised medical ethics committees is focussed on pharmacological research. For the review of research with human tissue, this composition is less applicable. For example, a clinical geneticist could replace the pharmacologist for this kind of research. Neither need all the clinicians serving on a medical ethics committee be involved in evaluating this kind of research. The jurist in a medical ethics committee could well be supplemented by someone with specific knowledge of the practical and ICT aspects of privacy protection.

There is also discussion as to whether patient representatives should not serve as such on an ELC (cf Smit 2010).

The FEDERA recommends therefore that a separate committee, the aforementioned ECHT, be used for scientific research with human tissue. The name chosen is not important. It would seem desirable to maintain a link with a medical ethics committee, for example, by setting up the ECHT as a separate 'chamber' of the medical ethics committee, with its own dedicated composition. That could be, for example:

- chairman, familiar with scientific research in general;
- 1 practising clinical doctor;
- 1 ethicist;
- 1 researcher (epidemiologist or biologist etc.);
- 1 (clinical) geneticist;
- 1 jurist;
- 1 representative on behalf of the patients or who is required to represent the interests of the patients;
- 1 person familiar with the practicalities of privacy issues and pseudonimisation.

Inasmuch as this composition is problematic for the review by a traditional medical ethics committee of the extraction of human tissue specifically for scientific research (see appendix 4), this ELC could report back to the medical ethics committee who in turn would endorse the report.

Part 3
Accountability

APPENDIX 1: ON THE DISADVANTAGES AND POSSIBLE RISKS OF SCIENTIFIC RESEARCH WITH HUMAN TISSUE**1. Introduction**

Scientific research with human tissue is now regarded as one of the most important promises for better health care and prevention. At the same time, this research has given rise to the necessary discussions in ethical and juristic literature. It is noted there that biobanking¹¹ can also have possibly serious disadvantages (for example Ploem 2010, who talks of ‘dangers’). These disadvantages can be categorised as follows:

1. Biobanking is about working with data. Data of many kinds but with one essential common characteristic, namely that they concern one and the same person. These data are linked to the analyses of the human tissue. It has to be about unique data from large groups of people (see also chapter 2), otherwise no meaningful conclusions could be drawn. That evokes the question as to whether the privacy of the donors are sufficiently protected.
2. This question gains significance because analysis of the human tissue provides new data. That can yield knowledge on the donors which could be a burden for them. It is possible that a disease or propensity therefore is discovered in a certain donor of which they are as yet unaware. Those are so-called ‘incidental findings’. The result of this research consists of statistical correlations between the data known about the donor and tests on the human tissue. This yields new knowledge about sickness and health and are the so-called ‘new findings’. Feedback of these findings to the individual donors can also be a burden.¹²
3. To use human tissue for research without the patients’ express consent would be a fundamental breach of their right to determine themselves the destination of ‘their’ human tissue left over after a treatment.¹³ This objection applies in general, thus irrespective of the safeguards under which the research is carried out.
4. Even when express consent has been given, the question remains as to its value. The actual research with human tissue often takes place much later. The exact questions concerning the material are as yet unknown. This applies as much to research with leftover material as to material specifically extracted for biobanking.
5. Through the publication of the results of research through biobanking, more is made known about the risks for certain groups in society. Even though the individual privacy may be well protected, the so-called group privacy can be affected. It is possible that improved knowledge about the origins if disease can lead to discrimination of groups that are at risk.

In this chapter, the possible disadvantages relating to the privacy of donors is dealt with (1-3, 5). Where required, details are given in the appendices. Points 3 and 4 on fundamental rights are dealt within the next chapter, by consent modalities.

¹¹ When talking of ‘biobanking’ here, it is in the sense of research with human tissue.

¹² ‘Incidental findings’ and ‘new findings’ are referred to in this Code of Conduct simply as ‘findings’.

¹³ For human tissue acquired specifically for scientific research, this does not apply of course. The question raised in the text applies solely to ‘further use’.

2. Biobanking and privacy

This problem has the following aspects:

- These data can end up outside the research domain, for example at insurers or the government (2.1)
- Privacy within the research domain (2.2).
- The question whether genetic material (DNA) in general can be anonymous (2.3).

2.1. *The 'leakage' of data outside the research domain*

Researchers constantly reveal data outside the research domain. That happens with the publication of the results of the research and is actually the aim of scientific research. It is nearly always the describing of data at group level. Individuals are never identifiable here. It does happen that a series of patients are described (case studies), but also here, the data is anonymised. In exceptional cases where this isn't possible, such as the publication of (facial) photos, naturally explicit consent is requested first.

Apart from research with human tissue, epidemiological research has long been based on the processing of personal data. Such research has taken place for years with large quantities of data. Not one single case has been publicised in Europe where these data have ended up in the wrong hands.¹⁴ Of course, researchers constantly need to employ security measures. That is done, too. In the context of biobanking, often much more data is involved and the security measures need to be even stronger. The next section deals with a number of these measures. The conclusion has to be that up till now, the 'leakage' of personal data from the research domain has been purely hypothetical. That doesn't mean that researchers don't need to do more to show that this danger remains hypothetical. See the comments in paragraph 2.3 of chapter 8 and Van Veen 2011. What follows deals with how working with human tissue and DNA affects this.

2.2. *Privacy within the research domain*

This is a complicated matter. Preferably, researchers should not have access to the personal data of donors. That also applies to all research with data, also when human tissue is not involved. Researchers are – in short – not interested in persons (in the person behind the data) but in general patterns deduced from the data surrounding the person. From that point of view, researchers have what they need with 'anonymous'¹⁵ data. However, it is important that data on lifestyle, medical history and the like can be linked to one unique individual. That is why it usually concerns coded data. A well-known expert in biobanking has even stated that the full anonymising of human tissue is a waste of valuable material. (Knoppers 2005a). Even when researchers work with cohorts of volunteers that, for example, are regularly approached with additional questions, the researchers analysing the answers do not know who they came from. These answers are also coded.

¹⁴ This is also the case outside Europe. In the United States a number of incidents have been reported where patient data from a hospital or a so-called 'health maintenance organisation' have been leaked or hacked. For the latter, see Kagle 2010, p. 201 ff. However, this never concerned data present in the research domain.

¹⁵ See Van Veen 2011 and Van Veen 2011a for a further discussion on this. Data regarded as anonymous by researchers and treated as such, are often held by watchdogs such as Data Protection Agencies to be indirectly identifiable. See further in the text.

