# Code for Proper Secondary Use of Human Tissue in the Netherlands

## Federation of Medical Scientific Societies

COLOPHON

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The Federation of Medical Scientific Societies (FMWV), founded in 1960, consists of 20 national scientific societies and 10 colleges of various branches of specialized medicine. All together it has about 17,000 members who pay a small annual fee for the following services:

- an annual multi-disciplinary scientific meeting followed by a meeting for the public
- a subscription on a monthly journal on biomedical research in the Netherlands
- advocacy and self-regulatory activities, e.g. development and implementation of Codes
- other activities of mutual interest

## PREAMBLE

Observational (scientific) research with human tissue is essential for the development of health care and is therefore a well-known phenomenon. In many cases, this human material became available within the framework of patient care. Subsequently this human material can be interesting for a large number of research projects. The research questions range from the unravelling of the fundamental characteristics of that material to the identification, at a much later stage, of the relationships between the original diagnosis, the subsequent condition of the patient and that which can be learned from new techniques about the correctness of that diagnosis.

Characteristic is the fact that the material in question was not collected for the purpose of the present research. After it has been used for the original purpose, it is then used in a research setting, to be distinguished from studies of quality of care (even if that includes scientific research) or education. It has long been undisputed that – with some exceptions, such as emergency situations or consent on behalf of the mentally incapacitated – consent of the subject (donor) is required before human material is collected. According to present-day views, the subject (donor) also has the right to consent if the material is subsequently used for a different goal, so-called "further use", such as scientific research. This right to consent applies not only for the "further use" of human material but also for the management of data associated with or derived from this material.

The purpose of this Code is to provide researchers with practical guidelines for the design and execution of scientific research with human material such that the right to consent is respected. The Code is an initiative of the Federation of Medical Scientific Societies (FMWV). In 1995 the FMWV welcomed the Code for Good Conduct, which defines the guidelines to be followed with regard to the protection of confidentiality for scientific research with data. Almost all professional societies whose members carry out research in the field of health care are members of FMWV. For the FMWV it is important that such research remains within the boundaries of current judicial and medical-ethical viewpoints. Research must be carried out in a socially responsible manner. This responsibility with respect to society also means however that conditions are created such that research can continue to take place. There are still numerous diseases for which adequate treatment is not available or the existing therapies have severe side-effects; there are also new threats to the health of mankind. Observational research is essential for the exploration of these problems, irrespective of whether it takes place at the fundamental cellular level or as epidemiological studies to identify the factors that determine the sickness and the health of groups of the population.

This Code therefore has a dual purpose. In the first place the definition of concrete guidelines for the design and execution of investigations within existing norms. In the second place the explanation of guidelines such that research will not encounter unnecessary obstacles. This double aim reflects the balance of interests. On the one hand there are the interests of those

PREAMBLE

from whom the human material for research is obtained. On the other hand there are the interests of those groups of the population who might profit from the results of this research.
A balanced normative framework for "further use" has been the subject (donor) of extensive discussion in the Netherlands since the 1990's and elsewhere. Laws have already been introduced or are still being prepared. The committee responsible for this Code has taken that discussion into account. In the trajectory leading to this Code it appeared that the discussions on so-called "new findings" almost blocked a solution for adequate reuse, because almost always informed consent would be necessary. The committee sustains that it has brought clarity in this respect, diverging from what was proposed in the recommendations of the Health Council in its 1994 report "Towards Proper Use" and which was also put forward in parliamentary and internal documents of the Department of Health, Welfare and Sport which were made available to the committee in the preparatory phase. The committee believes that its solution will yield a balanced system .
Since the aim of this Code is to offer researchers a guideline, it is considerably more detailed than legislation. The latter is per definition fairly abstract. By adhering to this Code researchers no longer need to delve into background legislation and discussions in literature. Aspects that are not regulated by law but are important in practice have been included in the Code. The above-mentioned considerations were extended to include the operational phase of an investigation.
New techniques in the fields of research and treatment offer the potential of extensive possibilities to combat diseases and deficiencies. They also give rise to many questions. This Code does not consider these new techniques explicitly. The Code is formulated in "technique-neutral" terms. It is a basic code that can be supplemented with partial codes for new techniques or fields of research. The "technique-neutral" formulation has the advantage that it is always applicable, even in the case of the sometimes dazzling new possibilities that may be developed in the near future.
There is another point of consideration in this respect: this Code describes how responsible research can be performed. It describes what may be done, not what can be done. The researcher who reads the Code will probably think of many situations which could be just that little bit different from the examples presented in the Code. In such situations, the Code should be applied analogously. Then it will become clear whether what can be done also may be done.

The Code was prepared by a subcommittee appointed by the board of the FMWV which consisted of constituent members of the FMWV as well as of the National Federation of Patiënt- and Consumers Organisations (NP/CF) and the Dutch Royal Society of Medicine (KNMG). The members of this committee are mentioned on page 2. The committee met in total 7 times. Preliminary versions of the Code were also circulated among the scientific societies through the FMWV website (www.fmwv.nl) and discussed in the Committee for Judicial and Ethical Aspects of the Royal Academy of Science (KNAW), division of Medical Sciences at an invitational conference on April 3, 2000.

The FMWV is therefore confident that this Code will become part of the professional research practice medical researchers. They can be called to account on their compliance with the Code within their own organisation or the institution where they are employed. To review committees the Code will provide insight into the norms which apply in the field of research.

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**OUTLINE OF THE CODE FOR PROPER USE**

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OVERVIEW

**The Code for Good Use in outline: an overview flow chart for the planning of observational scientific research with human material.**

(the underlined words are discussed in the Code).

1. This Code is applicable as soon as a combination of the following two conditions exists: "further use" of human material and scientific research.
2. Be sure in this case that the procedures allow for a strict differentiation between files of patient data (when present) and those of research data. Ensure by means of technical measures and procedures that files containing research data that are not directly identifiable (that is to say, coded or anonymous data) cannot be traced. Regulate access to human material for authorized researchers only and establish a procedure to ensure that when identifying human material is obtained, it will be coded before it is used by them in the investigation.
3. Describe the study question(s) and the method of investigation in a research protocol.
4. In particular, take into account the following questions (and include them in the protocol as prerequisites for execution of the investigation):
    - how can the investigation be set up so that there is the least possible violation of the privacy of the subject (donor)?
    - how will strict separation of the roles of the researcher and the treating physician be achieved, especially when both participate in the investigation?
    - how can the investigation be designed so that incidental findings will be prevented insofar as possible?
    - will the investigation likely yield unexpected new findings? if that is the case, what is the procedure that ensures that the subject (donor), who indicated the desire to be informed, will be informed appropriately, i.e. via the supplier in general terms about the results?
    - how long will the human material be stored (see also below)?
    - in general: how will compliance with the Code for Proper Conduct (which regulates the management of data in scientific research) be achieved for data accompanying human material, the eventual collection of additional data and data derived from the human material?
5. Regulate in an Agreement of Transfer how the human tissue will be obtained from whoever was in charge of it for original use or for another investigation. (appendix 1)
6. Be sure to determine whether the right to choice of the subject (donor) has been exercised. This means:
   if anonymous human material is to be used, then the subject (donor) or his legal representative does not have to object;

if coded human material is to be used, then the subject (donor) or his legal representative should not have objected or opted out;

if identifying human material is to be used, then the subject (donor) must have given consent;

in the event of coded and identifying material, the subject (donor) may have indicated that he wishes to be informed about the intended new findings or unintended incidental findings. Both the supplier and the researcher must be aware of this fact.

7. There are special guidelines for the use of human material from an individual who is unable to consent (mentally incapacitated or children) or research with foetal tissue, embryos or germ cells. They include, among others, that the investigation can only be carried out with human material from these groups of people (implying that the research can not be performed with human material from individuals who are capable of giving consent); with the exception of human material from the mentally incapacitated (for which the previously mentioned modalities of consent apply), consent must always be obtained.
8. Submit the proposed research investigation in a protocol (with the intended Agreement of Transfer as supplement) to an Institutional Review Board in the following cases:
   - when coded or identifying human material is to be used; (it is currently considered to develop procedures for institutional research programmes e.g. of laboratories or biobanks rather than for each specific study)
   - when an investigation using anonymous human material is expected to yield results of major consequence (in the practical or emotional sense) for a circumscript group of individuals or when an investigation is to be performed with (anonymous) human material from the mentally incapacitated or foetal tissue, embryos or germ cells.
9. The investigation should be carried out according to the protocol after obtaining the human material and the data according to the Agreement of Transfer.
10. Submit plans for an eventual mailing of the results of the investigation to the Ethical Committee. Subjects (donors), who wished to be informed about the results of the investigation in a general sense, can in principle only be informed after the results of the investigation have been accepted by a peer-reviewed journal for publication. In principle, the mailing should be addressed by the suppliers of the material.
11. The above applies in a similar fashion in the event of an evident necessity to inform, for example because the investigation has demonstrated that a concrete proposal for therapy can be made that a reasonable person would not refuse. In that case one must

also consider whether those who did not make use of the option to be informed should still be informed. In such a situation, the researcher should consult the METC.

