EUROPEAN JOURNAL OF CANCER 44 (2008) 1438–1450

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Obstacles to European research projects with data and tissue: Solutions and further challenges

*Evert-Ben van Veen**

MedLawconsult, P.O. Box 11500, 2502 AM Den Haag, The Hague, The Netherlands

ARTICLE INFO

Article history:
Received 30 January 2008
Received in revised form
14 March 2008
Accepted 17 March 2008
Available online 24 April 2008

Keywords:
Privacy
Consent
Observational research
Regulatory issues
Tissue
Tissuebanking
Ethics
Governance

ABSTRACT

Most European biomedical research projects are about data. Research with tissue is about data as well; data will accompany the tissue, and data will be derived from analysing the tissue. Data can be merged with data from various sources, copied and re-analysed in the context of European projects. Privacy enhancing technologies (PET) should be used for transferring data from participating centres to the level where data are being merged. PET provide coding techniques which allow donors to be anonymised and still uniquely discernable. It is defended that under certain conditions two-way coded data can be considered as anonymous data in the sense of the European Data Protection Directive. Divergent interpretations of this Directive and mos t of all about the concept of coded-anonymised data is one of the main obstacles to observational research in Europe. The Data Protection Authorities will have to relax the extremely high threshold before data cannot be considered personal data anymore. Arguments are given for such relaxation. Besides the logic and logistics of data transfer in European projects, it is also about trust and a realistic risk assessment. In spite of the massive dataflow in European research projects no breach of confidentiality has ever been reported. The ethical rationale of such projects can be based on the principles of citizenship and solidarity provided that certain safeguards are met by which that research will remain observational.

However, if the project does not preclude individual feed-back on the outcomes of research, as in theory would be possible with two-way coded tissue, that tissue cannot be considered anonymous. It is argued that in most tissuebanking projects individual feed-back should be excluded. Tissuebanking for research should not turn into medical screening without applying the established criteria for screening to it. If individual feedback is not foreseen, two-way tissue should be considered anonymous, under the same conditions as two-way coded data.

Good research governance is proposed as the way forward in the longer run. Good research governance is about a fair balance between the interests of all stakeholders. It should make the basic principles transparent on which observational research projects are based in line with European solidarity-based healthcare systems. It should encompass principles on how the general results of research will be disseminated, 'conflict of interests' policies, how the issues of intellectual property rights are dealt with, how the confidentiality of personal data of donors is maintained, etc. This should not become an extra bureaucratic layer. A good research governance framework should not establish rules but principles which provide enough flexibility for the specifics of a project, according to the 'comply or explain' principle. Such research governance should be developed bottom-up,

* Tel.: +31 70 3589772; fax: +31 70 3225236.
E-mail address: consult@medlaw.nl
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2008.03.011

by researchers together with the most interested stakeholders, patient organisations. Patients as 'biosocial citizens' are the natural allies of researchers against the 'paternalistic attitudes' of some ethicists and regulators.

1. Introduction

Cancer research often means international cooperation. For rare cancers it would be impossible to include enough patients in a trial without such cooperation. But also for more common cancers only large databases can contribute to the understanding of why certain patients fall ill and others do not, even though they carry the same risk factor such as the brca1 or brca2 gene.[1] It is commonly understood by now that the earlier results of research on tissue based on small amounts of samples contained many false positive correlations.[2] Modern techniques therefore reinforce the inherent trend by researchers to cooperate across national borders. The coffers of the European framework programmes (FPs) are another incentive of course.

All medical research takes places within a regulatory framework. This framework can already be quite complicated on a national level; different layers of national and international rules when cooperating across borders may complicate research even more.[3] Here, I will discuss some of these complications and suggest solutions for European research projects with data and tissue. Since Directive 2001/20/EC and its implementation in national legislation, perhaps even more problems exist for clinical trials in Europe, especially for investigator-initiated or non-commercial clinical trials.[3–7] However, it would require a separate paper to discuss all of them.

2. Observational research: first exploration

2.1. *Observational research: a definition*

The term observational research will be used here to mean

- the research that in principle could be performed without the active participation of the person whose data or tissue are being used for this research,
- without deviating from the standard of care for such a person and
- will not have any direct consequences for the person concerned.