Such coding is a so-called 'privacy enhancing technology' (PET) intended to offer the participant of a research as much privacy as possible. PETs are increasingly being employed. This does not automatically lead to anonymous data. The internal coding and separation of a database with research data and contact details is a PET but does not produce anonymous research data. To talk of anonymous data in the eyes of the law, high standards must be employed. A separate paper deals with this (Van Veen 2011).

The conclusion in that paper is that of the coding is sufficiently secure and the aggregation level of the research data is sufficiently high, then you have anonymous data in the eyes of the law. Unfortunately, some watchdogs assume 'identifiability' where no researcher would ever assume that or, even if it were possible, attempt to make use of it. See Van Veen 2011 for a – possible – solution to this problem.

Coded data can provide anonymous data and, thus, also, within the limitations dealt with in the previous paragraph, anonymous human tissue. Where further coded-anonymous human tissue is referred to, this is data (data linked to the human tissue and data derived from it) which is anonymous in the eyes of the law (or at least according to the nuanced view proposed in Van Veen 2011). It is thus anonymous human tissue, just like human tissue which is fully anonymised and not coded.

The Code of Conduct from 2002 was insufficiently clear on this, and another question was whether, in practice, the strict conditions for coding and aggregation level were always complied with.

As has been seen, biobanking is all about a chain. In short, from the person extracting the human tissue, via the person storing the human tissue, to the researcher. Very often there are other intermediate stages. In large biobank projects, coding once is not sufficient, and data and material is as a rule coded twice or three times. From the provider to a research database, within the research database and from this database to the researcher actually doing the research with the material and data (Van Veen 2008). Large international biobank projects are bursting with advanced ICT-systems which in the one hand (also) guarantee privacy within the research domain and on the other, enable the necessary linking.

Such complex systems are not always possible or efficient. The chain is shorter then. In those cases, sometimes one can still talk of coded-anonymous and sometimes not. When a treating physician, such as a clinical geneticist, does research with the material from his patients, there is no chain at all. Even with an internal coding, you cannot talk of coded-anonymous. He knows his patients so well that even when he just sees a number, he knows full well who it is. That also has consequences for the consent system.

Van Veen 2011 discusses the distinction between one-way and two-way coding. Two-way coding can also result in anonymous data. From the perspective of privacy protection, one-way or two-way coding has no fundamental difference. There is a difference in the ability to feedback the results of research with human tissue. With one-way coding, the results of analysis with human tissue (in combination with other data from the donor) cannot be fed back to the donor. The link between the code number and the identity of the donor has already been broken. With two-way coding, such feedback can theoretically take place. The consequences of this are dealt with in the next paragraph.

2.3. *Isn't human tissue always identifiable: the challenge of the guarantee of privacy protection versus common sense*¹⁶

The views expressed above are challenged by scientists who showed that individuals can be isolated within a pool of DNA-data (Homer 2008, Braun 2009). Ethicists and a number of jurists have drawn conclusions from these very complex statistical analyses (amongst others, Curren 2010). They suggest that the increase in 'datasharing' and 'tissuesharing' makes it impossible to guarantee privacy any longer. The most extreme form of this proposition is that human tissue is always identifiable since a genetic profile can be obtained from it.

Such views need to be addressed with a sense of proportion and nuance (cf also Riegman 2011).

A distinction must be made between:

- a. the acceptance that various DNA-data belong to a single person;
- b. the tracing of these data to a single identified individual.

What is stated in a is under certain very specific circumstances indeed true. But a does not automatically lead to b. And that is the point. Just as with fingerprints which are unique, in order to identify someone from their fingerprint (or DNA in this case), you first need a database in which this fingerprint (or DNA) is linked to a certain person. A researcher possessing such data (whether derived from human tissue or not), does not have access to such a database (even supposing such a database existed within the health care domain). The rebuttal of that is that more and more databases, via internet or not, are available also with linked phenotype data. The individual is at the very least indirectly identifiable.

In contrast to type a however, no concrete examples have been given of this, not even in the form of statistical chance. Such examples are not really conceivable. It is indeed possible, using various advanced 'searches', to reasonably identify participants on internetfora, particularly the more prolific writers, even if the individual uses different pseudonyms on each forum. But that is quite a different matter and does not apply here. This is about how a researcher could recognise someone on the internet from their DNA-data. For example, DNA reveals risk of obesity, red hair and so on, and the person can be identified on the internet. This scenario is too strange for words. Hundreds of thousands of people have such characteristics, and in the Western world, many of them use the internet. It would be a different matter if in a certain project, the participants had placed their complete sequenced DNA on the internet. Then they would be identifiable but that was then the aim of the project.

Then it is also the point that the researcher is not allowed to attempt identification and the question why they would even want to. As demonstrated there are more direct means of identifying individuals on the internet. Indeed it has apparently been possible to link 'anonymous' statistical data to sources in the public domain and thus identify the persons in the anonymous data (Ohm 2009). But that was not about anonymous DNA-data. Inasmuch as it would be possible to link such public databases to the DNA-data of participants, which is virtually inconceivable, the only possible conclusion is that it would involve 'unreasonable time and effort'. That is the criterium in Directive 95/46/EC and the relevant legislation in the Netherlands at least, to disqualify these as personal data.

The view that 'genomic sequencing studies' never yield research with 'not-identifiable' data is thus termed 'unnecessarily extreme' (Lowrance 2006). That was before the findings of Homer (2008) and Curren (2010). Those, however, concerned the a-domain, not the b-domain.

This does not mean that the data stream in research should not be firmly grounded in procedures and techniques to prevent identification. The data reach the researcher coded. The coding cannot be

¹⁶ This paragraph is taken from Van Veen 2011

traced back by the researcher. That is the basic assumption here. There is an interesting paradox here. The closer the data remain to the source, the greater the chance of identification through links with other databases where the identity of the donor is included. However, closer to the source, there is sufficient grip on the data the receiver has available. Hence there is also clarity over the supervision of the receiver. The further away from the source the data and material get, the less clear the supervision and the databases the receiver has available.