12. After completion of the investigation, the human material should in principle be destroyed or returned to the supplier. In connection with verification of the results of the investigation, the researcher should take measures to store source materials (including human material). Prolonged storage for another study is only permissible if the information provided at the time that the right to consent was exercised included this possibility and the Agreement of Transfer includes relevant guidelines.

13. Store the protocols of the investigations, the logbooks maintained during the processing of the data and the human material for at least 5 years after completion of the investigation or publication of the results (the latest of the two dates is used). By means of an audit, one can determine whether you have complied with the guidelines of the Code.

**Introduction**

This Code is structured as follows. The first part, the normative section, is the actual Code. In that section, guidelines are presented that the researcher will have to follow when human tissue is used for research which was not collected for that purpose. In the second section, the deliberations that led to this Code are considered in more detail and the discussion on the identifiability of data and human material – an important aspect of the Code – is described. Regretfully, for reasons of cost containment that section could not be translated.

Purposely this Code has not been written in article form, like a legal document, but as an essay. One criticism of the Code for Proper Conduct (for investigations with data) was the fact that the use of articles made it difficult to read and left questions unanswered. The aim is to overcome that criticism in this Code.

On the other hand the essay form may be too extensive when someone wants to look up the main points quickly. That is why the Code begins with a flow chart. The main principles of research according to this Code are given there. The flow chart serves as a summary, but cannot include everything. Thorough reading of the entire Code is preferable because it is not only complex, but one has to be able to negotiate.

The discussion about "further use" focussed to a large extent on the right of choice of the subject (donor) from whom the material is taken. The exercise of the right of choice takes place at the location of the doctor who has collected the tissue for the original purpose. As a rule this is not the researcher. Still the researcher should not ignore the question. He should only use the material for his investigation if he is reasonably certain that the person concerned has been able to exercise his right of choice. The discussion of the modalities for the right of choice or right to consent and the manner in which the researcher may subsequently acquire the tissue form the pivotal points of this Code.

The next point is how he may use this material. The investigation must also be legally accountable in order to do justice to the right to consent and the privacy of the subject (donor). That requires working according to a protocol and following standard operating procedures. Beforehand it should be determined what will be done with "new findings". In many cases accountability afterwards will not be sufficient and is it preferable that a proposed research project be judged before initiation. The Code describes these cases. Finally complaint procedures will be considered.

The success or failure of the Code however depends on a clear understanding of the applicability and the terms used. These aspects form therefore the beginning of the Code.

APPLICABILITY

## 2. Applicability

2.1 *Subject of the Code*

This Code refers to scientific research for the purpose of health care using human material that first became available for purposes other than for this investigation.

*Explanation*

This definition of the subject includes a number of terms that will be explained in the section "Definition of terms" below.

An essential feature is that the human material was not collected originally for the scientific research under consideration here. The scientific research of this Code for Proper Use is a form of "further use". The combination of "scientific research" and "further use" is therefore the subject of this Code.

The requirements for "further use" have been discussed extensively in literature and in Parliament. The discussion was not only about "further use" of human material for the purpose of scientific research in health care. In order to achieve a well-organized framework, however, this restriction is applied in this Code.

Opposite "further use" is original use. As a rule the original use will lie within the scope of patient care, but there are also other forms such as the examination of human material which has become available within the framework of scientific research with people performed according to the Law on Medical Scientific Research with People (WMO). These various aspects are considered in the Definition of Terms.

2.2 *Range of application*

This Code is meant for everyone who carries out scientific research with human material via "further use". Because this Code was drawn up by the FMWV, only members of the associations that belong to the FMWV are committed to comply with the Code. Members of these associations are committed directly to comply with the code if such is stipulated in the charter. Indirect commitment however extends much further. As the development of the Code has been a transparent and national initiative which took 3 years and many occasions were given for comment, other researchers will have a hard time explaining different procedures.

*Explanation*

Differentiation must be made between the direct binding effect of the Code and an indirect binding effect.

This Code is not a law (see 2.3). This means that one is committed to comply with the Code only if one has agreed to do so in one way or another. Associations that are members of the FMWV are committed if this has been approved at a General Meeting of the FMWV. For the individual researcher, direct commitment can then take place via the association he belongs

to. This could be the case for example if the association decides to incorporate the Code in its own Code of Conduct.

The material effect of this Code extends much further. As mentioned in the preamble, the FMWV regards this Code as a reflection of the professional ethical norms of every researcher in health care. Researchers can be reminded to adhere to norms for proper use beforehand when the research funds are granted or afterwards at an eventual legal proceeding. If, in the latter case, the judge needs a standard to gauge the commitments of a researcher, then it would seem logical that this Code will be used.

2.3 *Relationship to legislation*

This Code is a form of self-regulation. Where legislation exists it would be included in this Code, which therefore remains within the limits established by the law: the legislation has been translated into concrete directives for action in practice. At the time that this Code was drawn up, specific legislation about "further use" of human material had been announced but, except for the use of foetal tissue, had not been published as a bill. In that respect, the Code fills a vacuum by self-regulation. The manner in which this has occurred will, according to the expectations of the FMWV, presumably determine the direction of eventual legislation to come.

*Explanation*

Self-regulation is subject to a number of requirements. Thus, for example, it should be developed carefully by means of contributions from all groups involved. For this reason this Code was drawn up by a committee made up of many representatives, including patient committees, and drafts of the Code were discussed a number of times in the Committee of Judicial and Ethical Aspects of the Royal Academy of Science (KNAW) and the National Biomedical Research Organization (ZonMw).

The fact that there is at present very little legislation pertaining specifically to "further use" of human material does not mean that the Code exists in a judicial vacuum. There are general principles of law which form the basis of this Code. Because the use of data is inherent in an investigation with human material, legislation regarding privacy is of course exceedingly important. This is incorporated in this Code. In addition there are many regulations for original use which are also of direct or indirect importance for the Code. In the Explanatory section, a description is given.

Should specific legislation for "further use" be approved which differs from the system proposed in this Code, then the researcher will of course have to comply with it. This Code will then have to be rewritten. However, the FMWV does not foresee this for the time being. Quite the opposite, it believes to have proposed such a balanced system that legislation can be linked directly to it. Possibly, the need for legislation will be less if it appears that via this

Code the goals to be achieved by the legislator have already been realized. Researchers, but also the institutions where the system for the right to consent of the subject (donor) as described below is to be formulated, can keep the situation partly under their own control by consistently acting according to the system described here.

## 3. Definition of terms

3.1 *Scientific research*

By means of scientific research one hopes to gain new generally applicable insights in the field of health care or biomedical technology. Proper further use of human tissue in the framework of scientific studies of the quality of care does not belong to the domain of this code, because consent of the patient can be considered present..

*Explanation*

The aim of research is to offer generalized explanations for phenomena. The scientific research which is the subject of this Code aims to offer insights into the development of diseases, maintenance of health and the underlying biological processes in comparable groups of people. This information ultimately becomes available for the benefit of patient care by means of publications.

In order to avoid words, the term research will be used regularly instead of scientific research as described here.

3.2 *Original use*

Original use is according to the purpose for which the subject (donor) or his legal representative has given the human material.

*Explanation*

Original use of human material usually occurs within the framework of patient care, i.e. when material is used for diagnostic purposes or is excised for therapeutic reasons. If human material is excised for the purpose of medical-scientific research, then this usually falls under the Act on Medical Research Involving Human Beings (WMO) [3]. Analysis of this material for the purpose of the research described in the protocol is original use. This Code is not applicable in such a case. There is after all no question of "further use".

That is the case when subsequently a different research goal is proposed which is not included in the informed consent of the subject (donor) (research participant in the sense of the WMO).

3.3 *The subject (donor)*

The subject (donor) is the one whose human material is used for the purpose of the research as referred to in this Code.

*Explanation*

[3] In exceptional cases, the Law for Population Studies will apply.

This concept needs no explanation. As a rule this will be a patient whose material was used previously for diagnostic or therapeutic purposes. The subject (donor) can however also be an individual who has donated his blood for a blood transfusion, etc.

3.4 *Human tissue*

Human tissue consists of all parts separated from the human body plus foetal tissue.

*Explanation*

"Parts separated from the human body" can be everything that was a part in one way or another of the human body and now no longer is a part: everything from a hair to buccal mucosa, urine or an entire organ.

With respect to the examination of human tissue, broadly speaking two extremes can be differentiated: there is the investigation of basic information at the DNA level of this material which is unique for the person from whom it was obtained or the material is merely a carrier of an impersonal substance, such as a virus. As long as the virus is in the carrier and not in free air, one speaks of examination of a part of the human body.

One can of course think of curious cases in which the question of whether something is or is not human material is not easy to answer. For example, what if the virus is in the air that a patient has expelled into a balloon. The careful researcher will treat this air, which can be related in one way or another to a patient or groups of patients, as human material.

3.5 *Right of choice*

The right of choice comprises the rights that the subject (donor) or his legal representative are entitled to in connection with making human material available for "further use".

*Explanation*

The right of choice is an essential element of the Code. In the following paragraph the concept will be discussed in detail.

3.6 *Representative*

The representative is the one who may exercise the right of choice in the name of the subject (donor) whenever the subject (donor) is not capable of doing so.

