

Quality of Life and Management of Living Resources
European Human Frozen Tumour Tissue Bank

TUBAFROST

QLRI-CT-2002-01551

Milestone 7.2

**Code of Conduct for the use of residual
tissue for research**



1. Preamble

The TuBaFrost Consortium is a group of research centres. The aim of TuBaFrost is to facilitate research with residual tissue across Europe. In order to achieve this ambition TuBaFrost has set up a database of repositories of residual tissue at the participating centres (hereinafter: the members) and has decided upon quality standards for the storage of residual tissue for research.

Such research should be guided by ethical and legal principles in order to protect society in general and the legitimate interests of those whose tissue is being used. At the same time these principles can contribute to the ambition of TuBaFrost as the exchange of tissue would be impossible without a common understanding of the applicable and coordinating principles when each of the members is subjected to different regulations.

In the following sections the principles can be found on which the members have agreed upon.

2. General principles

2.1 Introduction

Respect is due to the patients whose tissue is used, and their interests should be protected.

This involves most of all:

- Left-over tissue may only be used for research if this does not jeopardise the relationship of the patient with his treating physician and when it may safely be assumed that it will not have any detrimental effects on his care in the future. Amongst others this means that the tissue will only be used for research if it may reasonably be assumed that this will not damage the use of this sample for further diagnostic procedures for the patient;
- strict privacy protection;
- appropriate consent procedures;
- appropriate procedures if research results in outcomes which may be of direct relevance to the future health of the patients whose tissue has been used or their direct relatives.

2.2 Strict privacy protection means amongst others the following.

- Tissue will be as far as possible anonymised before it can be used in research;
- Coding procedures are seen as an excellent way to combine privacy protection with the necessity to combine data from analyses of the tissue with clinical data;
- When coding is applied, as far as possible one way coding techniques shall be used;
- When tissue is transferred from the tissue bank to a centre which carries out the research, the tissue will be anonymised but it can be coded;

- Under no circumstances will directly identifiable data of the patient be transferred or made available to a third party (meaning any party other than the centre where the tissue was taken out or the patient or his legal representative). Identifiable data should be protected against unauthorised access by a combination of appropriate technical and procedural measures.

2.3 *Appropriate consent procedures mean at least the following:*

- If fully identifiable tissue is used for research the patient should have given his informed consent;
- If anonymised but coded tissue is used for research it is highly recommendable that the patient should have had the opportunity to oppose to the use of residual tissue in research. The information about possible use could be part of the general written information which is usually given to the patient when entering a clinical facility. It should be clear where the patient can make inquiries about the use of residual tissue for research and where he or she can opt out if he or she chooses so;
- If the tissue is two way coded above recommendation should, in principle, always be followed;
- Special attention should be given to tissue which was entered in the tissue banks before explicit consent or opt-out systems were implemented. In principle such tissue may only be used if the envisaged research cannot be done with tissue for which a full consent or opt out system had been implemented. If such tissue is necessary, it should again as far as possible be anonymised. For fully identifiable tissue it should be considered whether the patients or their relatives should be contacted. Apart from practical aspects, this also involves a consideration whether is ethically acceptable given the (psychological) harm that recontacting may cause to the patient or his or her relatives.

2.4 *Appropriate feed-back procedures*

- This issue concerns the question whether results of research which may be of direct consequence for the future health or treatment of the patient whose tissue has been used, should be told to him or her individually. It should be noted that such results are rare as usually there is a long way between outcomes of research and clinical application (including counselling on health prospects). Moreover, the techniques used in research do in many cases not allow predictions on the individual level.
- The question does not arise when fully anonymised or one way coded tissue is used as in that case the identity of the patient can not be retrieved from the data which accompany the tissue even if the specific code number would be notified to the centre from which the tissue was sent.

- There is no generally accepted standard yet as to whether individual feed-back is advisable in the circumstances where such feed-back could be possible. When fully identifiable tissue is used by the researcher who is also the treating physician of the patient, it hardly conceivable that these results are not discussed with the patient. However, if the patient has expressed a wish not to be informed, this wish should be respected, following from the ‘right not to know’.