This paradox is solvable. The Code of Conduct works on the premise of a finite chain. This entails transmitting as little data as possible with the samples, namely just those of importance for the common research question, and well-constructed contracts. In the event of a further common research question (about a link between genotype and phenotype) or a series of closely related questions, the necessary data is transmitted with a newly generated pseudonym. Furthermore, in certain situations, such as when the analysis of the human tissue takes place at another location (instead of what usually happens, that analyses from various centres are pooled), an audit certificate (for example SAS 70)¹⁷ could be required to show that the organisation indeed applies the data security they say they do and that they use the samples exclusively for the purpose agreed.

In the meantime, new possibilities are being suggested, such as the 'Datashield' (Wolfson 2010). In essence, these new possibilities amount to not creating one common database to pool the data from various researchers, but that per query, data is pulled from the databases on the various participants. This technique still has to prove itself and de facto does not differ so much from the situation whereby for each new query, the data on the various participants is transmitted under a new pseudonym, as is de facto already often the case. In that case, no single large, enriched database is generated, but various ones, per query or series of related queries.

The conclusion is that the chance of identifying the individual donor through DNA-data is theoretically possible, but implies that such an extreme scenario does not nullify the privacy protection of the donor.

In that connection, also something about the problem of so-called 'spontaneous recognition'. Spontaneous recognition means that a researcher, from certain characteristics, could recognise the donor as a person. The danger of spontaneous recognition can be a problem with privacy protection. The example mentioned earlier of photos in a publication is a case in point. But if a researcher 'recognises' a donor on the basis of certain characteristics, this means that the researcher already knew the donor in connection with these characteristics.

In everyday life, spontaneous recognition can mean that more is discovered about the person involved than should be known.¹⁸ In research situations, this is relatively inconceivable. By 'high throughput' analyses, spontaneous recognition is just as abstract and unrealistic as recognition through DNA. Such large quantities of human tissue pass through, as Borst called it, 'the DNA cruncher'.¹⁹ These are linked to large quantities of data in order, through complex biostatistical analyses, to arrive at possible explanatory patterns. There is no researcher who could recognise an individual person in those statistical results.

¹⁷ SAS 70 stands for Statement of Auditing Standards for Service organisations

¹⁸ An actual example concerned how in a psychotherapy lecture a certain casus was discussed, naturally, anonymised. One of the audience recognised in the description someone they knew.

¹⁹ 'de DNA vreter' in Dutch, Borst 2010

In small-scale research it is different. But then the following applies. The researcher recognises the donor on the basis of a portion of the data. He already knew the donor, more often than not as his treating physician, since we are talking about medical data that nobody else would have access to. It is relatively inconceivable that the researcher-doctor, through the research data, would get to know something about the donor that he didn't or couldn't already know in the context of the treatment relationship.

To finish, something about the danger of leakage outside the research domain of DNA databases through hacking or simple carelessness, for example, a cd-rom or usb-stick forgotten in the train. Even if that were already to happen, the crucial point is that it concerns abstract pseudonimised persons. For a hacker, such a database is perhaps of interest as a test lesson, but the data inside it are not. He (or she) cannot do anything with it. Even publishing the DNA-profiles of numbers 00001 to 20000 would not lead to the identification of those persons. This of course does not mean that the databases should not be well protected and that only very secure data should possibly be allowed to be taken home for further processing, if it all.

2.4. Conclusion

The conclusion of this paragraph is that the privacy of donors in the research domain is well guaranteed, but that constant vigilance is called for to keep it that way. That has always been the case, also when no human tissue was involved in research. Various European countries have a rich tradition of epidemiological research. It has never emerged that researchers have misused the data they had available to them. Even when in theory they could trace the identity of those involved, it just didn't happen.

Researchers cannot be tarred with the same brush as commercial bureaus that have an interest in marketing the data they have available.²⁰ Researchers have just the opposite interest, namely not to damage the trust of those that entrusted data to them. At the same time, in the present climate, more must be done to make the security of data handling transparent. The PETs already in use were described above. The research protocol should provide clarity on this point. In the future, there should be an audit trail possible on every research database, as set out in the Code of Conduct.

3. Feed-back of results

This is probably the most complicated topic. Appendix 3 goes into this in more detail. The conclusions are integrated in the Code of Conduct. The conclusion here is that the chance of 'findings', if this is dealt with as set out in the Code of Conduct, does not present a 'danger' to the donor.

²⁰ See for examples also Kagie 2010

4. Group privacy

In the literature, there has been much attention on so-called 'group privacy' which, through epidemiological research (Custers 2004, Ploem 2010), could be infringed. This also is a very complicated topic. Who, for example, is the group? For small ethnic groups, biobanking can indeed affect their group identity, if, for example, it were published that they are related to a population some thousands of miles away, while their own belief on their heritage is determined by region and myth.

This is not about such research.

This is about disease-driven research which for example can show which people run a certain risk and is aimed to limit that risk. The most well-known example, from long before biobanking, is that of smokers. The disadvantages of infringing the 'group identity' of smokers does not at all weigh up against the advantages, not only for the group themselves but for the rest. But this example will probably be thought too extreme. The 'group' is namely too amorphous, the risk too evident, and the method of prevention not injurious enough to act as an example of other 'infringement' of group privacy. In his seminal book 'The Politics of Life itself', the sociologist Niclas Rose described his own research and that of others into how people deal with the revelation of scientific data on the possible health threatening or promoting factors of a group they (can) count themselves in (Rose 2007). This research extended also to smaller, sometimes ethnically determined groups. It appears that these results almost without exception were not seen as a threat but as opportunities. Not only in respect of their own health, but also for the health of those they have a relationship with or enter into a relationship with. New alliances are forged around disease and health in which the results of biobanking are included and even specifically sought. Thus it seems that group privacy is more of an invention of paternalistic ethicists than of the groups themselves.

Biobanks initiated by patient organisations or even owned by them are another example. Where in the recent past certain ethnic groups had an aversion to biobanking, amongst other things, due to the possible discriminatory character of the results (Reardon 2005), now they embrace it. In the United States for example, a biobank has been set up which exclusively recruits among Afro-Americans in order to unravel the genetic causes of diseases which affect this group more than other ethnic groups (the GRAD Biobank). Another example is the research in the United States into the perception of the biomedical research among Ashkenazi Jews. Certain diseases occur more frequently in this group. They did not feel that their 'group privacy' was threatened by thus biomedical research (Brand-Rauf 2006). Patient groups also set up biobanks themselves. In the American system of conflicting interest groups, the absence of a health care system based on solidarity and the low perception of the government as protector of the general interest, these are even major players in biobanking (Fletcher 2008).

