EUROPEAN JOURNAL OF CANCER 42 (2006) 2914–2923

available at www.sciencedirect.com

journal homepage: www.ejconline.com

TuBaFrost 3: Regulatory and ethical issues on the exchange of residual tissue for research across Europe

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ARTICLE INFO

Article history:
Received 22 March 2006
Accepted 4 April 2006
Available online 6 October 2006

Keywords:
Exchange of residual tissue
Code of conduct
European regulations
Biobanking
Consent

ABSTRACT

The regulatory regimes for research with residual tissue and accompanying data differ widely between countries in the European Union (EU): from specific consent to opt-out or even no consent at all. This could greatly hamper research where the exchange of tissue and accompanying data has become the gold standard, like in TubaFrost. Instead of adhering to international guidelines, which have a democratic deficit, or an attempt for a new set of possible harmonising rules, TubaFrost chose to create a coordinating rule: if tissue may legitimately be used for a certain kind of research in the country where it was taken and under whose jurisdiction the patient falls, it may also be used for such research in the country where it is sent to in the context of a scientific program even if in that other country other regulations would apply for research with residual tissue taken from patients under their jurisdiction. This coordinating rule has a sound basis in EU law in general and will solve the problems related to diverging national regulatory regimes in the case of cross national research with residual tissue.

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doi:10.1016/j.ejca.2006.04.028

1. Introduction

TuBaFrost presupposes that residual tissue and accompanying data can be exchanged for research across the European countries.[1] By residual tissue I refer to tissue which was taken from the patient in the course of a diagnostic or therapeutic procedure, is stored and can subsequently be used for research. Tubafrost is not unique in this respect. Most of the projects under the EC 5th and 6th Framework Programs will exchange data and, in many cases, residual tissue between the participating research centres.[2]

However, a common international regulatory framework does not exist for research with residual tissue and accompanying data. There has been an 'avalanche'[3] of statements or guidelines on research with tissue and accompanying data but apart from the fact that they state ethical principles and do not give much regulatory guidance and diverge on many aspects,[4] they have another, more serious problem, as far I know never previously mentioned in the bio-medical literature, namely a democratic deficit. I will discuss these statements or guidelines and the democratic deficit in Section 2.

In some countries of the EU the legislator has intervened. The resulting legislation varies greatly. Some examples will be given in Section 3.

Research with residual tissue implies research with data. This type of research can only be fruitful when data about the patient accompany the tissue, new data are derived from the tissue and – in many cases – can be matched with data on clinical follow-up.[5] Therefore, the regulatory regimes of research with residual tissue can only be discussed in conjunction with that of research with patient data. As will be discussed in Section 3, these regimes are also divergent in the EU in spite of the Data Protection Directive,[6] which is meant to facilitate the exchange of data in the EU by harmonising the data protection legislation of the EU countries.

This seems to be a rather distressing state of affairs when researchers want to proceed with exchange programs for residual tissue. In Section 4 'Harmonisation or coordination', arguments are provided which clarify that for a variety of reasons, harmonisation is neither needed nor fruitful. Instead, a mutual recognition of the various regulatory regimes is proposed. The regulatory regime of the patient under whose jurisdiction the tissue was taken out decides whether the residual tissue can also be used for research in another country where a different regulatory regime for research with residual tissue might apply. This approach, however, is only feasible when certain common standards, especially regarding privacy protection and good research practice, are adhered to. These will be discussed in Section 5.

This paper will sometimes be detailed on the aspects of European or comparative law and the underlying political philosophy. As will be shown in Section 3, literature in biomedical journals on the regulatory issues of tissue banking has been rather superficial if not overtly incorrect on some of these aspects. To avoid that pitfall and to eliminate current misunderstandings, a more thorough discussion could not be avoided.

2. International guidelines and statements on the use of tissue for research

As guidelines or statements which only discuss research with residual tissue are rare, all those which deal with observational research with tissue or data, including genetic data, will be taken into account. For brevity they will all be referred to as 'reports', though it should be underlined that they claim to state normative principles. The differences and trends in these reports have been discussed at length elsewhere.[3,4,7,8] Knoppers detected a trend towards a less restrictive approach on the consent issues.[4] In another article, she and a colleague noted a Babylonian confusion in the terminology of the data accompanying research with tissue.[9]

For now, I want to discuss several issues which do not appear in these comparisons.