*Explanation*

For determination of who is entitled to exercise the right to consent, the provisions in the Act on the Medical Treatment Contract ((WGBO) about the exercise of patient-rights (informed consent, privacy, etc.) can be followed. These provisions are that a child below 12 years of age is represented by his parents or guardian. Young persons over 16 years of age may decide for themselves as long as they are mentally competent. For those between 12 and 16 years, the decision should in principle be made by the parents and the child together. The mentally

incapacitated are represented by a curator or mentor, a person with a written authorization, the partner or, if the former do not exist, a parent, child, brother or sister of the subject (donor). The subject (donor) need not therefore be the one who has exercised the right of choice with respect to “further use”. That can also be his legal representative.

3.7 *Researcher*

The researcher is the one who is responsible for the design and execution of the research project.

*Explanation*

There will be a number of people involved in the investigation. They will as a rule consider themselves as researchers, but are not as a consequence a researcher in the sense of this Code. Here he is the one who is indicated in the protocol as being responsible for the research project. The person can of course be called something else, such as project leader, section head, etc. Moreover, the position can also encompass several individuals.

The researcher is therefore not all of the co-workers involved in the investigation. For those involved in the investigation under the responsibility of the researcher, the guidelines of this Code are of course also relevant. For them there has long been a derived duty of confidentiality. The researcher, as described above, is therefore responsible for ensuring that they act in accordance with the Code. For this purpose he will have to take the necessary measures.

As a rule the researcher will work in an organization and within the hierarchy he will be accountable to several directors or a Board. Part of his responsibilities may possibly even be carried out via the directors. Therefore, when there is reference to the researcher hereafter, this can sometimes be read as “or the organisation to which he belongs.”

The individual who was in charge of the human material for original use, such as the treating physician or whoever was directly involved in the treatment such as the pathologist, is of course the researcher in the sense of this Code if he subsequently uses it for medical scientific research, as described above.

3.8 *Supplier and supply*

The supplier is the person who is in charge of the material for original use and supplies it to the researcher. To supply is the activity whereby the supplier transfers the human material to the researcher.

*Explanation*

As a rule the treating physician will be the supplier or, for example, the pathologist who examines the human material for the purpose of diagnostics or, according to the terminology of the WGBO, someone who "is directly involved in the execution of the treatment contract." But human material is not collected only for the purpose of therapy. If for example blood unsuitable for transfusion is made available for "further use", then the blood bank will be the supplier.

That which is stated in 2.6 about the responsibilities of an organisation in which one works is also applicable here. The responsibilities of the supplier described in this Code should largely be organised and executed by that organisation.

3.9 *To make available*

To make something available is the implicit (in the case of no objection) or explicit (in the event of consent) activity of the subject (donor) or his legal representative who thus exerts his right to give consent, allowing the human material to be used for scientific research.

*Explanation*

There is in other words a certain sequence. The human material is made available by the subject (donor) or his legal representative and is subsequently supplied. This process is preceded by the collection of human material within the framework of original use. Between making available and supplying, the human material will as a rule be stored by the possible supplier.

3.10 *Incidental findings*

An incidental finding is a (diagnostic) finding encountered by accident which applies only to one of the subjects (donors) and was not known at the time of original use.

*Explanation*

An example is a scientific investigation into specific immune factors in blood that has been collected for the purpose of virological determinations and it is discovered that one of the samples exhibits characteristics of a developing leukaemia.
It is obvious that such a finding gives rise to important questions: must this be reported to the person involved, and if so, how? If the material had not been newly investigated within the framework of "further use", the dilemma would not have occurred. How one should handle these incidental findings is discussed further in paragraph 5.5.

3.11 *New findings*

New findings are (general) results of scientific research that were obtained during "further use" and that have a predictive value for the present or future health of a group of subjects (donors) or their kin.

*Explanation*

A " new finding" has therefore a specific meaning. It is of course the aim of every scientific investigation to find something new, but that is not what is meant here.

New findings are the result of an investigation which offers a new insight into the present or expected future health of (groups of) the subjects (donors) or their kin. It is not an accidental finding because this result (for example, a diagnostic test or explanatory variable relating living conditions and future health) was not available at the time the human material was originally used. It is in fact the resultant finding of the investigation.

Such a finding sometimes leads to the possibility of therapy or prevention, sometimes it indicates risk factors which are not or barely susceptible to preventive intervention. Usually these results were expected as confirmation of a hypothesis of the investigation, sometimes they are revealed unexpectedly.

These new findings must be differentiated from incidental findings. New findings apply to a group of subjects (donors), as recognized in the investigation. As a rule new findings were already predicted in the protocol, although sometimes the investigation takes a turn in a new direction. But they are always the generalised results of the investigation. An incidental finding applies solely to the one patient whose human material yielded a diagnostic finding by means of diagnostic methods that were already available at the start of the investigation (see the former paragraph).

The chance of new findings leads to dilemmas which must be taken into account both in the formulation of the right of choice and in the design of the investigation. In the discussion on the right to consent for "further use" these dilemmas played a large role. In the explanatory section

the background discussion is considered in more detail. In paragraph 5.5 of this section the solution of the problem provided by this Code is described .

Obviously not every investigation will lead to new findings. In many cases, the significance of the results of an investigation for the (future) health of the persons involved is still not clear. A piece of the puzzle of the mechanisms underlying a certain condition may be elucidated. In such a case the result of the investigation is not a “new finding”.
If one finds a predictive variable, then this does not immediately mean that the path to clinical application is open. A large number of other factors is also important: how strong is the prediction, what is predicted, what can be offered to the subject (donor), etc. Only after an interpretative discussion of the significance of the results of the investigation, in the medical as well as the social domain, can an individual offer of assistance be made to a specific subject (donor). In paragraph 3 of the Explanatory Section this aspect will be considered in more detail.

3.12 *Differentiation according to the identifiability of the human material*

A distinction is made between:

- Anonymous human material: within reason it cannot lead to the subject (donor);
- Coded human material: a code, kept by the supplier (only), will identify the subject (donor);
- Identifying human material: the researcher can identify the subject (donor).

*Explanation*

For standardisation of research and the right to consent, it is exceedingly important to know the extent to which the human material can lead to the identity of the subject (donor).

If the human material cannot in any way lead to the identity of the subject (donor), then the problem of incidental findings need not be considered. The researcher may encounter such findings, but they will not have any consequences for the subject (donor).

For the privacy of the subject (donor) and for new findings, the situation is a bit more difficult. If for example the patient is not known but the group of patients he belongs to is known (and thus the group that provided the material), then privacy and new findings at the group level can play a role. See further paragraphs 3 and 4 of the Explanatory Section.

Although therefore one can identify something like "group-related" data, the above-mentioned three-way differentiation is the most relevant for the regulation of research. This applies for research with data (whereby the same three-way differentiation is maintained, compare the Code for Good Conduct) as well as research with human material.

For this reason it is important to understand the difference between the three types of human material. More specifically, the three can be described as follows:

| | | |
|---|---|---|
| a. | Anonymous human material | The data coupled to this material is such that it would require an unreasonable amount of time and effort to identify an individual person. Furthermore the researcher cannot arrive at the identity of the person by matching with a file already in his possession. In other words, there are no "keys" with which the material can be coupled to the subject (donor). |
| b. | Coded human material | A code has been attached to this material either by the supplier or an independent third party[2] such that it can be traced by the supplier back to the subject (donor). However, the researcher himself is not able, as in c, to identify the subject (donor). In other |

[2] In the discussion on privacy one is turning with increasing frequency to a well-known figure from commercial EDI and internet traffic ´the trusted third party' (TTP). The extent to which a TTP can guarantee privacy in scientific research or in fact makes the privacy of the subject (donor) even more precarious needs to be investigated further.

words the material is coupled to one key for identification. This key is not in the hands of the researcher.

c. Identifying human material — Here the data accompanying the material are presented in such a way that without intervention of the supplier and without spending unreasonable time and effort the researcher can determine the identity of the subject (donor).. Here too a key to the identification of the material is coupled to the material and in this case the researcher has the key. Even when this is not the case, the material must be called identifying whenever there are insufficient guarantees that matching of files in the possession of the researcher will not reveal the identity of the subject (donor). To continue in the metaphor of the keys, he does not have the key, but the drawer containing additional information is not tightly locked and in this way he can still gain access to the personal information of the subject (donor).

It should be noted that the (im)possibility to identify does not refer only to technical guarantees but also to institutional. The researcher will often be part of an organisation where there are more files of personal information which might possibly also include the subjects (donors) from another investigation. If the researcher were to compare the information provided for a particular investigation with that in other files, he might still be able to make an identification. This applies for both anonymous and coded data. The setting in which the investigation is carried out must prevent this. This will be discussed in more detail in paragraph 7.

Coded data and identifying data together are called “personal information” in the Code for Good Conduct. Further on in this code they will also be called “not-anonymous data”. The relationship between these concepts is discussed in paragraph 4 of the Explanatory Section in more detail.

## 4. Scientific research in accordance with the right of choice

4.1 *Introduction*

This paragraph is the core of the Code. Only if the right to consent has been exercised, may research with human material of the subject (donor) be carried out. In this paragraph the right to consent is defined in more detail.