It is the results that they particularly want, at least a part of the 'group'. Opposite the idea that some have that their group privacy is being encroached on are those who do want to know. That is, as is evident from Rose's research, the majority.

Assuming that it is meaningful research, with meaningful results in the sense of possible health gains for that part of the group that want to know, it boils down to a balance. The interest of those that stand to gain then weighs heavier. It can be of vital importance, for example if transfer mechanisms of infectious diseases are discovered in time. There is this a social interest involved to see the research carried out.²¹

Research with informed consent, as will be shown later, makes research more expensive and considerably less reliable. No-objection or opt-out expresses citizenship, namely that participation is a fundamental contribution to results of research becoming available for others. At the same time it leaves enough room to withdraw should the feeling exist that scientific research with human tissue (or data) should not take place.

5. The risk of discrimination following the results of research

The Code of Conduct can be quite brief here. Knowledge can be used for good and bad. This applies to all knowledge, wherever it comes from. Possible predictive knowledge on health cannot in this country be used as a reason to discriminate access to important provisions. Aside from the solidarity-based social provisions, including our health care system, there is a law on medical testing as a safety net for the private sector. Incidentally, The Netherlands and the other European countries differ enormously from the United States. Unfortunately, much of the juridical and ethical discussion from the United States, where both the health care system and the social provisions are completely different, is all too indiscriminately applied to the European situation.

²¹ For a more principled discussion of the disadvantages of group privacy, see Van Veen 2011a.

APPENDIX 2

CONSENT SYSTEM IN THE CHAIN

1. Introduction: no micromanagement

This would seem to be in the first instance the most important subject. The white paper published in January 2010 in the Netherlands on a law about the use of human tissue for scientific research is called simply Human Tissue Consent Act.²²

At the same time it could be questioned whether the focus on consent isn't a somewhat limited view of the normalisation. Consent by the donor should be seen in the light of the pros and cons of the use of human tissue for scientific research and the guarantees on how the theoretical 'cons' can be prevented. See appendix 1 and the Code of Conduct further, which are aimed at preventing the disadvantages. The whole chain must be viewed and all the steps in the chain normalised as appropriate.

The necessity for individual consent can be weighed against the guarantees for the responsible handling of human tissue. The more guarantees there are, the less need there is, as it were, for 'micromanagement' of the destination. Micromanagement means here that the donor can specify precisely for what ends the human tissue can and cannot be used and which 'findings' the donor does and does not want to know about.

Such micromanagement was used as a basis in the above mentioned white paper.

In the first place, this micromanagement presupposes a large measure of expertise on the part of the donor, in particular the micromanagement of decisions on the feed-back of 'findings'. It would entail enormous pressure on the consent system, the objection procedure, the research procedure and the intervening ICT to record the decisions on every sample and at the same time guarantee privacy.²³

If this micromanagement is allowed, it also needs to be realised. At the same time privacy still needs to be guaranteed.

Between micromanagement, in particular if the donor changes their mind later, and privacy protection there is an inherent tension. Privacy protection means the further down the chain, the more the identity of the donor is masked. The cost would run into millions and because that money is not there, this would mean that very little human tissue would become available for scientific research. That micromanagement is also not necessary. Empirical research has shown that patients do not want it (amongst others, Hansson 2006, Vermeulen 2009). In appendix 1 it is argued that the use of human tissue for scientific research, provided it takes place responsibly, coded-anonymous, does not have a down-side. Naturally, the human tissue becoming available must also be used in a sensible and responsible way. More on that later.

²² It could be questioned whether this is the most appropriate title. Wouldn't it be better called "Availability and use of human tissue for scientific research and quality assurance"?

²³ This is one difference between such a possible system and an ordering system on the internet.

2. Consent for 'further use'

From the research mentioned above (Vermeulen 2009) it appears that patients wish to be sufficiently informed, but have no need of an extensive consent system. The general public seems to think differently (Rathenau 2009). Incidentally, the public at large does seem prepared to participate in prospective cohort studies. A requirement for this is, of course, voluntary participation and informed consent. What this paragraph is really about is the consent procedure used for 'further use'. Thus for patients who involuntarily visit health care and where in the context of their treatment (which also includes the diagnosis) human tissue needs to be taken. There is informed consent for the extraction, as part of the agreed diagnosis or treatment plan. There is in principle at that moment no consent for 'further use' unless that were also requested.

In general there is a realisation, when confronted with a serious illness, that the treatment is based on the results of previous research (including research with human tissue). There is a preparedness to contribute to such non-burdensome research. There would even be surprise if that research did not take place. People want to be informed and taken seriously without being burdened with an extensive consent procedure. The result of the research among patients was a 'no-objection system plus' (Vermeulen 2009)

The no-objection system for coded-anonymous human tissue was proposed in the Code of Conduct of 2002. It is here likewise the position. It is clear that much more needs to be invested in information and low-threshold opportunity to raise objections. That is part of the 'plus'. Then there are a number of situations where the general no-objection system by 'further use' does not apply:

1. There is no guarantee on coded-anonymous use of human tissue and data. The guarantee of optimal privacy 'your details are anonymous in the research' cannot be honoured. Such situations need to be discussed with the patients involved. A no-objection system does not lend itself for this.
2. Due to the circumstances under which the research is carried out, 'findings' can certainly be expected and individual feed-back is even desirable. The reserved position on 'findings' then does not apply. This also needs to be discussed with the patients.
3. For a certain group of patients there is a project with human tissue specially reserved for them either already running or proposed. This group should be specifically informed about this. Following this specific information, a no-objection system is still possible. The information should be more specific because there is more specific information to give. The general principle is that the patient should be informed as clearly as possible.
4. It concerns a pharmaceutical trial and clinical markers are sought with the help of human tissue from test patients who can explain the reaction to the medicine. The patient is not a donor but a test subject and participates on the basis of detailed informed consent. This also needs to include the related biomarker research. It is possible that during the research this leads to an adjustment in the treatment.
5. It does not concern research into the origin of diseases or their treatment for which social consensus can be presumed. The principle is that the patient contributes for the benefit of other patients. That principle does not apply if matters are researched which have nothing to do with the improvement of prevention of disease or its treatment. Research into biomarkers that could explain delinquent behaviour cannot take place on the basis of no-objection. That kind of research can only be conducted voluntarily and on the basis of informed consent.