If two way coded tissue is used by researchers who are not the treating physicians, it must be considered whether these results will not reach the patient anyhow via state of the art medicine. It should be noted that these results are not only of interest to patients whose tissue has been used in research, but to all other who share the same medically relevant characteristics. Therefore it seems that there must be a special reason to notify these patients separately. As a general rule, it should never be a researcher who gives this feed-back, but the treating physician. The decision to notify the patient should be made by the treating physician, perhaps after having been advised by an ethical committee, and taking into account the ‘right not to know’ of the patient.

3. Research principles

Many principles are to be followed when conducting research, like impartiality and independency precision, accountability. These general principles, which are common to all researchers, form the basis for research with tissue as well. However, they are not sufficient to guide good research practices for research with residual tissue. The members find the following principles of utmost importance in this respect:

- Each research project should be described in a protocol.
- The protocol should explain why residual tissue is needed for this project and what data are needed. It should justify the amount of tissue and data which are deemed necessary and why less tissue and less data will not be sufficient. In particular it should argue why data of a certain kind¹ are necessary and why data of a less sensitive kind cannot be used.
- It is advisable that such a protocol is reviewed by an ethical review board, according to the procedures of the centre where the research will be carried out. Research with fully anonymous tissue may be an exception to this principle. Research on fully identifiable tissue always needs approval of an ethical review board.
- Procedures must be set up on who is granted access to possible identifiable information of the patient and who is not. Even if fully identifiable tissue is used, it may still be possible to apply internal coding, so that e.g. technicians do not have access to the identifying data.

¹ Meaning ranging from more to less sensitive: fully identifiable, anonymous but two way coded, anonymous but one way coded, or fully anonymous.

- A centre should be transparent about its research projects. Researchers should try to establish cooperation between groups which represent interested patients and inform the public at large about the relevance of residual tissue banks for research centres.
- Results of research should be announced with caution in order to avoid undue anxieties or raising false hope.
- Research will be aimed at publication(s) which will be shared with the scientific community, if necessary subject to a 'term of grace' if a patent application can be involved. Between the centre which provides the tissue and the centre which receives the tissue for research, a Materials Transfer Agreement (MTA) should be agreed upon. In this MTA arrangements can be made on authorship of publications based upon research with the exchanged tissue according to accepted academic standards, and on possible patents.

4. Principles on exchanging tissue for research

- In principle only fully anonymised or anonymised but coded tissue and data can be exchanged.
- Tissue will only be exchanged to meet the requirements of a specific research protocol of the receiving institution. This protocol should in principle be approved by the ethical review board of this institution.
- For each exchange a MTA will be agreed upon between the institution of the tissue bank and the receiving institution.
- This Code of Conduct acknowledges that each country or even each institution may set its own conditions for appropriate consent preceding the use of residual tissue for research. The basic rule is that tissue, which may legitimately be used for research in the centre where the tissue was taken out, may also be used for research in another centre even if to that other centre other consent procedures (stricter or more lenient) would apply. This can be seen as an application of the principle, often seen in EC regulations, of 'home country control'. However, all institutions taking part in the exchange program should endorse the general principles mentioned in section 2.
- Following the principle of 'home country control' the centre which originally processes the patient data (usually that is also of the centre where the tissue was taken out) is also responsible for the legitimacy of the transferral of accompanying data. Fully anonymous data may always be used. The situation is rather complicated for anonymised but coded data. In some countries these data are still considered personal data in the sense of EC Directive 95/46 although they are not identifiable at the level of the receiving institution. In that case they might be subject to certain consent procedures or approvals from a competent body. In other jurisdictions they are considered to be anonymous data provided that the condition of anonymity at the level of the receiving centre has been

met. It is one of the basic rules of this Code of Conduct that this condition should always be met and that adequate control mechanisms are put in place to guarantee compliance with this condition. Therefore the researchers and others endorsing this Code of Conduct maintain that such data may safely be exchanged for research and should not be subjected to further control mechanisms.