All the three elements are important. The first means that no active action, like filling in a questionnaire or allowing a skin biopsy, is needed from the person concerned to make the data or tissue available for research. The data and tissue are there already. It does not mean that regulations will never require the consent of the person concerned. It simply means that without such regulations, the data or tissue could be used without actively involving the person concerned. The second element means that these data and tissue have to be acquired in the context of appropriate care – if they stem from the healthcare system – and not, in the example given, by taking an extra biopsy for research without saying so. Although this may seem obvious to almost every researcher and clinician, a definition should also be clear for those who believe in bad intentions. And the famous Moore case has showed that such ill-intent exceptionally does occur. Moore was called back to the clinic several times for additional biopsies and data under the pretext of clinical care although it was, in fact, for research purposes.[8] The third element is somewhat more complicated as 'no direct consequences' can be the matter of interpretation. Here it is meant that this research will not lead to decisions about or proposals directed towards the particular persons whose data or tissue have been used in this research. If performing the research leads to a change in the clinical management of the persons concerned it is not (purely) observational anymore. If it is meant to achieve results for the clinical management of all persons in a similar condition, by generalisation of the results achieved in the research, it is observational. This distinction between generalised results which apply to everyone with the same conditions and results which are specific to the donors concerned, is sometimes easily overlooked. No direct consequences means of course as well that no breaches of privacy take place where the information can be used against the persons concerned. Though this may also be seen as a condition to performing such research.

Observational research can be regarded as being the opposite of clinical research. In that case the research will mean that in the interests of research the clinical management of the patient concerned will be changed from the professional standard that is usually applied by the treating doctor. Clinical trials are the most obvious example. Some research can have elements of both such as when incidental findings of observational research are fed back to the patient's clinician. The standard of care would not have led to such analyses of tissue and hence without the observational research there would not even have been the possibility of such feed-back. Or, observational research may follow from clinical research, such as the use of tissue taken for research purposes for further analyses which were not originally foreseen. In some instances the clinical aspect, like taking a blood-sample, is completely subordinate to the observational aspect, as in the UK biobank project.[9] Each of these more or less 'clinical' aspects should be merited on its own distinguishing features.

The distinction between observational research and clinical research matters for regulatory and ethical reasons. It has been argued that 'if we insist that all medical practice requires informed consent the entire field of. . .all retrospective research will have to close down'.[10] All the retrospective research – if done correctly – is observational, but prospective research with data and tissue can be observational as well. There is sufficient evidence that 'informed consent' for

observational research often leads to bias especially for less privileged groups.[11–14] Both arguments might also be used against informed consent with clinical research. However, the ethics are different and so are the regulatory aspects. The main difference relevant in this context is that observational research by itself does not lead to a change in the clinical management of the patient as seen fit for this patient by the treating doctor, whereas clinical research does. Clinical research carries burdens and risks for the person concerned which are absent in the case of observational research. A more extensive argumentation will be given in the remainder of this paper. To mark the difference between clinical and observational research, whose data and tissue are being used for observational research will be described as donors[15] and not as research subjects or participants as is usual for clinical research.

2.2. *Observational research is all about data*

All medical research results in data to be analysed for possible correlations of cause and effect and its consequences for treatment or preventive measures. Even when, as in clinical trials, the correlations seem at first sight rather straightforward, pharmacogenetics may enter the picture.[16] Translational research using tissue for biomarkers as surrogate or additional end-points of a study is about data derived from analysing the tissue. Tissue analysis outside the context of a clinical study is about data as well: from the tissue, from exposure (whether environmental, lifestyle or iatrogenic) and from fenotype and other consequences for the donor. And of course still there are the classical epidemiological studies about exposure and consequences without the inference of data derived from tissue-analyses. So, it is all about data and nowadays large multinational databases are needed for the more nuanced correlations researchers hope to find.

Research with these databases is usually observational research. Even if at the start, data or tissues are gathered for a specific project with the participation of the persons concerned, as in a panel-cohort study, when merging data in a larger (European) database and opening this for additional questions and queries, the research will become observational.

2.3. *Threat or chance?*

For researchers data, in contrast to almost all tissue, have the great advantage that they can be copied, transmitted, merged and analysed without any major difficulties. Data used for one purpose can in principle be used for another purpose if sufficiently common definitions have been used. For the donors this proliferation of data may pose a threat to their privacy. In a more far reaching view, their autonomy to decide about possible observational use of data is at stake, even if these data do not relate to them personally anymore. The fact that these data can be genetic and can be derived from residual tissue has sharpened this view.