6. It concerns a project specifically aimed at finding a commercial application, or a deviation from what is mentioned in the chapter on acceptable 'commercial use' of results from research with human tissue. This also is in line with the principle that the patient benefits from good health care and contributes to the general interest of good health care. When 'profit' is the aim of a research, that principle no longer applies. As will be argued in the chapter on 'commercial use', this needs to be looked at with some nuance. The registering of a patent by a public institution to prevent a commercial company doing so does not conflict with that general interest.

These exceptions are an important nuancing to the 2002 Code of Conduct. Coded anonymous 'further use' of human tissue for scientific research and a corresponding no-objection system is, as it were, the 'default situation' but cannot be applied across the whole range of 'further use'. This 'default situation' needs to be determined from case to case. The majority of the exceptions fall under the responsible custody and use of human tissue. The Code of Conduct deals with how this can be guaranteed in the chain.

3. Consent for extraction specifically for scientific research.

This is an easier matter. The material cannot become available without consent from the donor. They need to give consent of course on the basis of sufficient information on what effect the procedure whereby the material is extracted will have on their health. Such a procedure should only entail minimal risk and the consequences and burden of the procedure should be in proportion to the aim of the research. It is sufficient when the aim of the research is described in broad terms such as with the English biobank study and the feed-back of 'findings' is set out as proposed here. In other words, not micromanagement through specific consent for each subsidiary query or analysis which could be carried out with the material nor the micromanagement of 'findings' as proposed in the white paper referred to above. Under the micromanagement proposed in the white paper, such a UK (or Dutch) biobank would be impossible in the Netherlands. This conclusion also applies to the already existing Dutch 'population based' biobanks.

This does not hinder a more specific description of a biobank project or, for example, that agreement is reached with donors to provide more details on the results of the analyses on their material. Also, for example, that following the first extraction, that their material is screened for certain common conditions as a sort of 'medical check-up'. This would fall under 'incidental findings' at the start of the project. This would however need to fall within the bounds of any applicable legislation on medical treatments, such as the Act on Medical Screening (WBO) in the Netherlands. With smaller, specific projects, further contact with the donor is quite possible. Then each project should be able to determine this for itself in discussion with the stakeholders involved, such as the group of donors they want to reach. It should not be the guiding principle of legislation however.

APPENDIX 3

FEED-BACK OF 'FINDINGS'

This is a complicated subject which is widely misunderstood. To begin with: this is not about the feed-back of diagnostic research which the donor is sometimes offered upon the start of their participation in a biobank project. Amongst others, this is the case with the UK Biobank and Lifelines. That is a kind of medical check which, in the Dutch situation, needs to abide by the terms of the WBO, and does not raise any special questions.

This appendix is about the question of how to deal with the results of the actual research with the material provided by the donor.

There is much discussion in the literature on this (Wolf 2009, Dressler 2009, Bovenberg 2009a).

There are many arguments against a general policy of individual feed-back about findings specifically related to one or more donors. Some are practical, others are ethical.

Of the practical arguments:

- The research is trying to find statistically relevant correlations. It does not then generally take place under GLP-conditions. Should something be discovered on specific donors, the test would need to be repeated under GLP-conditions to determine if this does indeed apply to this donor.
- The research takes place long after the material was taken from the donor, sometimes even after their death. The results are very seldom applicable to the current treatment or lifestyle decisions of the donor.
- It almost always concerns a first hypothesis, an assumption of a connection between treatment and care, or between a donor's genetic markers and the origin of disease. There is usually much more research necessary to confirm this connection.
- Much of that research yields the – possible – explanation of a slightly increased risk of a condition or increased chance of its cure. It is almost always unclear what clinical meaning such an explanation has at this time, or in other words, in what way it could be applied to prevention or treatment.

Of a more ethical nature, the following, which was also partly dealt with in chapter 2:

- One does not become a donor in order to benefit oneself. Participation in biobank research should take place voluntarily in order to contribute to better health care for everyone. The spurious thought in the background that the donor would be the first in line to be offered a new treatment must not play a role.
- If something of importance is discovered and can be clinically applied, that is then for everyone, donor or not. There is a rebuttal possible to this, namely "but the donors are at least known and you can warn them". More about that later in this appendix.
- Research with human tissue cannot become a veiled form of 'medical screening'. Such screening is permitted under certain conditions. In the Netherlands, the WBO also applies here and is cautious in its approach. The conditions for screening also apply correspondingly to research with human tissue. In order to be of value to the donor, feed-back can only occur when the other conditions for screening have been complied with (Wilson 1968), as reformulated in this country by the Council of Health (Gezondheidsraad 2008). A recent perusal of the Council of Health revealed the many pitfalls of GWA-screening (Gezondheidsraad 2010).

The following summarise the arguments in favour of feed-back:

- The donor should expect something in return for their participation in a biobank research. In American literature in particular this argument is called 'benefit sharing'. The American culture and health care is not particularly based on the principle of solidarity though.
- The donor has a right to know what is known elsewhere about their future health, even if that information is as yet unclear. Possible unnecessary worry and unnecessary medical follow-up tests count for less in American literature.
- The researcher has a responsibility towards the participant or donor. This does not weigh as heavily as that of the treating physician who is deemed to actively monitor the health of their patient and investigate the cause of disease. The researcher does not have to actively look for possibly pathology. If they come across this by chance however, this should be fed back.
- This is only different if the donor has indicated not wanting to know certain information (the right to not know).

In the American literature this has led to complicated consent procedures, where the intentions of the donor concerning individual feed-back or not must be determined and noted down in all their complexity. Naturally, the donor's chosen variant on possible feed-back needs to figure in the data which are linked to the human tissue.

Such an approach to feed-back is neither achievable nor desirable. It has the following disadvantages:

- It does not reflect the Dutch approach in health care where diagnostic research steered by medical complaints should be evidence-based and screening is only offered if the unease and risk of iatrogenic damage is sufficiently compensated by the health benefits for those involved.
- It leads to a very heavy burden on the consent process and the ICT-systems which follow the preferences of the donor in the chain and the research, without compensating concrete advantages for the donor.
- It undermines the basic assumption of participation, namely without vested interest. Some that wants to be informed on the chances of ill health can do so elsewhere. It cannot be the motivation for contributing to a biobank.
- It leads to confusion between the treatment domain and the research domain. The latter contributes to the treatment of the patient via generally applicable guidelines. Patients are not approached as individuals but as a group with certain characteristics where, all things being equal, the guidelines can be applied.