The first is the legal status of these reports. A legal order presupposes a kind of hierarchy of norms. Essential in that hierarchy is the appointment of institutions with the authority to issue binding general norms. In the uncritical discussion of the recent proliferation of international pseudo law on tissue banking, this hierarchy of norms is overlooked. From a constitutional point of view international instruments can only be binding *within* a national legal system by some national act of ratification, which usually involves parliament. How this is achieved depends on the national system and all systems differ in this respect.[10] After ratification some, the so-called monistic systems, like the Netherlands,[11] are more permeable for international law than other, more dualistic systems like the UK. The philosophy behind the latter system is that of parliamentary supremacy.[12] The differences between the two systems have been mitigated due to developments both on the national and the international level and the European Union has superseded this original position by establishing a separate legal order.[13] But one thing is clear, namely that none of these reports have been ratified. Most of them are also unfit to be ratified as they stem from non-governmental organisations or are simple declarations.[14] The hierarchy of norms applies to these international reports as well, which again is overlooked in the international comparisons. A Treaty has a much higher authority than a Recommendation. This distinction is important to assess such a report within its political context. An organisation might issue norms in a declaration, which would have been impossible to issue at the status of a Treaty. Unlike a declaration, a Treaty is meant to be ratified and therefore, a Treaty is discussed and scrutinised to a much greater extent by the parties (read governments) who are called to sign it.

The next issue is the debate on the legitimacy of international organisations to keep on issuing human rights-like documents. I have not seen a reference to that debate in the comparisons. The legitimacy is questioned in the context of global ethics, as these organisations fall short on democratic control or transparency as the next best solution.[15,16] This is not to say that international organisations, whether governmental or not, cannot and have not greatly contributed to raising awareness on human rights in general and biomedical research in particular. The World Medical Association (WMA) Declaration of Helsinki[17] stands out as a landmark in this respect. The new emphasis is on 'global justice' when bearing

the burdens and receiving the fruits of biomedical research. The latest version of the WMA declaration has elements of the latter as well at points 9 and 19. Nevertheless, it should never be forgotten how they came into being, namely in a not always democratic nor transparent process of 'experts' chosen by the organisation and of civil servants or staff members. In western democracies, we have a system for making law which, with all its flaws, is invaluably better than how international organisations make pseudo law. This is not only because in the end the democratically elected parliament decides, but also because of the process leading to this decision: open, transparent and thorough discussions in the lay press and specialised periodicals where all stakeholders can intervene. This is in stark contrast to the process in which the (self) selected group of experts draft the international reports on bioethics or medical law.

The last issue and connected to the former, is that the proliferation of international pseudo law also makes one anxious about the reasons behind it. One may wonder whether the reports are not a mere rhetorical keeping up with the Joneses than an essential contribution to the mission of that organisation.

In my opinion, this could be one explanation why, where Parliament has enacted norms for the use of residual tissue for research, these norms tend to be more 'lenient', or – in my view – more balanced, on the consent issue than those of the international reports. There is – uptil now – one exception (see the following section). As follows from the arguments put forward above, national legislation ultimately matters.

3. National regulations

A general overview of all European countries will not be given, as this would be far too complex. Overviews of regulatory issues in the biomedical literature tend to be superficial and usually fall short on accepted standards of comparative law. By focussing on some examples I hope to avoid this pitfall.

First of all, we are discussing *residual* tissue for research. If the tissue would be specifically taken out for research, usually a completely different regulatory regime would be applicable. Remarkably, in many comparisons this distinction is overlooked. An example of this misunderstanding is found in the publication of Matschke.[18]

Second, there is a caveat. Legal norms on a specific issue are embedded in the general system of legal norms of a country and are influenced by, give expression to, and at the same time, further develop the constitutional and regulatory principles *and* cultures of that country. On this specific topic they are embedded in the organisation of the national health care system as well. Despite being more inclusive than others, perhaps even to the point of becoming boring to non-lawyers, many of these related issues remain uncovered. If, for example, the conclusion is that under similar circumstances in two countries a permission or authorisation is needed from an authority like the national Data Protection Authority (DPA), this conclusion carries only partial information if one does not know how long it takes to obtain it in each of them. I did not investigate time schemes for authorisations or possible remedies if the authorisation is not granted. Another issue which I did not investigate is whether researchers have access to the data of other registries such as death or cancer registries. This can be of great importance to this kind of research. However, this would need a separate study.[19]