An important basic principle is the fact that the right to consent must be organised correctly by the individual physician or the care-institution where the material is obtained for original use. The researcher does not have direct responsibility for this (unless of course he is also the one who collected the human material for original use). He should therefore within reasonable limits satisfy himself that the human material supplied is indeed available according to the right to consent.
A major portion of this paragraph concerns the routing of human material from the original user to (successive) researchers.

An important element of the right of choice is how new findings will be used. What can the subject (donor) expect within this framework and how he can exert influence on it. How the researcher must subsequently manage eventual new findings will be discussed in a following paragraph in which the other requirements for research will also be considered.

4.2 *Description of the right of choice to consent*

The following basic items form the core:

- For the use of identifying material the subject (donor) or his legal representative must have granted explicit consent.
- For the use of coded or anonymous material it is sufficient if the subject (donor) has <u>not objected</u> to this use. The system of (no) objection should be based on sufficient information and a low threshold for objection.
- Consent is again required from the subject (donor) or his legal representative in order to be able to inform him of new findings or incidental findings. For this purpose one must know whether the subject (donor) wishes to be informed or not. In the case of identifying material this will be considered as a matter of course during the talk about consent and the information given at that moment. In the case of the "no objection" system it is stated in the information given to the subject (donor) beforehand that in principle he will not be informed about the results or new findings. If he wants to know, then he can so indicate during the low threshold procedure. In both cases (consent or no objection), it is possible that the design of the investigation will be such that the subject (donor) will not be given any information about new findings. If the subject (donor) has stated that he wants to know, then this means that the person's material may not be used in the investigation.

*Explanation*

Use of coded material will have to be the starting point (see also below). The procedure for the system of choice for coded material is as follows:

The choice system assumes that considerable informative material will be made available in the institution where the human material is collected for original use. The informative material states that "further use" of human material does occur, in particular for scientific research. It also states that as a result of this "further use" new findings and incidental findings can occur. If the subject (donor) (or his legal representative) objects to "further use", he may so indicate. Where and how are dependent upon the institution; the thresholds may never be high. It must also be possible to obtain a more detailed explanation or background information on "further use".

The informative material states that, if the subject (donor) has not expressly so indicated, he will in principle not be informed about new or incidental findings. If someone wishes to be informed then he must so state at the information centre or inform his treating physician. In the informative material, it must be made very clear that scientific research seldom immediately yields hard facts which are of direct value for the subject (donor). The subject (donor) will not of course be informed about unclear relationships, possible chances and/or findings of controversial clinical significance. Everyone is free to acquire knowledge via the relevant (popular) medical literature.

Only in a limited number of cases will the investigation yield something relevant to the future state of health and/or treatment options for the subject (donor). Such information can only be presented within the framework of a medical consultation arising from the situation in which the human material was collected. Then too a finding can be reproduced within the framework of a quality controlled clinical determination.

At that time one will have to consider the advantages and disadvantages of the knowledge and therefore eventual disclosure. Thus providing the subject (donor) with information about new or incidental findings will be based on the subject (donor)'s carefully considered permission.

The institution where the material is collected (and which will supply it for scientific research) should also arrange a follow-up trajectory where the objection or consent can be noted in such a manner that even if the human material is uncoupled from the medical records, the fact that the subject (donor) objected will remain known. Preferably the supplier will define these requirements for making human material available for the purpose of "further use" in a set of guidelines. For background information about this system of the right of choice, see the Explanatory Section.

The researcher is not responsible for the formulation of the right of choice. That is the responsibility of the supplier. He is however responsible for performing research with human material in accordance with the right of choice. That is why he cannot ignore this issue. See also below.

4.3 *The basic norm*

The researcher must respect the right of choice with regard to "further use" in every phase of the investigation. The researcher requests information about formulation of the right to consent from the supplier. In the Agreement of Transfer (Appendix 1) between supplier and researcher, it is stated that according to the right to consent the material supplied may be used for the intended purpose.

*Explanation*

As mentioned in the introduction to this paragraph, the essence is that in the chain from the original user to the researcher the latter may reasonably assume that he has received material that he may use for research purposes.

Within that framework, several situations can be discerned. The researcher can obtain the material in three ways:

1. he receives the human material for original use and supplies it – as it were – to himself for the purpose of an investigation
2. he is not the original user and obtains it from a person or organization who had the right to original use;
3. he obtains it from someone who also obtained the human material for "further use".

In all cases the right of choice of the subject (donor) must be respected.

In *case 1* the researcher, usually within the institution where he works, is (jointly) responsible for both the formulation of the right to consent of the subject (donor) and for the fact that the material may not be used for research if the right to consent has not been exercised.
In *cases 2 and 3* the researcher is not involved in organisation of the right to consent and for him it is now important that the material is supplied legitimately. In these cases, the following applies. In case 2 the point will be the relationship between the treating physician (or the institution where he works) and the researcher. The researcher must satisfy himself within reasonable limits that the material may legitimately be used for research. For this purpose, the researcher must do three things[3].

- Ask about the arrangement of the right of choice as described in the paragraph above.
- Ask whether the permission and no objection (opt out) systems are truly functional

- Obtain with the material a declaration from the supplier that the subject (donor) or his legal representative has given permission for use (in the event there is identifying material) or has made no objection (in the case of coded or anonymous material). And also that the subject (donor)'s wishes about being informed about new findings are included in the data accompanying the material. This sounds more complicated than it is. A brief agreement between the one who supplies the material and the one who will use it is sufficient. This is subsequently called the Agreement of Transfer. A model of such an agreement is to be found in Appendix 1.

The model assumes mutual agreement between the researcher and the one who supplies the material. After all, if the subject (donor) has not been able to exercise the right of choice then not only may the researcher not use the material but also the supplier may not make it available.

The agreement has therefore significance not only for the researcher (he knows that he may use the material) but also for the one who supplies the material. The latter may presume on the basis of the agreement that the researcher will comply with the Code and will use the material only according to the modality of the choice made by the subject (donor) and that he will comply with the eventual declaration of the patient about new findings.

There are also other situations involving original use, see the Explanatory Section. Then the above holds in a similar manner. For instance if the researcher receives coded material from a blood bank, then he is obligated to make sure that this is permitted according to the regulations of Sanquin Nederland (the national Bloodbanking organization) or the blood bank[4], and that the donors have been informed about eventual "further use" and did not make any objections.

The Act on Organ Donation (WOD) itself includes an example of a specific situation of "further use". Primary use within the framework of the WOD is the implantation, eventually after initial – for tissues – processing and storage. Article 13 states that an organ that is found to be unsuitable for transplantation may also be used for research that is focussed on transplantation, unless the subject (donor) has specifically objected to this at the time he gave permission for organ donation.

The next step in further use would be if the organ is not considered suitable for transplantation and a researcher wishes to use the material for research not focussed on transplantation. If the researcher is the one who removed the organ or the person who

[3] At least insofar as he wishes to use human material which does not fall in the transitional phase for humanb material, as discussed below.

[4] Blood banks also know the concept "further use" and it does happen that a sample is made available to a third person. This is not regulated in the WiB, with the exception of article 13 which states that only blood which is not suitable for administration to humans may be supplied and that it may only be given to institutions for scientific research.

received the organ for the purpose of transplantation[5], then accordingly case 1 is applicable. But if he wants to make it available to another researcher, then that other researcher should ask the original user whether he may use material originally meant for transplantation for his intended purpose.

In the third case a chain of individuals is involved. In the Agreement of Transfer it can be stipulated that the human material may not be made available to a third party. Should there be a third researcher who is interested in the material, then he will have to go back to the one who was the first to make the material available to arrange a separate Agreement of Transfer. Subsequently the one who now has charge of the material can in fact turn it over to the third researcher.

If such an objection has not been formulated in the Agreement of Transfer, then it depends on the circumstances and whatever has been set down in the transfer agreement. In the case of anonymous material it is conceivable that the material can be turned over directly, also in the legal sense, to the third researcher without intervention of he who made it available in the first place.

The same applies for data. The Code for Good Conduct is also based on the transfer agreement when the transfer of personal information is involved. Obviously the transfer of human material and data can be handled in the same agreement.

[5] Article 13 of the WOD does not mention when the article 13 situation (the organ is found to be unsuitable for transplantation) is discovered. As a rule that will be by the one who wants to implant the organ or an organ bank. But in theory it could also be the one who removes the organ and if this person has an ongoing research programme on trransplanation, then he could reserve the organ for it.

4.4 *Special requirements for research with human material from persons who are not able to consent.*

4.4.1 The norm

Human tissue from the mentally incapacitated (for whom the legal representative exercised the right of consent) or children may only be used for research if the research question is such that an investigation with this particular material is required. If human material from children is involved and the period between the availability of the material and the investigation is long, so that the subject (donor) is now over 16 years of age at the time of the investigation, identifying material may not be used unless the subject (donor) – that is, the now older child – is again given the chance to exercise the right to consent himself.

4.4.2 Explanation

The mentally incapacitated cannot exercise the right to consent themselves. For this vulnerable group therefore extra protection is needed.