Under certain specific circumstances, other factors weigh more heavily. That is, in short, when it becomes known that the chance of serious damage for one or more individuals can be averted by intervention. A duty of care arises to at least attempt this.

This means that feed-back (or an attempt at least ²⁴) can and even should take place providing a number of conditions are met. They are the following four:

1. It should concern the real serious risk of a serious condition.
2. There should be a real treatment option available to the donor either by treatment according to the applicable professional standard or lifestyle intervention.
3. It is not certain whether the 'finding' is already incorporated in the actual treatment of the donor. The 'finding' applies to everyone with certain characteristics, not just to the donor. But not everyone is under treatment at that moment or can be warned since not everyone has been screened for that risk factor. In that case the donor should be alerted since they are already known.
4. The treating physician must also conclude themselves that feed-back is desirable for a particular patient.

These criteria allow room for discussion. This is not up to the researcher. A committee should be convened to determine if and when the first three criteria apply. This task could be delegated to an ECHT, although often specific knowledge of the disease concerned would be required. The research protocol should be clear on the procedure to be followed.

The next question is whether this should apply to family members of the donor, particularly when the 'finding' concerns the prevention of a hereditary condition of the disease is hereditary. The second criterium could be expanded:

- Even if the 'finding' can no longer benefit the donor, individual feed-back should occur if it is possible for their family members. Great caution is needed here. In the first place, just because the condition is 'hereditary' does not mean that the family member is affected. Then there is the principle that such a 'finding' should be broadly implemented in health care. What applies to the donor, namely that they are already known, does not necessarily apply to the members of their family. In as much as that is the case, it isn't as donor but as patient or as member of a family running a certain risk. The 'finding' might be incorporated in the counselling of these family members. The third criterium remains completely applicable. It prevents difficult dilemmas for donors and treating physicians. Only when the certainty of a prompt and effective treatment for family members of the donor is not offered already in the health care systems is it time to consider whether individual family members should be approached.

In the previous Code of Conduct, a distinction was made between 'incidental findings' and 'new findings'. Incidental findings are findings which are not the result of the scientific research with human tissue but which could have been found with existing techniques at the moment of acquisition but which were not looked for or not noticed. 'New findings' are the results of scientific research. This distinction was illuminating in the context of 'further use'. For the question of feed-back or not, it is irrelevant. The four criteria mentioned above apply.

²⁴ Sometimes the pseudonimising prevents this.

Much large-scale biobank research is no longer 'hypothesis-driven' but attempts to find chance statistical correlations. Large quantities of human tissue are compared to large quantities of (anonymous) data from donors and reveal possible correlations. Which correlation is unclear at the start of the project. Any such discovered correlation is then subjected to further research which is, then, hypothesis-driven. The correlation discovered is the hypothesis. You can no longer speak of 'incidental findings' because you are now baiting that 'chance' (Bovenberg 2009a).²⁵ This development is also not of importance for the question of feed-back. Only whether the application of the four criteria leads to the conclusion that individual feed-back should take place. The majority of non hypothesis-driven research leads to findings which on the basis of the first criterium does not give cause for individual feed-back.

Should feed-back be deemed necessary, this will not be done by the researcher. They usually do not know the identity of the donor. Feed-back will be done by the treating physician or general practitioner and embedded in adequate counselling of the patient. Very often, the test will need to be repeated because the initial testing did not take place under GLP-conditions. Should the applicable health insurance not cover such diagnostic research, the research budget should provide for this.

The above of course does not apply if the treating physician does research with the data and human tissue from their own patients. Then there is no distinction between the treatment domain and the research domain. The doctor has a responsibility as researcher and as treating physician. The latter takes precedence. See section 3, final bullet, of the norms.

A distinction must be made between the general publishing of the results of research and feed-back. See the Code of Conduct itself where the case is made for involving donors in general in the results of research.

²⁵ A somewhat comparable development can be seen with research into image rendition techniques. These become so refined that you can always see something (Morris 2009; Lugt 2009), even something which had nothing to do with the patient's complaint for which the research was requested.

APPENDIX 4

LEGAL GROUNDS

This appendix has not been translated for the English version since its contents apply specifically to the Dutch situation and those requiring that information will by definition be able to read the corresponding text in the original Dutch publication.

APPENDIX 5

THE BACKGROUND TO THE CONCEPTION OF THE CODE OF CONDUCT

This Code of Conduct is the culmination of the intense involvement of two committees and their grassroots support (for their constitution, see appendix 7):

- The FEDERA/VvE committee on research regulation: COREON
- A committee of readers instigated by the FEDERA, comprising a number of involved scientific associations and patient organisations.

The list of versions below shows when these committees were directly involved in the various stages of drafting. The specific request was for the members to discuss the draft with their grassroots supporters. The commentaries received show that this indeed happened. Furthermore, the standing committee of COREON added commentary on the intermediate versions of the draft.

The composition of the committee of readers ensured the influence of patients the members were also invited to attend the COREON meeting on 19th November 2010 – and there was a personal link with BBMRI-NL and PSI (Parelsnoer initiatief, a collaboration between eight university hospitals in setting up a national biobank). The jurist from BBMRI-NL was also present at the COREON meeting referred to. Version 8.2 was also discussed at a discussion afternoon of the medical ethics committee of the Leiden university hospital on 16th November 2010. This discussion was especially fruitful and led to a tightening of the terms on ‘commercial use’. The chairman of the Nijmegen METC submitted a brief commentary. That led to an expansion on what has been included on scientific research with human tissue from minors. Commentaries were also received from the in-house jurist at the Nijmegen University Hospital and Mr J Bovenberg. We are very appreciative of all these contributions.

A week after the COREON meeting of 19th November 2010, the members of the reading committee received a short summary of the comments made during the meeting and the other commentaries which had been received, and guidance on how to act on them. Subsequent comments were likewise incorporated. Then towards the end the coordinating author held a number of bilateral talks, amongst others with patient organisations and the Dutch Association of Clinical Chemistry (NVKC).

Following an intermediate version 8.3, all the commentaries were incorporated in version 8.4 according to importance.