5. Principles on ‘ownership’, intellectual property rights etc.

- The tissue bank exists only for the purpose mentioned in the first two sections. Those in charge of the bank with residual tissue are merely the custodians to assure that the tissue bank can fulfil its promises. Though it may be said that they own the bank (as a collection of tissue) in a legal sense, this ‘ownership’ is subject to the purposes for which it is set up and for which patients have entrusted the storage of the tissue at the bank. All decisions regarding the bank should serve these purposes and respect the principles mentioned in this Code of Conduct. Decisions of individual patients to have ‘their’ tissue destroyed should be respected if practically feasible. Therefore, the custodianship of the researchers cannot be regarded as ‘ownership’ in the classical sense.
- In most legal systems the patient cannot be considered the owner of the specific tissue samples which were left over after his or her treatment or diagnosis. He or she has a right to opt out or to have the tissue destroyed but usually does not have a claim to receive the tissue back, even if that would be practically possible. ‘Selling’ his tissue is not accepted in most legal systems either and definitely not in the European systems.² These facts do not easily fit into the doctrine of ownership in the classical sense.
- Therefore, it seems wiser to abandon the term ‘ownership’ in this context and focus on who may do what with the tissue under what circumstances. The centre where the residual tissue was taken out and is originally stored, should use it for research, and make the tissue available for research, according to the principles of this Code of Conduct. The possibilities of the receiving institution are even further limited as the received tissue should be used, not just according to the principles of this Code of Conduct, but according to the conditions which are laid down in the MTA as well.
- The tissue used for exchange has first been collected in the context of health care to patients and with the help of the (public) funding for such health care. This origin of the tissue and the ‘trust’ character of the tissue bank mean that the tissue as such should not give rise to financial gain, neither for the donor nor for the tissue

² See the explanatory notes hereinafter.

bank. However, a contribution in the costs for maintaining the tissue bank³ may be charged. Costs of the shipment of tissue will be charged to the receiving institution.

- The above does not preclude that research may result in the establishment of intellectual property rights (IP's) like patents based on the original contribution of the research. This is an added value resulting from the tissue collection and clinical data as a whole which was used in the research. It cannot be attributed to one single sample and to one single patient. Therefore recital 26 of EC Directive 98/44 does not apply to such inventions. Nevertheless, in the general information to patients it should be mentioned that such IP's might result from 'further use'.
- Patents will be vested according to the regulations of the centre where the researcher is employed subject to possible specific arrangements in the MTA. These patents should be primarily meant to strengthen the position of research into diseases or health care in general. Given the public character of tissue banks and 'further use' the possible revenues of IP's should as much as possible be reinvested into those objectives, again subject to the regulations of the centre where the researcher is employed.
- The above does not preclude certain public-private partnerships of banks with left over tissue or of the receiving centre with commercial companies. Under certain circumstances the combined resources of the public not-for-profit institution and a commercial partner can achieve more than when tissue and the results of the research would remain in the public domain. However, the objective of such cooperation should remain as just stated: to strengthen research into diseases or health care in general. Public-private research agreements should be carefully drafted in order to achieve this objective.
- Above mentioned rules also apply to 'start-up' or new commercial enterprises where the commercial partner originates from a not-for-profit research centre. Whatever its origin, the start up must be considered as a commercial third partner. Researchers should be aware of possible 'conflict of interests' which may arise from such a situation and should adhere to the applicable conflict of interests policies.

³ Including preservation of the tissue according to the quality standards, the coding procedures for additional information, etc..

EXPLANATORY NOTES

Ad the Preamble

Information about TubaFrost can be found at the site of TubaFrost: www.tubafrost.org The database which is referred to in the text is hosted at the EORTC. It is accessible after a registration procedure.

The starting point of TubaFrost is the use of residual tissue for medical research. Left-over tissue is human tissue which was originally taken out from a patient for diagnostic or treatment purposes. After that procedure has been performed, with informed consent, and the necessary diagnostic procedures have been applied to it, it or part of the tissue will usually be stored for some time. It forms part of the medical file. The physician or the patient may want to re-use this tissue to check the original diagnosis. After a certain time period it is usually destroyed (according to the regulations on hazardous waste applicable to the centre).