The WMO (Law on Medical Experiments) also provides extra guarantees for medical-scientific research with the mentally incapacitated. This Code does not include the requirement that the investigation must also be for the good of the group of mentally incapacitated to which the subject (donor) belongs. This requirement does apply for non-therapeutic medical-scientific research with the mentally incapacitated. Since here the subject (donor) does not have to endure a burden and risks are absent, it is sufficient that there is no other alternative than the use of this particular material. In many cases this will be the case because the aim of the investigation will be to understand the problems that can occur in this group in particular.

Research with material from young children encounters the following problem. The original right of choice, i.e. no objection or permission, will have been given by a representative. But at the time of the present investigation the child may already be legally able to consent. It is not acceptable that the subject (donor) be bound to permission given by his representative long ago when the privacy of the subject (donor) is now directly involved. This is the case for identifying human material. If one wants to include such material at a later time in an investigation then the subject (donor) will have to be asked for consent or anonymous or coded human material will have to be used. The researcher in charge of identifying material of the group will therefore have to anonymise it or have it coded. To code the material oneself does not make the material coded (see paragraph 3.11). It is after all essential that the researcher himself does not have access to the key. The researcher may let the material be coded by a third person, such as a “Trusted Third Party”.

The age limit of 16 years is in accordance with the limit established in the WGBO for a young person, if mentally capable, who may decide for himself about treatment.

The guidelines for the manner in which objection can be made or consent can be given are as follows:

- below 12 years of age, the right to object or give permission is exercised by the parents or guardian, whoever has authority over the child.
- Between 12 and 16 years both the child and the parents or guardian, whoever has authority over the child, should have no objection or give permission, respectively. Permission of the child alone is not sufficient.
- Between 16 and 18 years it is sufficient for research with anonymised and coded material that the young person has not objected. According to the WGBO he is qualified to decide on his own about the treatment agreement.
- In the event of research with identifying material, permission of the parents with authority over the child will also be required. Such an investigation can directly endanger the privacy of the subject (donor) as well as his family in the long run. In this case one must use the general age limit of 18 years instead of the lower age limit of the WGBO. The WMO also maintains this general age limit.

4.5 *Special requirements for foetal tissue, embryos and germ cells.*

4.5.1 These complex ethical topics are treated in separate bills which are at present under discussion in Parliament, i.e. the Act on foetal tissue (WFW)[6] and the draft Act on Embryos (EbW), respectively [7]. They are so specific and subject (donor) to so many changes that no guidelines can be included in this Code at the present time. See the already existing measures for self-regulation in the field[8].

[6] TK 1998-1999, 26639, nr. 1 and further.

[7] TK 1999-2000, 27423, nrs. 1-2

[8] Compare the reports of the Health Council on these topics and the answers of the Cabinet to questions from Parliament, in particular TK 1999-2000, Supplement Proceedings p. 2153.

## 5. Design of the investigation

5.1 *The protocol*

5.1.1 General

The researcher should draw up a protocol for the investigation. It should include not only a methodological discussion of the research question but also a description of how the investigation will comply with this Code.

*Explanation*

The protocol has three aims.

For the researcher the task of drawing up a protocol is the time to consider carefully whether the investigation will be carried out with the least possible burden for the subject (donor) in accordance with the stipulations of this Code.
For the co-workers of the investigation the established protocol offers guidelines on how one should proceed with the execution of the investigation.
Finally third parties who carry out an eventual control can gain insight into the deliberations made and the necessity of carrying out the research in the manner described.

In the first exploratory phase of the investigation the research question and the design have not yet crystallised. In that case it will be impossible to draw up a complete protocol. It is in fact also not necessary at this stage in view of the above-mentioned three functions. The researcher should however describe the research question to be explored. If he feels it is necessary to make use of one of the exceptions to the requirements for consent described in the Code for Proper Conduct for the use of data, then he must explain his reasoning. Although in principle identifying data can only be used after consent of the patient, the researcher is allowed to study several medical records in this phase of the investigation for the purpose of determining whether the research hypothesis and the design of the investigation are feasible (Code for Proper Conduct, article 6.3). For the use of human material on the other hand he will have to comply with the right to consent in this phase too. In the exploratory phase therefore it is for example not permissible to evaluate identifying human material if the subject (donor) has not (yet) given permission. The researcher could however use anonymous material, as long as the subject (donor) has not objected.

5.1.2 Other considerations regarding the protocol

In the course of preparing the investigation, the researcher should take into account the following questions in particular:

- What type of data and material must be used so that the privacy of the subject (donor) can be respected as much as possible?

- Can this material be provided by the supplier when the right to consent has been exercised?
- Will incidental findings be prevented as much as possible?
- Will the investigation lead to new findings?
- How will these new findings be managed?
- Which technical and institutional guarantees have been made to ensure compliance with the prohibition of linkage

These questions will be discussed in further detail below. The last question is treated in a separate paragraph. Here it can already be mentioned in this connection that the protocol should also include clear specifications about how data are to be managed (whether in an appendix or not):

- how are the data accompanying the human material presented;
- how are eventual additional data to be collected;
- how are data derived from human material to be managed;
- access to the data and the eventual – anonymized – output for third parties;
- safeguarding and guaranteeing prohibition of linking (see paragraph 6.4 and paragraph 7);
- the eventual storage of the collected human material and data on behalf of a subsequent investigation (paragraph 6.6 and paragraph 7.4).

5.2 *Choice of the type of data and human material*

The researcher must make a justifiable decision at the time he designs the investigation about the type of data and human tissue he needs. He should find a balance between the data and human tissue which he would like to use for methodological reasons and protection of the position of the subject (donor). The latter refers in the first place to the privacy of the subject (donor) and in the second place to a responsible organisation of the chance of incidental and new findings.

From the standpoint of privacy the researcher should select a design whereby his staff will know as little personal information about the subject (donor) as possible. If possible therefore anonymous data and human material should in principle be used for the investigation. Problems from the perspective of confidentiality and in the event of incidental findings will then after all be minimal.

On the other hand major limitations are inherent in this approach, especially if the investigation takes an unexpected turn and additional data on the group involved must be collected. Often this is not possible and a whole new investigation using data which can be linked directly or indirectly to the subject (donor) must be set up. Ultimately therefore one does not gain much and

it could be that the total burden of privacy in this form will be even greater[9]. The preference is therefore for "coded material and data". The word "encrypted' is also used by some. The consent procedure with regard to human material does not differ between coded and anonymous material: in both cases the subject (donor) should have no objection. The researcher may only propose the use of identifying material if there is no other choice in view of the nature of the investigation or the relevant conditions (he is also the treating physician and can link anyway; the number of subjects (donors) is small so that the design and introduction by a third party or codes is not very efficient; he can already identify the subject (donor) spontaneously). In that case the subject (donor) must also have given consent for use of his material in a scientific investigation.

5.3 *The collection of material and data*

The researcher requests the human material from the person who can supply it. That can of course involve several institutions. He must show why it is this particular material that he needs and why this is in accordance with the Code. Subsequently an Agreement of Transfer is drawn up.

5.4 *The chance of incidental findings*

If there are various methods available for analysis of the human material, the methods chosen should be as specific as possible with regard to the research question so that the chance of incidental findings can be kept to a minimum. This is of course not always possible. An insufficient reason for adjusting the tests specifically to the research question of the investigation is however the fact that certain analytic computer programmes are designed to do a large number of determinations.

When incidental findings might be encountered and identifying or coded material is used, the researcher should reach an agreement with the supplier of the material about what to do with this incidental finding. By exploring this beforehand the researcher and the treating physician (if they are not the same) will not be taken by surprise. It is incorrect for the researcher, unless he is the treating physician, to contact the subject (donor) himself about an incidental finding. Only the patient's treating physician or general practitioner can estimate the consequences of such a finding.

5.5 *Management of new findings*

If the investigation can lead to new findings, then - in consultation with the supplier - a strategy for informing the subjects (donors) (those who have said that they want to be informed) must be decided beforehand. For example an investigation into the presence of a specific gene that codes directly for genetic predisposition to the development of a certain disease will, in the case

[9] Compare the HUGO statement on DNA sampling.

of a positive result, lead almost inevitably to a new finding. For the manner in which communication with the subject (donor) takes place, it makes a difference whether it is a low penetration predisposition or not. The (clinical) relevance of a new finding for a subject (donor) is of course not always the same for every subject (donor). There is a continuum from little to significant importance for the subject (donor). The researcher can almost never determine that himself. There will have to be various deliberations before the results of the investigation have clinical significance for a patient. In the Explanatory Section, this is considered in more detail.

In the event that the result of an investigation is found to be significant for the subject (donor), therefore, the question must first be asked whether the significance is so immediate that it must be passed on in one way or another to the subject (donor). If it is decided that the new finding must be passed on to the subject (donor), of course via the supplier, then two options can be distinguished:

- the results are passed on in a general sense to all subjects (donors) (who have indicated that they wanted to be informed about new findings) by the supplier; then the subject (donor) can decide whether on the basis of this information he wants to contact the supplier or his general practitioner (or whomever was listed as contact person in the information provided) in order to be informed about the relevance for himself and eventually to start a follow-up course.