This version reflected a broad consensus of the ‘field’ on normalising the scientific research with human tissue. It was widely publicised. The idea was not to invite discussion on this consensus but to have possible omissions pointed out and generate wider support. This round of consultations led to version 9.

Version 9 was put before the KNMG and the NFU. The KNMG did not as such review the Code of Conduct, but a number of associations did react positively. One pointed out an important omission. It was not explicitly stated (although it was an assumption) that a donor provides human tissue without expectation of remuneration.

Version 9 was also discussed with the NFU (who has also reviewed version 8.4.1). This discussion led to a tightening of the passage on compliance in the opening chapter and the emphasising that ‘controller’ refers to a function and not a person. In addition there were countless editorial adjustments. It was also said that the Code in outline was too detailed and could not determine what was expected of institutions. This was not incorporated. A professor in health care law, Prof. J. Hubben, provided chiefly positive commentary around the same time, while pointing out that the passages on compliance needed to be tightened up. As mentioned, this was also done.

Version 10 was then shown to a number of readers (including the NFU). From then on it was a question of proofreading and layout, which of course applied to the Dutch version. The Code of Conduct was finalised in April 2011. Literature after that date has not been taken into account.

The standing committee of the FEDERA approved the Code of Conduct in April 2011 and a small circle of readers were given the mandate to suggest amendments based exclusively on the discussions taking place at the time.

Versions:

- 1-2 Internal MedLawconsult 2009
- 3 Standing committee COREON November 2009
- 4 Meeting COREON April 2010
- 5 Standing committee COREON
- 5.1 To readers (1-5-2010)
- 6 Amended version for readers' meeting on 9-7-2010
- 7.1 Total revision (6-9-2010)
- 8.0 Amended version, complete Code (October 2010)
- 8.1 Suggested amendments standing committee COREON
- 8.2 Summary of norms; version to readers and COREON (November 2010)
- 8.3 For faculty chairmen NFU. Commentary from readers and COREON incorporated (December 2010)
- 8.4 Comments from readers evaluated and where necessary incorporated, following separate discussions with NVKC (mid December 2010)
- 8.4.1 Editorial amendments, particularly in appendix 5)
- 8.4.2 Improvements, typing errors, layout adjustment
- 9 Following talks with NFU and professor of health care law
- 10.0 Amended following the various talks with NFU delegation (May 2011)
- 10.1 Amendments to text
- 12 Final amendments to text

APPENDIX 6

COMPOSITION READERS' COMMITTEE AND COREON

Readers' committee

M. Boeckhout, trainee assistant scientific philosophy, UvAmsterdam
(working on thesis on Governance PSI)

Mr. dr. J. Bovenberg, lawyer
BBMRI-Nederland

J.M. Broekman, pathologist (Legal committee NVVP)
Jeroen bosch Ziekenhuis, Den bosch

Prof. dr. M. Cornel, population geneticist
VUMC EMGO

Dr. Laura Creemers, biologist, dept. Orthopedics, UMC Utrecht
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Prof. dr. P.J. van Diest,
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Dr. F. van Kemenade, secretaris NVVP
patholoog, VUMC Amsterdam

Prof. dr. L.A. Kiemeneij, genetisch-epidemioloog
UMC Radboud Nijmegen (Bestuur BBMRI)

Prof. dr. A.C.M. Kroes, medisch microbioloog
LUMC Leiden (bestuurslid Ned Ver v Med Microbiologie)

Dr. A. Langerak, medisch immunoloog
Erasmus MC Rotterdam (Ned Ver v Immunologie)

APPENDIX 7

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APPENDIX 8

GLOSSARY

1. Donor

The person whose human tissue can be used for scientific research. This donor can be a patient whose human tissue is stored in the course of treatment and subsequently can also be used ('further use') for scientific research, or a person, patient or not, that donates human tissue specifically for scientific research.

2. Anonymous

Human tissue or data that cannot, by those to whom they are available, or not without unreasonable time and effort, be traced back to the donor.

3. Coded-anonymous

Coded-anonymous is a sub-form of anonymous. The term plays an important role in this Code of Conduct. The basis is (the 'default situation', as it were) that human tissue and data reach the researcher anonymously. The researcher cannot trace the identity of the donor without unreasonable time and effort. Human tissue is usually coupled to a unique code number. This makes it possible to link the human tissue to data concerning the donor (only identified by a number). This coding is applied by the one that makes the human tissue and data available to the researcher. In the case of one-way coding, the supplier cannot, on the basis of the number, return to the identity of the donor. In the case of two-way coding, this is possible. The researcher cannot, however. The coding is secret from him. Coded data or human tissue is not necessarily anonymous in the context of relevant national legislation. Neither are they also necessarily personal or patient data. Whether the coded data and human tissue made available are anonymous depends on:

- The safety of the coding (the researcher should not be able to crack it)
- The aggregation level of the data (the researcher should not be able on the basis of these data and human tissue to discover in an indirect way the identity of the donor).

Coded-anonymous in this Code of Conduct means that these conditions have been met.

4. Totally anonymous

This is another sub-form of anonymous. The material (or data) is anonymous and not coded.

5. Aggregation level

Aggregation level refers to the level of detail of research data which apply to one individual. Research data can, in combination with each other, also be indirectly traceable. Age and gender are all important research data. The aggregation level of this detail is increased by, for example, grouping ages in classes of five years.

6. Pseudonym

The code number under which human tissue or data from a donor are used in scientific research. This pseudonym is generated from the directly identifiable data of the donor. See for more on coding the comments above on coded-anonymous. ISO talks consistently of 'pseudonised' data where the Code of Conduct refers to coded-anonymous human tissue or data (ISO 2007).

7. Coded-indirectly traceable

Sometimes it is not possible to talk of anonymous data, whether due to the aggregation level of the data or because of insufficient distance between the researcher and the treating physicians or the 'controller' of the biobank whereby the identity of the donor behind the pseudonym could possibly be

revealed by the research. In this case, PET should be employed as far as possible so that the researcher does not have direct access to the identifying data. The researcher then uses the human tissue and data as coded-indirectly traceable.