The countries that will be discussed here are Denmark, France, the United Kingdom and the Netherlands. The first three countries enacted legislation on the use of residual tissue for research, with very different outcomes. In the Netherlands, the so-called self-regulation on this issue was established already in 2001. Some anecdotal references will be given to other countries when discussing the data protection regimes.

Two issues should be distinguished. First, whether the tissue of a certain type may be used for research. Second, whether the researcher may use the data which accompany or can be linked to the tissue.

As some data will always accompany the tissue and new data can be derived from it, the type of tissue which may be used cannot be explained without a discussion of the terminology in data protection law.

3.1. *Anonymous and personal data in general*

Within the European context, we should start with the terminology of the European Data Protection Directive.[6] Such a Directive must be implemented in the legal systems of the member-states. Differences in implementation are allowed where the Directive leaves room for such differences. This was the case with respect to data for medical research and the member-states arrived at different conclusions on this issue.

The Directive names the entity which holds the personal data *and* decides upon their use as the 'controller'. It states that to determine whether data are personal, 'account should be taken of means likely reasonably to be used either by the controller or by any other person to identify the data subject' (Recital 26).

On the level of the controller, one usually distinguishes between directly and indirectly identifiable data. Directly identifiable data contain direct identifiers of the data subject, like name, address, *etc*. Indirectly identifiable data do not do so. The latter are still considered personal data as the *controller* could in principle retrieve the data without excessive means. This is of course a rather subjective criterion. In another publication I have described instances where no researcher in his right mind would consider the data indirectly identifiable, but the DPA did.[20]

Indirectly identifiable data can be coded, but that does not change their status. They are already considered personal data due to their identifiability by the controller.

Data which are non personal data, so are anonymous data at the level of the controller, can be coded as well. They will arrive at the controller, the researcher, with a code number which usually has been transcripted from the direct identifiers of the data subject by the original controller of the data. On this subject, some major differences between the legislative solutions of the various European countries exist. The majority of the countries hold this category of data, which are unidentifiable at the level of the controller but with a code, to be personal data. Other countries, like the Nether-

lands and the United Kingdom, do not.[21] Hardly ever mentioned in the discussion is the elegant solution of the Austrian data protection Act.[22] This Act distinguishes a category of data, which could be identifiable if the controller would use illegal means. A lighter regime applies to these data.[23] This means that in practice, researchers may use these data without the consent of the data subject, even if they are 'sensitive data', like data pertaining to the health of the data subject, in the sense of the European privacy Directive.[24]

A study on the implementation of data protection in the member-states was published in 2002.[25] The European Commission in its report after this evaluation noted the aforementioned difference in interpretation but did not decide upon the question whether data which are anonymous on the level of the controller but are coded, should be considered personal data or not. It did state, however, that the definition in the Directive should be applied with some – in my words – common sense.[26] In my opinion this implies that the Commission is in principle sympathetic towards the view that these data are not personal data or at least should not be treated as personal data.

3.2. *Tissue and data*

Knoppers and Saginur have rightfully argued that the reports in the previous paragraph lead to a Babylonian confusion on the terminology.[9] The type of (residual) tissue to be used for research is named after the data, which are or can be attached to it and there is an abundance of such names. Regretfully, their article contributes to the confusion by stating that the European Commission 'intervened with a rational and simplified approach' by distinguishing four categories: identified, identifiable, anonymised and anonymous. The report they refer to at their note 4 was written by an ad hoc working group established by the Commission with no legal status and which was dissolved after the presentation of its report.[27] The only statement of the Commission in this respect has been discussed in the previous section. The distinctions made in the above-mentioned report are also at odds with the distinctions made in the data protection Acts as described above. Anonymisation or anonymised have never been recognised as categories separate from anonymous in these Acts or the Data Protection Directive. Which is logical as it is the result, which should count. However, different systems consider this issue differently. Assuming that the tissue arrives at the researcher with neither directly identifiable or – to the researcher – indirectly identifiable data attached to it, this tissue is anonymous on that level. To be meaningfully used for research a coded number is attached to it. This code number makes it possible to add additional data such as clinical follow-up by the entity which holds the key to the code. The researcher does not hold the key to the code, otherwise the data (and tissue) would be indirectly identifiable on his level.