- the results are passed on individually by the supplier to every subject (donor) for whom the result is or can be of importance.

The first option would appear to be preferable and in accordance with the approach in genetic research involving humans in general. Certainly in genetic research the greatest possible care is required and information should be handled in accordance with the guidelines of the clinical genetic centres in this respect. See also the Explanatory Section and the procedural aspects described below.

The first option can also be applied as emergency procedure if the results are of such immediate importance for all subjects (donors) that one believes that the information cannot be withheld from any of the subjects (donors), not even from those who indicated that they did not want to be informed. In an extremely unusual case, one might come to the conclusion that a severe illness has been discovered in a group of the subjects (donors) for which a therapeutic modality is available which no reasonable patient would want to miss.

When deciding whether to inform those who said they wanted to be informed as well as whether an eventual emergency procedure should be used, one should also take into account the fact that these results might reach the subject (donor) via another route. For example if the patient is being treated and the results - via the professional journals - are incorporated in patient care,

then logically a variation of the second option applies for those who did want to be informed and the emergency procedure is not an option.

5.6 *Report funding of the investigation and eventual interests of sponsors.*
The protocol should include a report of the position of the researcher within the organisation where the investigation is to be carried out, the manner in which the investigation will be funded, eventual connections of the researcher with the organisation sponsoring the investigation and eventual other sources of a conflict of interests[10].

[10] Compare the WMA Declaration of Helsinki, adapted version, Edinburgh, 2000

## 6. Management of human material

6.1 *The norm*

The researcher manages the material in accordance with the protocol and thus with the right to consent and the Agreement of Transfer. If he has identifying material at his disposal then he will introduce coding so that the co-workers do not have access to the personal information. The extraction of data from the material occurs via standard operating procedures (SOP). The subsequent management of the data thus obtained is also stipulated in the SOP's. Compliance with the prohibition of linkage can be demonstrated.
Storage of the tissue after the investigation is only possible if the (adapted) Agreement of Transfer includes a stipulation for this, it is not in conflict with the right to consent and guidelines have been established for this purpose.

*6.2 Introduction*

This paragraph concerns management of the human tissue: use, storage and, when applicable, giving it to others. The aim of "use" is to obtain data from it. This paragraph is therefore about obtaining data from human tissue. The following paragraph focuses on what one may subsequently do with that data. At the same time the question of how one may use the data accompanying the material will be considered.

6.3 *General guarantee of privacy*

The researcher makes sure that there are procedures in operation such that those who analyse the tissue under his responsibility do not obtain more data than strictly necessary for the analyses. At the level of the researcher therefore coded human material is in principle always used. If identifying human material is supplied, coding will be performed by the research institution and the key to the code will be in the hands of the person who is in charge of the research or who is the head of the research institution (for example, chairman of a discipline). This key must be carefully safeguarded. If the human tissue is supplied under a code, the key to the code is always in the hands of the supplier or a third party (see footnote 2.)

The researcher uses subsequently careful procedures about storage and use of the human tissue and associated data and takes all measures needed to ensure that the material and the associated data are safeguarded against loss, damage, unauthorized perusal, change, linkage and supply.

6.4 *Guarantee of the prohibition of linkage*

This Code is based on the assumption that the researchers will adhere to the applicable norms. It is expected that supervisory bodies will allow sufficient space for coded tissue to be used on

the basis of the "no objection" system, even if the researcher could in theory link it to the subject (donor).

The researcher must therefore be able to prove that he has complied with the linkage prohibition. Work is to be carried out according to SOP's (standard operating procedures). A logbook is maintained of the processing of data (attached to or derived from the material). At the time of an eventual audit, it must be possible to demonstrate that the institutional guarantees which are meant to prevent the illegal linkage of the human material or data were enforced.

6.5 *Management in accordance with the right of choice.*

The researcher uses the human tissue in accordance with the manner in which the patient has given his consent about the further use of the tissue or has not objected to it..

According to the Agreement of Transfer, the researcher will receive only tissue with which he may carry out the investigation described in the protocol - unless the person who supplies the material has made an administrative error.

At the same time, the following aspect is also important. Without prior information the subject (donor) is not able to exercise his right of choice. If the subject (donor) did not object or has given consent for research, then this form of permission must be covered by the prior information. In general the information will be presented in fairly broad terms (certainly for the no objection modality), but it is still possible that research will be proposed which is not in agreement with the prior information and as a result possibly not in accordance with the intention of the subject (donor).

The researcher is however not responsible for the information procedure (unless he is also the supplier) and therefore does not know exactly what information has been presented (compare paragraph 5). It is the responsibility of the one who supplies the researcher with the tissue to judge whether, on the basis of the request of the researcher, the proposed research and the information provided to the subject (donor) are in sufficient agreement. This must be expressed in the Agreement of Transfer. On the basis of that agreement, the researcher may assume that, as long as he follows the terms of the agreement, the material is used according to the right of choice. Limited deviations from the goals of the research as described in the agreement are possible without having to change the agreement. In the event of a fundamental change in the direction or goal of the research or if the human tissue can be used for another investigation, then this must be submitted to the person who supplied the material and the data.

If all other aspects remain predominantly the same, then a supplement to the Agreement of Transfer will have to be prepared. If the changes in the investigation are more substantial, then it may even be necessary to draw up a new Agreement of Transfer.

### 6.6 *Extraction of data from human material*

Subsequently data may be extracted from the human material. In this connection the aim is not to derive data pertaining to one person but data about a group of people who can be distinguished within the databank according to the research question. It is however conceivable that the characteristic or relationship in question can only be demonstrated in one sample.

If an incidental finding is done, then this reported to the principle investigator. The latter finds out by means of the coding whether the subject (donor) wished to be informed about an incidental finding or not. If so, then the code is used to determine who is the contact person or treating physician of the subject (donor)[11].

### 6.7 *Storage of human material*

Human tissue is only stored by the researcher if:

- this is necessary for an ongoing investigation, as described in a research protocol, or
- it is considered likely, in view of the nature of the material, that this material will have immense value for a new investigation,
- the Agreement allows for the prolonged storage of the material, and
- this eventuality was covered by prior information which was the basis for the consent given by the subject (donor) (in the case of identifying material) or the lack of objection (in the case of coded material).

If one of these requirements is not satisfied, the human material will be managed as regulated in the Agreement of Transfer: return it to the supplier or destroy it.

If the human material is saved for the benefit of future research (in accordance with the second to fourth items above), guidelines will be established for this purpose. Storage is carried out under strict conditions to ensure the inaccessibility of the material except by authorized

researchers within the framework of a new research protocol. These aspects are specified in the guidelines.

For the storage of the data associated with the human material (whether supplied together with the material or collected during the investigation by analysis), see paragraph 7.4.

### 6.8 *Safety*

The researcher takes all legally required safety measures and those otherwise normally followed for the management of human material in order to guarantee the safety of the co-workers who handle this material.



[11] If the material is identifying material (which is coded at the level of the research institute) then he must first contact the one who has charge of the coding (if this person is not the same).

## 7. Management of data

### 7.1 *The norm*

The management of data that accompanies human tissue, data derived from the tissue or additional acquired data occurs in accordance with the Code for Good Conduct. SOP's must provide demonstrable evidence that work was performed in accordance with the right to consent, that prohibition of linkage was enforced and that the privacy of the subject (donor) was protected insofar as possible.

### 7.2 *Introduction*

This norm refers not only to the data supplied together with the human tissue or collected later via the coding, but also to data derived from the human material.

That makes this paragraph of the Code of crucial importance. As described in the Explanatory Section, human material as such means nothing. It is the data that one has derived or can derive from it. A DNA sequence is not human material, but data derived from human material. The same applies for genotyping of a virus found in the blood of a patient. Although crucial this paragraph is relatively brief. The management of data is after all described in the Code for Good Conduct. When necessary one can fall back on that code.

*Management in accordance with right to consent*

Data too must be managed by the researcher in accordance with the right of choice. See the guidelines for human tissue described in the former paragraph.

As previously mentioned, human tissue and data will as a rule be treated as one entity in the Agreement of Transfer. That which applies for human tissue applies also for data already supplied. In a later stage of the investigation additional data might be requested from the treating physician or other sources via the coding attached to the data. The supply of additional information must flow from the research protocol and may not lead to the situation that the intention of the patient when consent was given or no objection was made, is abused.

When additional data are obtained one is bound to comply with the Code for Good Conduct. In particular the important aspect is the prohibition of linking: if one has stated that he plans to work with coded or anonymous data (as is stated in the research protocol), then one may not in second instance use the human tissue or data to link up to the subject (donor).

*7.3 Protection of confidentiality*

The researcher takes such measures that only those whose collaboration in the investigation is strictly necessary can use the data. The categories of these co-workers are described in the research protocol.

Paragraphs 6.2 and 6.3 are similarly applicable to collections of data only.

7.4 *Storage of coded and identifying data*

7.4.1 Identifying data

Identifying data are used only as long as this is essential for the aim of the investigation. Subsequently they are either destroyed or converted into anonymous data or managed as described below.