The EC has issued a Data Protection Directive,[17] which has not resulted in harmonisation regarding the use of data for medical research.[3] The balance between privacy and autonomy on the one hand and the interests of other patients or the public at large to profit from the results of observational research on the other hand has been, and remains, a topic which divides many lawyers and medical scientists, and influences the interpretation of the Directive both on the national[18] and on the European level. To put it bluntly: as against remarks from lawyers who see the possibilities of using 'personal data' for observational research without full consent as infringements of privacy which should as much as possible be curtailed,[19,20] medical scientists see the present hindrances of observational research as an abortion of possibilities to prevent disease or offer adequate cure once it has occurred.[21–24] When data are used for observational research, people in general, and patients in particular, seem more inclined to the scientists' view than to that of the lawyers who claim to protect them and seem ready to waive consent.[25] However, when residual tissue is being used for research, people seem to prefer consent or authorisation, though this preference is towards much more general and broad consent than some lawyers or regulators have suggested.[26–28a]

2.4. *Ethical point of reference*

The brief discussion in the previous section raises difficult ethical, regulatory and practical questions for observational research. Discussing the ethics of observational research in full would by far exceed the scope of this paper. The remainder of this paper will be dedicated to the regulatory and practical issues on the European level. However, regulations contain phrases which are ambiguous or leave a margin of discretion to be translated into actual practices of compliance and control, ranging from giving guidance as a regulator in a governmental agency at the central level or reviewing a protocol in an ethics committee at the institutional level. These interpretations will be influenced by the conceptions of the ethics of observational research that applies to a certain extent to the solutions proposed in this paper as well. Hence a brief clarification.

In this paper, the ethical aspects of observational research are seen from the angle of a just society where data and tissue can be used for observational research, if certain safeguards are met, as a form of solidarity and citizenship.[29–31] This suggestion can be linked to newer trends in ethics towards reciprocity, mutuality, solidarity and citizenry described elsewhere.[32] Such an approach is broader than regarding donation for observational research as an act of 'beneficence'. Medical ethicists seem to have certain problems with finding a moral basis for beneficence,[33,34] though it could very well be argued that even in the more restrictive views of this concept the balance between doing well and the individual sacrifice for such an act would lean in favour of 'beneficence' as there is no individual risk or sacrifice with observational research as defined here. Both aspects, no risk and no sacrifice, need a brief discussion. Regarding the risk, sometimes the concept of possible 'group harm' or 'group privacy'[35–37] is invoked against observational research. However, for disease-driven observational research this concept seems more of an invention by ethicists

[a] The problem with such surveys of preferences is that the question posed will already bias the answer. Hence, this 'empirical normative research' will be largely ignored in the remainder of this paper.

and lawyers than something felt by patients. It cannot be seen in publications as to how patient groups look at observational research. If anything they want to become real stakeholders in more observational research,[8,38,39] which is altogether different from protection against such research. Patients have become, in Rose's 39 terms, 'biosocial citizens'. People add biosocial knowledge to their life plans and look at their next of kin, their friends and peers to see whether this applies to them and how to cope with this knowledge, sometimes forming new alliances and forms of solidarity and knowledge. Even when the monogenetic causes for disease are concerned, the results of research are usually not seen as possible threats to their 'group privacy' but as new pathways for coping with their condition.[39]

The sacrifice could be seen as a sacrifice of the autonomy of the donors. That is the position of some lawyers and ethicists[19,20,40,41] and in many international recommendations on the ethics of observational research, where the issue is seen as a balance of individual rights and the possible necessity to 'transgress' these in the interests of society. Though this may lead to the same outcomes, it is a different and usually more restrictive approach.[3]

This approach presupposes that autonomy extends to decisions which do not have any direct consequences for the person concerned, hence the decisions which are not about someone's lifeplan anymore but could affect others. It would by far exceed the length of this section to discuss that position. It should be sufficient to say that in a democratic society such decisions are usually made on the political, aggregate level within the context of a discussion, to which all can contribute and all have a vote, of what constitutes a just society. The European healthcare systems are solidarity-based: the healthy contribute part of their income to the sick, the younger to the older, etc. It is difficult to see why it may not be expected that someone should contribute to observational research which does not effect the personal lifeplan of the donor but from which other patients will profit on the longer run. Basing the ethical rationale for contributing to observational research on solidarity and citizenship, as these are embedded in the solidarity-based European healthcare systems already, will also help to avoid ending up in a conflict-ridden debate about ownership of tissue as is the case in the US.[42] It has been shown elsewhere that 'ownership of tissue to patients' leads to a 'tragedy of the anti-commons'.[43,8] Viewing the healthcare system as 'commons' will be more appropriate to Europe than to the US.

3. Using data (and tissue) for observational research in European research projects

3.1. A 'multi-level' approach

The basics of European projects are, with hardly any exception, characterised by the following approach:

(a) Data and/or tissue are collected on the national level by the participating institutions (hereinafter PIs).
(b) Data from donors at the PI or about tissue at the PI are transferred to a European database on the project (B).
(c) In this database, data are merged and can be used for research with a much higher statistical power (C). Though C depends on B, B and C should be analytically distinguished, as will be shown later in this paper.These are the very basics. See Fig. 1 (with two-way coding). Especially when tissue is involved, the following variations can be seen:
(d) Database B is not used as in C. Data about the available tissue at the PI are transferred from B to a database D, which is accessible to researchers under certain conditions. The researcher will see what tissue is available and through the guardian of database B can contact, again under certain conditions, the PI to gain access to the tissue to perform research on it. It will depend on the degree of 'centralisation' of the project what the conditions are to get access to collections from the PI. This situation can be referred to as a 'virtual tissuebank' (see Fig. 2).
(e) The tissue is analysed for research purposes at a laboratory other than the PIs. Data from this laboratory are sent to database B, usually to be merged with data about clinical outcomes from the PI which has sent the tissue to the laboratory, as with data from other PIs.
(f) There is a central European tissuebank for the project.