At this point, one should distinguish between the coding mechanisms. This can be either one way or two way. With one way coding, the key holder has only one key, namely from the patient identifiers to the code number. With two way coding, there are two keys. That second key is from the code number to the patient identifiers. In most biomedical literature this difference seems to be indicated by single and double coding. These terms and their description are inaccurate. It is not used in the information technology literature on this subject and it is confusing because it also can refer to a situation where upon one layer of coding another layer of coding is applied by another entity as an extra safety standard. Yet, also in these situations one can have one way or two way coding.

With one way coding the results of the research on tissue and data cannot be traced back to the patient, even if these results were transmitted to the key holder. In my opinion this would mean that the tissue has to be considered anonymous by all systems in the EU. When the data are two way coded, we arrive at the different solutions seen in the previous section. Some systems would consider this as anonymous data and therefore consider the tissue as anonymised (the UK, the Netherlands, Austria). However, most legal systems in the EU do not.

To summarise, tissue can be discerned from the viewpoint of the European data protection legislation in:

1. Tissue with personal data attached on the level of the researcher, either
   (a) Directly, *or*
   (b) Indirectly identifiable on his level.
2. Tissue without type 1 data attached, but where a code number is attached to the data. This code number can be:
   (a) Two way coded, *or*
   (b) One way coded.
3. Tissue not having type 1 data or a code number attached to it.

All European systems would consider type 1 identifiable and type 2b and 3 anonymous. There might be differences in appreciation though with regards to sub-type 1b. Some DPA's might be more inclined to consider a certain aggregation level of the data as non-indirectly identifiable than others. However, the most important difference is with sub-type 2a, as discussed before.

3.3. *The use of residual tissue for research*

3.3.1. *Denmark*

Denmark amended its Act on patient rights in 2004 with an article which states (in brief) that if a patient wants his residual tissue to be used for his own health care only, then the patient should indicate this. This will be noted in a national register. A researcher who wants to use residual tissue for research should consult this national register and can only use tissue from patients who have not been registered.[28] Thus, with some delay the legislator followed an advice from its national medical research council on this issue in 1996 which proposed such an opt-out system for tissue of types 2 and 3.[29]

The aforementioned provision in the patient rights Act does not distinguish between types of tissue but here other provisions on the use of data for research step in. These are the rather lenient approach in section 29 of the Act on patient rights together with that of the Danish data protection Act. In short, these provisions state that personal sensitive data can be used for research, also without the consent of the patient, provided the Danish DPA has granted permission for its use.[30]

This DPA has issued guidelines on the conditions under which this permission is granted. These relate to the use of Privacy Enhancing Technologies (PETs) when using these data, so that the researcher will only have access to type 2 data and tissue.[31]

3.3.2. *France*

The situation in France is in sharp contrast to the Danish approach. The French regulations on research with tissue and data form no exception to the highly bureaucratic and centralised French regulatory regime[32] in general.

Nevertheless, also in France we see the same stepwise approach of first regulating whether residual tissue may in principle be used for research and then regulating whether and which data may be used for that research, though with many complications. Article 1235-2 of the Code de la Santé Publique (CSP) states that residual tissue may be used for research if the patient has not opted out. However, for the assembling of, or banking of residual tissue for research one needs a permission from more than one authority (art. 1243-3 CSP). The use of data in medical research is regulated in a specific section of the French data protection Act.[33] The second sentence states that if 'identifiable tissue' is to be assembled for research, informed consent, specific for this project, is needed from the persons concerned. In France, as in Denmark, type 2a data (and therefore tissue) is considered to be identifiable data/tissue. In addition to the informed consent of the patient, the researcher would need to have an authorisation of the French DPA, after first having obtained the advice of another administrative body on the scientific merits of the project.[34]

To complete the picture of the complicated French regime, article L. 1245-5 of the CSP should be mentioned which states in the last sentence that for the import or export of tissue for scientific purposes one needs the authorisation of the French ministry of research.