This can all be represented in the following table (Van Veen 2011) (That speaks of data; the same applies for human tissue)²⁶

Anonymous data		Personal data		
Fully anonymous data	Coded anonymous (pseudonymised) data	Indirectly identifiable data		Directly identifiable data
		Coded but either insufficiently secure Or Aggregation level too low	Not coded but aggregation level too low	

8. PET: Privacy enhancing technologies

Technical (ICT) means employed in the chain of data in order to mask the identity of the subject involved certainly from the end user of the data (in this case, the researcher). PET can be used to arrive at coded anonymous data and human tissue, but also at totally anonymous or to coded-indirectly traceable (see the table above). What PET can and need to be employed depends on the circumstances, such as the details of the research protocol, but also the consent procedure used. (see Van Veen, 2011)

9. Further use'

The use of human tissue for scientific research when this tissue had originally been extracted for other purposes and the patient has given permission for this other use. As a rule, this concerns the remainder of material acquired in the context of diagnostics or treatment. It can however also concern human tissue specifically extracted for scientific research and subsequently can be used for an alternative scientific study than was intended in the original 'informed consent'. The rules on no-objection dealt with in this Code of Conduct do not apply here. Such 'further use' of material not extracted in the course of patient treatment will need to be examined from case to case.

10. Biobank

A collection of human tissue whereby the individual samples stored there can be used for scientific research. There is a wide variety of biobank (KNAW 2006), Ploem 2010). For this Code of Conduct it is important to distinguish how the human tissue has become available:

- a. Biobanks comprising of tissue extracted from the patient during diagnosis and treatment. The biobank consists of tissue left over from this. This can be diagnostic material but also tissue removed in the course of surgery as part of the treatment.²⁷ This is referred to in this code of conduct as a 'further use' biobank.

²⁶ See appendix 1 section 2.3 for why the same applies to human tissue.

²⁷ See Riegman 2011

- b. Biobanks set up for the purposes of research, whereby the material is extracted specifically for research. This is referred to in this Code of Conduct as a 'de novo' biobank. The procedure whereby the material is extracted can be exclusively for scientific research or can be one or more supplementary extractions to those carried out for diagnostic purposes.²⁸ This distinction says nothing in itself about the scientific value of the two types of biobank or the manner or location in which the material is stored. This Code of Conduct deals with norms for activities in the chain of human tissue for scientific research. That is why the way the material became available influences the normalisation of the biobank.

11. Human tissue

Tissue originating from natural persons and consisting of cell tissue from these people or containing cell tissue. A natural person as defined by law is anyone that has been born (alive). By way of explanation, the following. It can be a particular virus has been isolated in the tissue. Should the virus become viable separate from the tissue in which it was isolated, that virus is not human tissue in the sense of this Code of Conduct. The conditions under which the virus may be isolated do fall under this Code of Conduct inasmuch as no specific legislation applies (see point 1 of the norms). Insofar as data are coupled to the virus on the origins of the tissue, the relevant privacy legislation will apply and the possible exceptions as determined in Public Health legislation. This explanation is irrelevant to the majority of scientific research with human tissue. Among those involved with infectious diseases there appears to often be misunderstanding about this.

12. Data

Text or characters, in whatever form (for example also numbers, computer codes, images, medical codes) and on whatever media (on paper or digital), to which meaning can be accorded by anyone accessing them or processing them into fresh data, whereby communication with others is possible. By way of explanation: the term data is used all over the place but is very difficult to define. Legislation in the Netherlands, for example, defines the term 'personal data' but not directly 'data' as such. This is, on the one hand, remarkable, but on the other also explicable. We all understand in general terms what is meant by 'data', but every attempt to further define it quickly leads to philosophical discussions. Law makers prefer to distance themselves from such and that applies equally to this Code of Conduct. All the terms in this Code of Conduct are determined by their context. The context here is scientific research resulting in text. In the steps in-between, use is made of human tissue and text in the sense of letters and numbers/symbols. That is the distinction. Text communicates meaning, human tissue does not. Data and human tissue both take on meaning to those able to read them. A researcher can also derive meaning from human tissue. He will, however, communicate this to others via text. That is data in the sense of this Code of Conduct. The human tissue is thus a source of data, much like an X-ray photo.

²⁸ 'Further use' and biobank are hereby different concepts. The former is an activity, consisting of a certain way of handling human tissue. The latter is a certain state, namely the way in which human tissue is stored, as in suitable for scientific research. This Code of Conduct deals with the norms for activities in the chain of human tissue for scientific research. Hence the way in which the tissue became available influences the standardisation of the biobank. The activity closely connected with a biobank is its control. Through the control suggested the biobank can function as an infrastructure for scientific research.

13. The chain of human tissue

The chain refers to the different steps the human tissue for scientific research passes through. The human tissue is extracted, made available by the donor, is stored, released for scientific research and is used in scientific research which results in publication. Human tissue is always linked to data. By scientific research the chain can be extended. The human tissue could, be 'sequenced' in a location remote from where the researcher, responsible for the research protocol, is based. The resulting research data can be analysed in a location remote from where the combination for research of human tissue and linked data originated, namely when research data from several such researches are combined. The Code of Conduct contains norms for the whole chain.

14. The main terms in the chain

In this Code of Conduct, the following terms are used in a certain technical way to indicate steps in the chain: - Extraction: the medical procedure whereby human tissue becomes available. - Make available: the wish of the donor, explicit or not, whereby the human tissue can be used for scientific research. -Control: actions in connection with the human tissue whereby following extraction and prior to release for scientific research it is stored suitably for scientific research, and the decision-making process over its release and provision. -Release: the decision that (samples of) human tissue or data can be passed on to the researcher. Release is not licence, however. There are always conditions attached to the decision. Issue takes place under these conditions as laid down in the MTA. - Transfer: the actual transmission of the human tissue or the data with the use of the normal (adequately secured) means. - Use: the analysis of human tissue in the context of scientific research and the reaching of scientifically responsible results in the research.

15. Commercial enterprise

An enterprise wholly or primarily funded by capital investors who run the risk that the value of their investment will not be compensated, but when the enterprise makes a profit, the value of their investment rises. The term 'enterprise' is derived from European law which, in short, describes an enterprise any entity which undertakes activities which are not typically government tasks (and which can be provided in a market-driven environment).

16. Governance

The system whereby a certain entity is governed (in other words, whereby decisions with legal and societal consequences can be taken), internal supervision of its board and external accountability.

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- Afd. Sociale Geneeskunde

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Initiative

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Text of code

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