The members find it of utmost importance that this residual tissue can be used for research and therefore that it will be stored in such a way that it can be used for that purpose. Such research has a long history in modern medicine and is part of the 'public good'. It has contributed to our understanding of the pathogenesis and to the prevention and care of diseases. New techniques have made this type of research even more valuable. In combination with the availability of clinical data of the patient this research can lead to results which cannot reasonably be gained in any other way, at least not in the near future. If tissue would be taken out from healthy volunteers, one would have to wait until some of the volunteers develop a disease before it may be possible to establish a link between the causes of disease and certain medical characteristics of the volunteer as can be found from the analysis of his tissue.⁴ Using left over tissue makes it possible to 'look back' using new techniques which did not exist at the moment when the tissue was taken out, or using the new clinical data of the patient which could not be predicted when the treatment was started. In cancer research especially the affected tissue is needed in order to unravel the relationship between the specific characteristics of this (sub)type of cancer as can be found by using new proteomic and genetic techniques, the development of the disease and response to treatment.

Once the results of this research have reached the stage of practical applicability and are implemented in the health care system, patients will profit from them, and others who would have become patients but for the preventive tools which this research will have generated. TubaFrost is more than making residual tissue available for research. It aspires to create the conditions that this tissue can be exchanged for research purposes between the members.

⁴ This is of course not meant to say that de novo population based biobanks cannot be extremely valuable as well. As much more is known about the volunteers in these banks – because of the questionnaires which they have completed when entering the bank and sometimes during the existence of the bank – than the rather limited patient's history which is available in the clinical file, these banks are e.g. much better equipped to investigate the relationship between genetic and environmental and/or behavioural factors and health.

Such exchange is necessary in order to fully benefit from the potentials of bioinformatics and genomic and proteomic approaches for the study of rare diseases, as often large numbers of samples are needed to trigger the desired significant outcome.

These goals both give the rationale for the efforts of the members and the limitation to the use of residual tissue. The members will cooperate with each other to ensure that residual tissue will be available for research, both at their centre and for other centres which endorse this Code of Conduct. At the same time, when the tissue has become available for research, it should solely be used for research which ultimately⁵ may result in benefits for the health care system as an aspect of the public good.

Ad the Preamble and sections 2-4

Many lawyers and ethicists have raised objections against the unrestricted use of residual tissue for research. One may say that parallel to the growth of an 'industry' of research with residual tissue an 'industry' of ethical and legal concern with this use of tissue has arisen, leading to an "avalanche"⁶ of declarations, reports and advices from international and national organisations and regulatory initiatives. These explanatory notes are not the proper place to discuss these issues. However, they form the background of this Code of Conduct and therefore the main topics should be explained, albeit very briefly. These topics can be headed under the following categories:

1. protection of the privacy of the patient whose tissue is used in research;
2. protection of the autonomy of the patient whose tissue is used in research;
3. protection of his other interests, like the 'right not to know';
4. protection of the interests of groups of persons, whether their tissue has been used in research or not, against discrimination by third parties, like insurers, when the general results of research would be published.

The Code of Conduct is very strict with regards to protection of interests of the *first type*. No compromises can be made here. A visit at the database of the TuBaFrost consortium will only show numbers for tissue samples. A double coding system lies behind these numbers. There is virtually no possibility to retrieve the identity of the patient from these numbers. When residual tissue will be exchanged between centres other safeguards are put in place to protect the patient's identity for the centre which receives the tissue and accompanying clinical data.

The protection of the interests of the *second type* has probably been the subject of most debate. Autonomy of the patient in this respect has to be balanced against the possible benefits of research for others, the practical possibilities to practice this autonomy and the moral reasons why the patient should have this autonomy, namely as a value as such to decide what will happen with 'his' tissue (where 'his tissue' already means that a certain

⁵ Ultimately, as there may be a long distance in time and efforts before results of basic research can be applied in care or prevention.