3.3.3. *The UK*

The use of residual tissue is governed by the UK Human Tissue Act of 2004, which will be fully implemented in September 2006. At the heart of the Human Tissue Act lies the need to obtain consent for the removal, storage and use of bodies or human tissue for scheduled purposes. However, the Human Tissue Act does allow for research of residual tissue without donor consent when the tissue is anonymous on the level of the researcher. The text of the applicable section in the Act clearly indicates that this applies to type 2a tissue as well.[35] There is one condition: an ethical review committee should have approved the research. The approach of the Human Tissue Bill proposed to Parliament was more restrictive. Some form of consent would have been needed, further to be developed by the Human Tissue Authority (HTA), a public body established by the Act. This was in line with an interim statement of the Department of Health of 2003 regarding the taking, storage and use of human tissue from the living and the dead, which proposed written consent for the use of residual tissue for research, pending new legislation.[36] Considerable debate in the scientific and lay press regarding this issue led to a government amendment (no. 69), which was explained as follows:

> 'the Government are clear that they do not wish to impose excessive burdens on those who process the *many* (my emphasis) diagnostic and clinical samples of blood, urine and tissue taken in the NHS. Obtaining consent to all such samples to make them available for research would be a disproportionate burden'.[37]

The recent Code of Practice of the HTA somewhat complicates this picture. In a draft Code it was proposed that best practice would at least be that that patients should have the possibility to opt out of research on 'their' tissue.[38] The more recent Code of Practice on Consent states, after first repeating the relevant provisions of the Human Tissue Act, that 'consent is preferable to developing more complex systems for keeping samples unlinked'.[39] Thus, the HTA recommends that obtaining donor consent in all instances is the best practice. This is in line with the basic idea behind the Human Tissue Act but seems to be at odds with the idea behind amendment 69. It therefore remains to be seen whether researchers will be able to carry out research on residual tissue where no consent was obtained, particularly as gaining ethical permission to use samples in this instance will require a justification.

The data protection legislation is rather complex as it is a layered system of provisions in the general Data Protection Act, in the Health and Social Care Act 2001[40] and Regulations and recommendations made by the Department of Health for the National Health Service.[41] These complexities have led to a debate[42,72] but the result seems to be that type 2 data can be used for research without the consent of the patient.[21,41] Recent initiatives in the National Health Service with respect to the electronic patient record[43] do not seem to change this.

3.3.4. *The Netherlands*

The Netherlands was probably one of the first countries to enact a provision on the use of residual tissue for research. This was the result of the rather heated debate on the possibility of anonymous HIV prevalence studies on residual tissue.[44] It states that type 3 tissue cannot be used for research or statistical analyses if the patient has objected to this use.[45] This provision was laid down in the general Act on patient rights, which came into force in April 1995 and was embedded in the Dutch Civil Code.

In the Netherlands the so-called 'self regulation' is often used to lay down detailed norms on a specific topic applicable to a specific group.[46] The provision on Codes of Conduct in the European data protection Directive[47] stems from a Dutch proposal. Self-regulation should involve all relevant stakeholders in an open and transparent process and of course remain within the boundaries of the law. In 2002, the Dutch Federation of Medical Scientific Societies, together with patient groups and the Royal Dutch Medical Association, established a Code of Conduct for the use of residual tissue in research.[48] This Code of Conduct uses an opt-out system for type 2 tissue. It has been opposed by health lawyers who had been involved in previous debate on the HIV seroprevalence studies and the Report of the Dutch Health Council of 1995[49] which had proposed a broad consent system for the use of this type in research.[50] Legislation has been announced but has not been presented to parliament as yet.

On the level of data protection, type 2 data can be used as anonymous data,[20,21] so consent of the data subject is not needed to use these data. Another Code of Conduct has been established to regulate the use of data for health services research.[51] Amongst other things, it regulates under which strict circumstances also type 1b and even, but more exceptional, type 1a data can be used without the consent of the data subject. This Code of Conduct has been approved by the Dutch DPA. It should be stressed, however, that according to the Code of Conduct for the use of residual tissue type 1 tissue may only be used with the consent of the donor.