If the original consent of the subject (donor) does not include an objection, identifying data can be stored in coded form after completion of the investigation. In that case the data are processed such that they can only be linked after an unreasonable amount of time and effort, and a code is attached to this data. Since the human material at the level of the research institute has already been used in coded form, this code already exists in principle. The key to the code is however now no longer in the hands of the person in charge of the research institute (or head of the discipline) but is turned over to an independent third party.

Together with this third party the researcher draws up guidelines which specify the circumstances under which the code may be used by the third party. The transfer can only take place if this party is in agreement. If these requirements cannot be met, then the material will be destroyed after all.

7.4.2 Coded data

Most of the data accompanying the human material will be supplied in coded form. The data which are obtained by means of analysis of the material are then of course also coded data. Linkage is after all forbidden on the basis of the prohibition of linking.

Coded data are supposed to be destroyed or must be converted into anonymous data unless the original information given to the subject (donor) does not prohibit longer storage and it is conceivable that these data will be important for a later investigation. In such a case the same conditions apply as described in paragraph 6.6 for the storage of human material.

## 8. Procedural aspects

There are many types of research with human material. It is not necessary to have all research with human material evaluated by a medical ethical committee or a review committee. Research with anonymous material need in principle not be evaluated unless it is research with foetal tissue, embryo's or germ cells. In addition review of anonymous material is indicated if:

- the results are expected to have major consequences for a recognizable group of people which includes the subjects (donors);

Consider for example the situation that the investigation yields results that can influence the social position of this group (insurance, stigmatisation).

Research with coded or identifying material should always be reviewed. In the exploratory phase when several samples are examined to see whether an idea can be converted into a worthwhile research hypothesis and protocol, review is of course not yet a consideration[12].
Incidentally the guidelines of the institution where the researcher works may impose stricter requirements, for example that all observational research must be reviewed. Of course the researcher is also bound by these guidelines and he may not avoid them by falling back on this Code.

Within this framework, the committee proposes that for the review of observational research (with data or with human material) the WMO review criteria should not be used. They are after all designed to ensure that the test person will not be subjected to futile or disproportionate interventions and can decide in a deliberate manner whether or not to participate. This is not the question in the case of investigation of material already present. The framework for review of this type of research is the Code for Good Conduct (for data) or the present Code for human material. Both incorporate relevant laws such as the Data Protection Act (WBP).

[12] This point and the preceding one on anonymous material lead to the question of whether these stipulations are enforceable. The idea is then that if everything has to be reviewed, then the chance that something will "slip through" is much smaller. The committee does not agree with this view. A researcher who works with anonymous material with a research question for which he knows or can know that the results according to expectations will have major consequences for the subjects (donors) and who does not have the protocol reviewed has not complied with the Code. At the latest this will be discovered upon publication and a sanction could follow.

**9. Management of the results of the investigation**

The most well-known problems around scientific research are not due to violation of the right to consent or privacy of the subjects (donors) but originate from incorrect expectations induced by the premature publication of non-validated research results. The researcher should keep to the prevailing guidelines for review of his investigation. The general media may only be informed after the investigation has been validated within the scientific community and preferably has been published or at least accepted for publication in a scientific journal. The Code of Conduct for the Organization of Biotechnology and Society contains further guidelines in this respect. It has been included as a supplement to the Code for Good Conduct.

### 10. Guidelines for the period of transition

An important question is how to manage human material that has been supplied before this Code went into effect. As a rule, that material will have been supplied without an Agreement of Transfer and without the researcher having to be sure that the right of consent discussed here was implemented in the institution of the supplier. The spirit of the code is of course relevant.

The researcher in the Netherlands should realize in this respect that the right to consent is not "new". For research with anonymous material, article 7:467 (WGBO)[13] – in effect since 1 April 1995 – states that it is only allowed insofar as the subject (donor) has not objected. This then also applies for coded material of course. For identifying material there has long been the requirement of consent. After all the data associated with this material represent personal information which in principle cannot be passed on to a third party without consent of the subject (donor).

This leads to the following transitional guidelines:

- For identifying human material the researcher must make sure – in the event this has not yet been done - that the subject (donor) has given consent. If it appears that this has not been given or that the supplier does not know, then this consent will have to be obtained as yet or the material will have to be coded or anonymized by a third party.

- For coded and anonymous material supplied after 1 April 1995 (or part of it was supplied after 1 April 1995), the researcher must as yet determine whether the subject (donor) had the opportunity to object.

- If it appears that this was not the case or that the supplier does not know, then for coded material this opportunity will have to be offered. Since the researcher does not know who the subject (donor) is, the supplier will have to take care of it.

  At that time differentiation can be made between large and small populations. In the case of a large population it is sufficient to place an advertisement in the regional or national newspapers in which the possibility of an objection is pointed out. For small populations the supplier must inform the subjects (donors). The code numbers of those

[13] This article is a fairly unusual part of the provisions on the medical treatment contract because it is not directed solely toward the care provider, as contract partner of the patient, but to everyone who wants to use this material for research. Thus the question is justifiable whether this guideline also applies to collections of human material which were prepared before April 1995. A positive answer would then also apply to very old collections which would have impossible consequences. It is reasoned here that the regulation thus applies for collections of human material at least one part of which was obtained after 1 April 1995.

who subsequently do object are passed on to the researcher and this material is then removed.

- In the case of anonymous material this approach does not work because the supplier does not know who the subject (donor) is. This would mean that the lack of objection could not be repaired and that this material may not be used. This is a paradoxical conclusion: for human material which is sensitive from the standpoint of privacy the lack of an option to object can be repaired if the material is coded but not if it is anonymous.

If the proposed investigation is of exceptional importance and alternatives to the execution of the investigation are not present, then the researcher could consider approaching the relevant patient organisation(s). If they support the investigation, then the problem of the lack of an option to object may be avoided. The researcher must however subsequently present the research proposal and the report of the above-mentioned procedure to the institutional review board. The latter must ultimately decide whether the exceptional importance of the investigation and the method by which an attempt was made to repair the lack of an option to object offset the fact that the procedure described in the WGBO was not followed.

## 11. Complaints

11.1 *Introduction*

A distinction should be made between complaints:

- about the supply of human material (and data) by the original user;
- about the use, etc. of human material and data by the researcher.

These situations are discussed below. Finally the other legal possibilities for an eventual complaint are considered.

11.2 *Complaints about the supply of human material*

The researcher himself is not the focus of this type of complaint. It must be directed to the supplier of the material and will be treated according to the relevant provision for complaints, in addition to other legal possibilities for complainants (see 11.4). As a rule the supplier will be a care provider who is subject (donor) to the Act on the Right to Complaint of Clients in the Care Sector.

What if the subject (donor) or his representative calls the researcher to account for the provision of material? Every complaint against the researcher should be forwarded to a national committee, to be described below. The researcher can and may not exert any influence on the handling of such a complaint. If it turns out that the complaint concerns the supply and not the execution of the investigation (which often only becomes apparent at the time the complaint is heard) the complaint is dismissed and forwarded to the one who supplied the material to be handled by the complain committee of the institution to which he belongs. The national committee keeps track of the progress of the handling of the complaint. If it appears that the one who supplied the material continues to fail to have the complaint handled, then the committee (to be described below) will pass on this information to the Dutch Data Protection Authority (see 11.4).

The researchers are - in other words - responsible for making sure that the incorrectly addressed complaint is handled, but may not exert any influence on the process itself.

A similar situation can occur in the opposite direction. The complaint is sent to the one who supplied the material and during the process it appears that the researcher acted incorrectly, for example by not conforming with the Agreement of Transfer. The complaint against the supplier must in principle be dismissed, unless he knew or could know that the researcher was acting incorrectly; in that case, the supplier should have intervened. Here too there is an obligation to pass the complaint on to the national complaints committee to be described below.

11.3 *Complaints about execution of the investigation*

Here two types of complainant can be discerned:

- the subjects (donors) and their family or whoever complains in the name of the subject (donor).

- the individual who supplied the human material and who believes that the researcher has not complied with the Agreement of Transfer.

There is one complaint regulation for both types of complainant.

Because complaints about the execution of scientific research have so far been found to be very rare, it is not considered worthwhile for every research institution to set up its own complaints procedure. It appears that in practice it requires a great deal of work to establish a procedure which would have to be in accordance with the Law on the Right to Complain of Clients in the Care Sector (WKCZ); moreover once the committee is appointed it will lead a somnolent existence and the members therefore will not be able to build up the necessary expertise.

For this reason the FMWV has appointed a national complaints committee which starts its activities on January 1, 2003. This will function in accordance with the WKCZ. In the information provided to the (potential) subject (donor), reference will be made to this committee. That is an added advantage of such a committee. There is one address for complaints which can be included in all information about scientific research. For example, the information provided by the hospital about research with human material can be uniform in this respect. Within the framework of research with data, the national committee will make use of the following criteria, among others:

- did the researcher act in accordance with the Agreement of Transfer;
- did the researcher comply with this Code and the Code for Good Conduct;
- did the researcher further comply with the guidelines which apply or with conduct which may be expected from a responsible researcher from the standpoint of protection of the privacy and other interests of the subject (donor).