⁶ A. Cambon-Thomson, The social and ethical issues of post-genomic human biobanks, *Nature Reviews Genetics*, 2004, p.866-872, at p. 866.

point of view in this discussion is taken) or to protect his other interests like that of privacy or the right not to know. A trend might be seen from very strict approaches to less strict solutions. The development of the Human Tissue Act in the United Kingdom can be seen as an example of this development. In the final Act the consent system for this use of every type of residual tissue for research, as proposed in the original Bill which was forwarded to the Parliament, was amended in a no consent system at all for the use of anonymous, even when it is coded, residual tissue for research. The members of the TuBaFrost consortium (hereinafter referred to as 'the members') did not take a common standpoint in this discussion. As the purpose of this Code of Conduct is also to facilitate the exchange of tissue between centres from different countries where different solutions concerning this subject may be found, any attempt to find a common denominator would be futile as it could not be applied to a country which would have a solution above, in the sense of being more strict, this common denominator. A solution to establish the common denominator at the level of the strictest system would not be justified towards systems where the balance has been struck differently, for good reasons as perceived by that system. Therefore, instead of formulating a common harmonised principle, the members have formulated a *coordinating* principle. This principle is worked out in section 4 of the Code of Conduct. It means, in short, that if residual tissue may legitimately be used for research at the centre where the tissue was taken out from the patient, according to the regulations applicable to that centre, it may also be used at a centre where the tissue is sent to for research purposes, even if other regulations would apply to that centre. However, this coordinating principle applies only conditionally. The condition is that both centres (that which originally holds the residual tissue and that where the tissue is sent to) endorse this Code of Conduct and the guarantees for proper research practices embedded in it. One of these guarantees is that minimum level of consent must be established for the patient whose residual tissue could be used for research. This means that the use of anonymous but coded tissue⁷ for research is allowed only if at least an opt-out system is implemented at the centre where the tissue is taken out. This Code of Conduct focuses mainly on that type of tissue as following from the privacy protection principles fully identifiable tissue may not be exchanged for research. Fully anonymous tissue may of course be used and would be the preferable option from the point of view of privacy protection. However, usually coded tissue will be exchanged as the possibility of adding additional clinical data if necessary is one of the advantages of this type of research.

With regards to protection of the *third type* of interests several principles and guidelines have been put in place most of all in section 2.4. The interests of the patient should always prevail over that of research, see also section 2.1 first bullet point. It should be noted the researcher will not interfere with the relation between the patient and his physician. The protection of interests which this third type refers to must most of all be found in that relation and the responsibilities of the physician therein.

⁷ These terms will be explained in the next section of these Explanatory Notes.

The protection of the *fourth type* of interests lies largely beyond the possibilities of researchers. The members are aware of the fact once the general results of research have been published, other applications, outside health care, are possible as well. E.g. insurers might derive 'risk profiles' from these publications which can be used against those who apply for a private insurance. Within the European health care systems, these effects are unlikely to happen because of the principles of income and risk solidarity on which these systems are based. The members welcome initiatives which ban unwarranted risk discrimination in the private insurance sector, like can be seen in the legislation of many European countries. Another aspect of these interests is the possibility that people may start to worry whether certain results of research will be applicable to them if they see these results published. This is an intricate subject which again cannot be explored here. In section 3 at the 6th bullet point a principle of proper research practices is laid down which specifically refers to this aspect. However, given that the principles of proper research practices as described in section 3 are adhered to, the members find that in general there should be no limitation to publish validated data of medical research. Against those who might become anxious there will in general be a much larger group who may profit from these. In general the public should be educated what risk profiles mean for individual situations and the health care system should be ready to answer questions in this respect. As members of the civil society researchers will have a role in this clarification as well. As a last remark about this subject it should be noted that research with residual tissue as described in this Code of Conduct is research aimed at improving health care. Other possible uses of residual tissue which may give rise to important societal concern, are simply not allowed within the exchange program of the TuBaFrost consortium.

Explanation of some of the terms

Where the Code of Conduct uses the phrase 'tissue banks', it refers to repositories of residual tissue. Residual tissue is tissue which is stored in e.g. pathology laboratories after it has been taken out when this was deemed to be necessary for the treatment of the patient. When the necessary diagnostic procedures have been performed, it becomes 'residual tissue'. There are other types of tissue banks as well than banks with residual tissue. In some countries 'de novo' tissue banks are established, using tissue from volunteers of a sample of the population. The initiative for the UK tissue bank of the Wellcome Trust and others⁸ can be seen as an example of this. That type of tissue banks are not referred to in this Code of Conduct.

Very important in any type of regulation of the use of (residual) tissue in research is the way a tissue sample can be linked to the patient from whom the tissue was taken out, or better, to the clinical data of this patient. The following distinctions are made in this Code of Conduct:

⁸ See <http://www.ukbiobank.ac.uk/> (last visit January 2005).