4. Harmonisation or coordination

4.1. *At the level of Tubafrost*

Though Tubafrost is far from unique in its exchange of tissue and data, Tubafrost was probably one of the first projects to start addressing the problem of how this can be achieved if the rules for the use of tissue and data are diverging so much.

The first option which was considered was to establish a new set of Tubafrost regulations on this subject. This idea was soon abandoned. The regulations in the respective countries vary to such an extent that it would have been hard, if not impossible, to find a consensus based on a so-called 'average'. Even if a consensus were found, that would not have been of any help to researchers from countries which have regulations and which are stricter than this 'average'. Therefore, setting TubaFrost rules would have had the tendency of raising the standard to the strictest regime. This would have been detrimental to researchers and patients who, as democratically agreed in the country where they reside, would be able to comply with less strict regulations and make more tissue available for research than they would have done according to this new Tubafrost regulation.

The next option considered was to abide by one of the international reports. The problems of these reports have been discussed in Section 2. Why should researchers and patients not be able to follow the recently adopted national law instead of the international pseudo law? Therefore, this option was discarded as well.

The need to respect national regulations and at the same time find a way to exchange tissue between countries with different regimes led to the solution of the coordinating rule according to the so-called 'home-country principle':

> If tissue may legitimately be used for a certain kind of research in the country where it was taken out and under whose jurisdiction the patient falls, it may also be used for such research in the country where it is sent to in the context of a scientific program even if in that other country other regulations would apply for research with residual tissue taken from patient under their jurisdiction.

However, this coordinating rule is conditional. These conditions relate first of all to privacy protection. Another condition is that if the patient has objected to the use of 'their' tissue for research, the tissue may not be exchanged in the context of the Tubafrost project. Some 'levelling up' has taken place, with respect to countries which might not have this opt-out system. This provides an ethical baseline and will make the Code of Conduct acceptable to all partners at the European level.

4.2. *Aspects of European law*

The first question which needs to be addressed in this context is the following: can an authority from a country of a strict regime ban the use of the residual tissue for research which became available under conditions of a country with a less strict regime?

It is hard to predict how local ethics committees would look at this issue. The views of local ethics committees are sometimes unpredictable, especially when it concerns observational research.[52] However, as soon as the authorities are instituted by law, the European law comes in. Here as well, the distinction should be made between the use of tissue and that of data. On the use of tissue for research nothing has been regulated yet at the EU level. In the next section, it is discussed whether that is recommendable. In the absence of such regulation, the standard clauses of the EC treaty on the free provision of services apply and its interpretation in the numerous cases brought to the Court of Justice of the EC. To discuss this issue at length would go far beyond the scope of this paper. There are exemptions on the free provision either as they are laid down in the Treaty itself or follow from the so-called 'rule of reason' doctrine. The latter means that a country may hinder the free trade of goods or provision of services in that country if it is done in a non-discriminatory way, – in principle, as there have been some exceptions in the field of the free provision of health care services[53] – and this is necessary for, and proportional to, protecting a (compelling) public interest.[54] As the example of betting shows, EU law recognises that different countries can have different public interests. Some countries have a more liberal attitude to betting services than others. The latter can, when the conditions of the 'rule of reason doctrine' are met,[55] protect their subjects against betting services from those countries with a liberal regime.[56] But that is exactly why the 'rule of reason doctrine' cannot be invoked here, even if a certain country would hold that protecting the more strict regime would constitute a public interest. The 'import' of residual tissue for research, which has become available under a less strict regime, does not at all affect the rights of their subjects or the obligations of their researchers. The strict regime would of course still apply for the availability of tissue coming from their own subjects. If, on the other hand, the tissue is transferred in the opposite direction, from a country with a strict regime to a country with a less strict regime, this would still hold true. That would only be different if in the latter country the tissue would not be used for approved research projects and not under adequate standards of privacy protection. But even if that would be imaginable in a European country, this cannot be the case under the Tubafrost Code of Conduct as it provides such safeguards, as will be explained in the next section.