The committee is also a body for the independent settlement of disputes, such as the recognition of a code of conduct provided in art. 25 first paragraph of the Act for the Protection of Personal Data (WBP)[14]

The composition of the Complaints Committee is limited: an independent chairman, a representative of the patients/consumers of healthcare and a representative of the researchers. Deputy members are essential in connection with continuity.

The committee will be empowered, because the medical research societies or research institutes will recognise the competency of committee in this matter. The committee can as a result also be empowered to handle complaints about research other than research with human material or data via “further use”, such as population studies or medical scientific research with healthy volunteers. Such research is often carried out by academic groups which, other than those who carry out clinical medical technical research with people do not fall under the WKCZ.

[14] It is not the intention that the committee evaluate the merits of the design of the investigation or the results, although this may play a marginal role in the assessment of whether an investigation serves “general interests” (WBP art 23. second paragraph under a, in art. 5.1 of the Code for Good Conduct translated as “deugdelijk en zinvol”).

*11.4 Legal options*

In addition to the national committee the complainant of course has the right to turn to legal authorities, for example the civil court or the Dutch Data Protection Authority (art. 51 WBP). These options will be mentioned in the information provided by the national committee.

**Appendix 1**

Model Transfer Agreement

For material of human origin for the purpose of scientific research

## 1. Purpose and implications of this agreement

This agreement is concerned with the supply of human material for the purpose of scientific research in such a manner that the right of choice of the subject (donor) with respect to this material can be satisfied, such as expressed in the Code of Proper Use and relevant legislation. This agreement does not concern the eventual intellectual property rights of findings that can be derived from the human material or derivatives thereof. Should parties wish to reach agreement in this respect, then they can do so in a separate agreement. In the event of discord between the latter agreement and that which is determined in the present agreement, the present agreement has precedence.

## 2. Definition of terms

| | |
|---|---|
| 1. Supplier | he who has obtained the human material for original use, |
| 2. Receiver | he who obtains the human material from the supplier for the purpose of scientific research., |
| 3. Code | the Code for Proper Use as drawn up by the Federation of Medical Scientific Organizations on 22 June 2001, |
| 4. Human material | human material such as described in paragraph 5.5.2 of the Code |
| 5. Subject (donor) | the individual from whom the material was obtained, |
| 6. Original use | the purpose for which the human material was collected from the subject (donor) with informed consent, |
| 7. Incidental finding | an accidentally found (diagnostic) finding which involves only one of the subject (donor)s and was not seen at the time of original use, |
| 8. New findings | (general) results of the investigation which have a predictive value for the present or future health situation of a group of subject (donor)s or for their family, |
| 9. Protocol | the description of the research investigation with human material as meant in this transfer agreement. |

## 3. Parties undertaking this agreement

The Parties undertaking this agreement are the supplier and the receiver.

The **supplier** in the sense of this agreement is:

Name of the institute:

Address:

The person directly responsible for the obligations of the supplier as defined in this agreement is

Name:
Contact address:

The receiver in the sense of this agreement is:
Name of the institute:
Address:

The individual with direct responsibility for the execution of the investigation for which the human material is supplied is:
Contact address:

After the supplier has read the protocol, the parties agree as follows:

4. Responsibilities of the supplier

- The supplier provides human material such as described in an appendix of this agreement. This appendix describes the type (at the biological level), amount and nature (in the sense of identifying, coded or anonymous, such as is described in the Code) of the human material to be supplied.
- At his institute, the supplier satisfies the prerequisite of the right of choice of the subject (donor)s, such as defined by the Code and relevant legislation.
- The supplier knows from the protocol about the research investigation proposed by the receiver and declares that the supply of material of this nature can take place in accordance with the right of choice of the subject (donor).
- If the subject (donor) has stated that he wishes to be informed about incidental or new findings then the human material or the accompanying data must be marked in such a way that this will be quite clear to the receiver.
- The supplier is not responsible for the safety of the material, for the absence of pollution or for bacterial or viral pollution that possibly can be harmful to those who will use the human material at the site of the receiver or which make the human material less suitable or not suitable for the planned investigation; he cannot accept any responsibility for eventual damage that arises from the use of the human material, unless expressly so stated in the appendix to the agreement in which the material is described.
- The supplier will/will not request a fee for the supply of human material. If so, then said fee will be described in the appendix and will be based on the real costs made for the purpose of supplying the material (such as the costs of preservation but not for original use and the costs of shipment, coding, the eventual preparation of the data that accompany the material).

5. Responsibilities of the receiver

- The receiver declares that he will use the human material only as stated in the research protocol.

- The receiver will act in accordance with the Code and all other guarantees that the human material will be used according to the right of choice as expressed by the individual.
- The receiver recognizes the authority of the national Complaints Committee as far as the execution of observational research of the Federation of Medical Scientific Organizations.
- The receiver accepts the above-mentioned restrictions with respect to the safety and usability of the material, unless otherwise stated in the appendix.
- The receiver will pay the agreed fees for the supplied material within 21 days, unless otherwise agreed.
- After termination of the investigation the receiver will handle the material as described in the protocol or .....

Thus drawn up in .....

For the supplier For the researcher

Explanation

With this agreement both the supplier and the researcher can assume that scientific research with residual material will take place according to the right of choice of the subject (donor). For the supplier, for example, this means that the researcher will use coded material according to the proposed purpose (stated in the protocol) and will not try to identify the subject (donor). For the researcher this means that he or she may assume that at the institute of the supplier there is a system for determining objection to or permission for use of residual material for scientific research and that the subject (donor)s indeed did not object to (or gave permission for) research with the material supplied.

The agreement is kept as simple as possible as far as legal terms are concerned. There are no references to compensation or exemption of liability and so on. This would be necessary if there was any possibility that one might have to fall back on such provisions.
Furthermore this would make the agreement so sensitive legally that agreement would have to be reached between legal representatives of the institute of the supplier and that of the receiver. The manner in which the agreement is formulated here is a guarantee for the careful handling of human material which, for example, also can be applied between the laboratories of the supplier and the receiver. However one of the institutes can of course always decide that this agreement must be signed at the level of management or even the Board of Directors.

This agreement is based on the presumption that a system for the right of choice is known and has been introduced in the institute of the supplier. For this system see the Code for Proper Use or the summary for researchers. The latter also offers the suppliers sufficient insight into what is expected of them. For the current regulations see the WGBO and the Law for the Protection of Personal Data. For the use of data in scientific research in the health care sector, the latter has

been worked out in a new version of the Code of Proper Conduct which is expected to become available in 2003 on the website of FMWV.

**Appendix 2**

Elements of the Research Protocol

The following elements must be defined or described in the research protocol.

- name of the research institute
- name of the person(s) responsible for this research programme
- the research question of the investigation
- justification of the research question
- expected results
- justification of the design; this includes, in addition to the scientific aspects, the elements of responsible use of human material and data such as described below.

- types (anatomical) of human material that are to be used for the investigation

- nature of the human material: anonymous, coded, identifying

- manner in which human material is obtained ( which suppliers, concept agreement of transfer added as appendix to protocol)

- explanation of why (in view of the research question) this human material in particular has to be used. If it is identifying material, then give a clear explanation of why this cannot be done in a different way.

- in the event of identifying human material, note how it will be coded at the level of the staff who carry out the work, where the key to the code will be kept, etc.

- describe the analyses to be performed with the human material

- describe the guarantees that ensure that identifying material will not ultimately be identified by means of linking with other files
- how the chance of incidental findings during analysis will be avoided insofar as possible

- which new findings may ultimately result from the investigation
- how will they be treated, in particular:
- the manner in which, if the subject (donor) has indicated that he so wishes, eventual incidental or new findings will be passed on to the supplier
- the manner in which (for example described in the Standard Operating Procedures) human material will be used so that the right of choice of the subject (donor)s with respect to this material is continuously satisfied and the wish of the individual with respect to new findings is clear.

- nature of the data needed for the research investigation

- explanation of why exactly these data are to be used. Explicit justification if the exception clause is to be applied in order to use identifying data without permission (according to the Code of Proper Use).

- how the data were or will be collected:

- together with (coupled to) the material

- acquired from the material

- collected from other files

- the guarantees that keep non-personal data from becoming personal data after all.

- at least how long will the human material and data be stored

- explanation of this period of time in view of the research question (and in view of what is stated about this in the Code for Proper Use and the Code for Proper Conduct)

- what will be done with the human material and the data at the end of the established period of time for storage.

- when, insofar as relevant, will the processing of personal data be reported to the relevant Data Protection Authority.

- evaluation of whether the protocol must be presented to one of the review committees that work for the institute. If evaluation according to the Code of Proper Use is considered necessary, then the results of evaluation must be positive and the report of the review committee must be attached to the definitive version of the protocol.

- groups of personnel who will carry out the investigation (such as analysts employed by the research institute)

- manner in which the personnel undertakes the promise of confidentiality

- the safety regulations against loss and unauthorized knowledge of human material and data

- if available, validation by means of an audit or something similar

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- declaration that the responsible researcher feels bound by the Codes for Proper Use and Proper Conduct and recognizes the authority of the national complaints Committee of the FMWV.


Biochemie en Moleculaire Biologie


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