- fully anonymous tissue means tissue which by itself or the added data cannot be reasonably linked to the identity of the patient from whom the tissue was taken out;
- anonymous but coded tissue means that the tissue is anonymous in the above sense to the researcher who uses the tissue. However, it has a code-number. This code-number corresponds to a coding mechanism available at the party who has issued the tissue and clinical data to the researcher. In the case of 'one way coding' the coding mechanism provides only for the possibility that by entering some identifiable data of the patient the same code-number will appear as has appeared earlier when the same procedure was performed. With two way coding, it is also possible to perform the procedure the other way around: by entering the code-number one gets the identifiable data of the patient.

Researcher in the above means the research centre which receives the tissue if the tissue is exchanged between two centres. No one at that centre will reasonably be able to retrieve the identity of the patient from the tissue or accompanying clinical data. If the tissue (still) remains at the centre where the tissue originally was taken out, researcher means what is says, namely the researchers – and those working under his supervision – who use the tissue for research. Others might of course still be able to link the tissue to the identity of the donor. Research and the clinical use of the tissue are two separate worlds here. This also means that those who have access to the tissue and clinical data for clinical (= treatment) purposes do not have access to the results of the research on the level of the individual patient, but for the conditions as laid down in the research protocol.

- Fully identifiable tissue means that the identity of the patient can be retrieved by the researcher without using extraordinary means. The most common example of this situation is when the treating physician also performs research. But also if research is performed by others at the centre where the tissue was taken out, and the tissue and clinical data are available to them under the patient identification number which is used throughout this centre, the tissue must be considered fully identifiable even though these researchers do not usually use this patient id to contact the patient. Only if very strict technical and procedural safeguards would have been put in place, amounting to 'Chinese walls' between the research and the clinical departments of the centre, it could be possible to label the tissue available at the research department as anonymous but coded.

Ad section 5

Apart from the scientific interest of research with residual tissue and its application to health care, there are increasingly commercial interests connected with this type of research as well. The members, though all being not-for profit health care institutions and research centres, cannot ignore the issues raised by possible commercial applications of research with residual tissue. This Code of Conduct is again not the place to discuss these issues in

full. Instead some coordinating principles should be established. The coordinating principles refer to the regulations which are already applicable at the centre where the research is performed and possible specific arrangements in the MTA. What has been established and found acceptable in that context should work in context of the TubaFrost exchange as well. The section starts with a short discussion of an even more complex issue, at least from a theoretical point of view, namely who 'owns' the tissue. From a practical point of view this issue is of much less relevance. What counts is who may do what with the tissue and under what conditions. This Code of Conduct lays down the principles for decisions of that kind, in addition to and connected with the regulations which apply to centres where the tissue was taken out from the patient. It once again is underscored that researchers who maintain a tissue bank are doing this for the public good. They store the residual tissue under appropriate circumstances in order that it can be used for research for health care. The patient who consents to the use of the residual tissue for research (either by explicit consent or by not opting out) does so for the public good as well. In the literature in the United States it has been forwarded that the patient remains the 'owner' of 'his' residual tissue and should receive a financial compensation if the tissue is used in research and/or share in the profits if commercially interesting inventions have been made. These trends have been discussed in an excellent article by Jasper Bovenberg, who – in short - concludes, both on theoretical and practical grounds, that such an approach could be the end of research with (residual) tissue.⁹ For the European situation it should be stressed that this type of 'property right' is against accepted standards. One can refer most of all to article 21 of the European Convention on Human Right and Biomedicine¹⁰ which states: "The human body and its parts shall not – as such – give rise to financial gain". The public good character of both making residual tissue for research and its following use in research is what lies behind this Code of Conduct and principles embedded in it.

⁹ J. Bovenberg, *Inalienably Yours? The new case for an inalienable property right in human biological material: Empowerment of sample donors or a new case of a tragic Anti-Commons*, Script-ed, 2004, no. 4, available at: <http://www.law.ed.ac.uk/ahrb/script-ed/issue4/bovenberg.asp>

¹⁰ Orviedo 4-4-1997, Council of Europe ETS no. 164.