The next step is the transfer of the accompanying data or adding data of clinical follow-up under the code number. As has been shown the EU has regulated the transfer of data. The Directive holds that when data are transferred between

countries the applicable regime is that of the country where the controller of the data is established.[57] This principle is very similar to that of the coordinating principle of the Tubafrost Code of Conduct mentioned above. When personal data are transferred in the context of research, the question arises whether the researcher who receives the data becomes the controller. In that case, the researcher should notify the DPA and perhaps get permission. The situation becomes very complex when these data, as it will be type 2a data, are not considered personal data in the country where they come from. This situation can be avoided. Next to a 'controller' a 'processor' can be defined, being the entity which processes data on behalf of the controller.[58] The researcher who receives the data must be considered a processor. The regime of the country where the data come from would still apply. This solution has been reached in the context of clinical trials, where the treating physician is considered the controller of the data which are transferred to the sponsor.[21] It is slightly questionable in that area as, amongst other things, the sponsor will become the owner of the CRF's. It is completely logical here, as tissue and data will only be transferred under the conditions of a MTA and in the context of a specific research protocol, which regulates the issue of which data may be transferred. The researcher may only perform agreed analyses on the data and is fully dependent on the provider of the tissue and data for additional information. If the patient would opt out at a later stage, the provider should notify the researcher and that specific tissue sample and related data cannot be used any more.

4.3. *Should the use and transfer of residual tissue for research be harmonised at the level of the EU?*

The ad hoc committee on genetic testing[27] made a recommendation in this respect (no. 22). A cry for harmonisation is sometimes also heard from the researchers. Much can be said on this topic, but again that would lead us too far into European law and politics. I will just make a few comments. The EU is only competent to regulate on specific issues, and only under certain conditions, as described in the EC Treaty.[12,53] Ethics or research as such do not belong to those issues as the European Commission has quite rightly argued in the discussion with the European Parliament on the draft Directive on the quality procedures for the processing of human tissue for therapeutic purposes.[59] So, it would first have to be established that the free provision of services is seriously handicapped by national differences in the use of residual tissue and data for research. That might have been the case, but is not anymore when the coordinating principle of the Tubafrost Code of Conduct is applied.

If one has less confidence in this principle, one should be confident that this eventual European Directive will end in a balanced set of regulations and yet takes away national differences. I am much less confident in this respect. The data protection Directive did not reach harmonisation in the use of data for research. The clinical trials Directive did not reach harmonisation either, but has detrimental effects for academic clinical research[60,61] [P. Therasse, (EORTC), EU Clincal Trial Directive: the way forward for member-states, presentation at the ERA conference on Access to Innovative Medicinal Products in the EU, Brussels, 12–13 October 2005] and – partially due to the European rhetoric of the 'utmost level of protection' – for the research to the benefit of certain patient groups.[61–63]

There is a more fundamental argument as well. The idea of Europe should be to cooperate whilst respecting national or even regional differences.[64] That cooperation is intense and the latitude for differences is further narrowed as Europe is – with all its diversity – a community of values as, amongst other things, expressed in the – binding – European Convention on Human Rights of the Council of Europe[65] and the case law of the European Court of Human Rights. Binding instruments on the level of the European Union have been necessary to foster economic growth or to protect us from global environmental risks.[66] It is the dilemma or even paradox of the modern state that it should not interfere with our basic rights and at the same time should achieve a just society and protect us from risks. Some of these protections, both against undue interference and against risks, can only be safeguarded at the international level, overriding national law. But there remains a – large – area where European law should refrain from intervening as expressed in the 'margin of appreciation' doctrine of the European Court of Human Rights or the 'subsidiarity principle' of art 5 of the EC Treaty. The use of residual tissue for research should be one of those realms where the national legislator is competent when at that level a balance has been found between the various human rights at stake here. A sufficient way out of the national differences is reached by the coordinating principle, together with the fact that the hospital where the accompanying data are sent from should be considered the controller of the data. By analogy it should be considered the 'controller' of the tissue.

5. The principles of the Code of Conduct

I will not discuss them at length. The Code of Conduct is a concise document and is easily accessible through the TuBaFrost web site (http://www.tubafrost.org). A detailed discussion of the principles here would be superfluous.

Three of the main principles of the Code of Conduct have been mentioned already, being:

- In principle only fully anonymised or anonymised but coded residual tissue can be used in an exchange program.
- If fully anonymised or anonymised but coded residual tissue is used, the basic consent option is that the patient concerned should have had the possibility to opt-out.
- The coordinating principle: the regulations of the country where the tissue was taken from the patient and was stored decide whether the tissue may be used in another country with possibly different regulations.

The Code of Conduct further issues strict rules of privacy protection:

- Only type 2 data and tissue can be exchanged. The researcher should never be able to retrieve the identity of the patient. On the level of search engine the privacy protection has been further tightened by an extra layer of coding.

The Code of Conduct clearly emanates from research in an academic context. The starting point is that research with residual tissue is meant to improve health care. Researchers are the mere 'custodians' of tissue so that it can be used for that purpose. In the literature the 'charitable trust' model[67] has been proposed in this context. It is not used in the Code of Conduct as such a model is not applicable in continental legal systems. However, the underlying idea is the same. The Code of Conduct leaves it to the participating centres as to how it will secure the aforementioned purpose and other principles of the Code of Conduct like transparency about research projects and cooperation with interested patient groups. This is inherent to a cross-national Code of Conduct which must take into account that national and institutional practices will differ. The 'public' character of research with residual tissue can also be seen in the way the Code of Conduct deals with the delicate issues of patents on the results of research with residual tissue and the 'ownership' of tissue. It does not exclude that patents can be vested but underscores that possible revenues should as much as possible be reinvested in research or health care in general. In the United Sates we see a lively debate about 'ownership' of tissue, recently summarised by Bovenberg.[68] The Code of Conduct avoids this issue, as from a European perspective tissue as such cannot give rise to financial gain.[69] What should concern us is who can do what with the residual tissue under which circumstances. The Code of Conduct gives clear guidelines on this type of question. Most of these have been mentioned above.

6. Summary and conclusion

We have seen a proliferation of international pseudo-law on bio-banking. Though this might provide interesting 'topics' for debate, it should be remembered that this is not law and cannot, for various reasons, surpass national legislation on this issue. This national legislation has led to different outcomes in Europe. This could greatly hamper cross European research projects with residual tissue and accompanying data if the various legislations would be piled upon each other and every project would have to comply with all the rules of all the countries where tissue and data originate from, might be temporarily stored and used for research. There is an easy way out: namely, the rules of the country where the tissue was taken from the patient and stored for further use in research projects decide whether the tissue can be used for such research in another country with different rules. The same applies to the data. The hospital or clinician who provides anonymous but coded data with the tissue sample remains the controller of these data in the sense of the data protection Directive,[6] even – but then by analogy – if these data cannot be considered personal data in the sense of that Directive according to the legal system where they originate. By analogy, the institution where the tissue was originally taken from the patient and subsequently stored for 'further use' for research will remain the 'controller' of the tissue as well.

This and other principles have been laid down in the Tubafrost Code of Conduct. This Code of Conduct emanates from academic research. The direct purpose of academic research with residual tissue is that it will be to the benefit of patients. The Code of Conduct contains several principles which guarantee that this purpose will be achieved. Thus the Code of Conduct stands in the European tradition of health care systems which are based on solidarity, equal access, quality and cost control.[70,71]

Conflict of interest statement

None declared.

Note added in proof

Several developments have taken place since the work for the Tubafrost project was ended and this article submitted. Only a few can mentioned here. On the international regulatory level the Recommendation of the Council of Europe on research with biological material of human origin became available (see: http://www.coe.int/t/e/legal_affairs/legal_co-operation/bioethics/news/Misc%20_2005_%203e%20REV%20final.pdf). The UK Human Tissue Authority started licensing biobanks for research (see www.hta.gov.uk). My critique on Maschke's article, somewhat apodictically mentioned in the text (at note 18) was published in the May Issue of Nature Biotechnology together with her comment. These texts can be found on http://www.medlaw.nl/nl/publicaties/index.html.

Many other publications relate to the present debate on the use of human tissue for research and the proper regulatory regime for such use. It should be remembered that the legal texts refered to in this article are only valid in early 2006 and might change in the future.

Acknowledgement

The Grants are from the European Commission 5th framework Quality of life and living resources QLRI-CT- 2002-01551.

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