3.2. A brief remark about the first level and a caveat for European projects

How data or tissue can be made available for research at the PI will not be discussed here. That will depend on the national

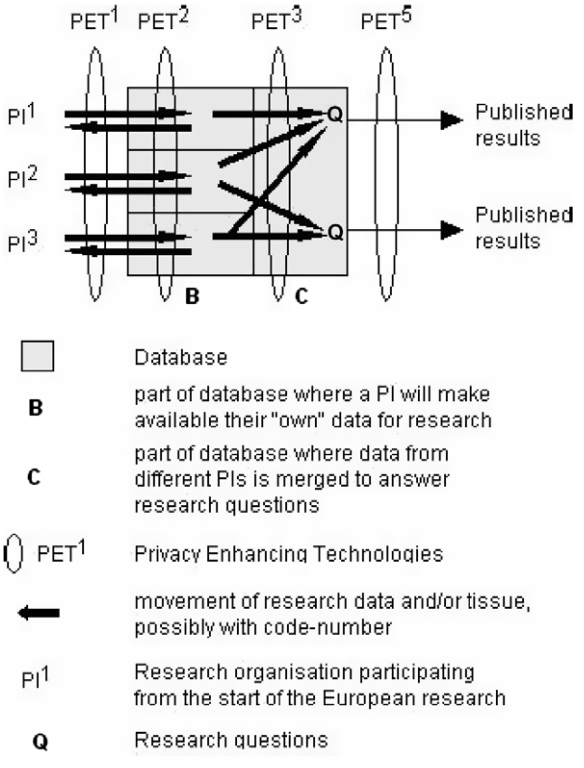

Fig. 1 – Dataflow in a European studies.

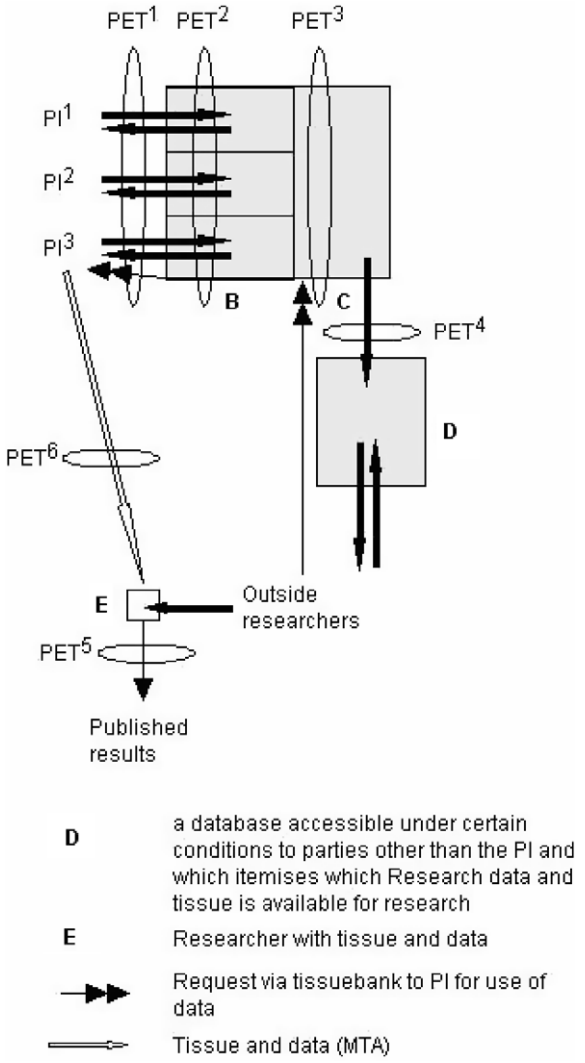

Fig. 2 – Dataflow for a virtual tissuebank.

legislation. The starting point here is that it has become available for research according to this national legislation. The following discussion is concentrated on how this material can then be used for steps leading to B, etc. But one caveat should be made in this context. Often one sees in an European project a 'uniform informed consent' model being used. However, national legislations differ. Some countries are more strict about observational research than others.[3,19] 'Uniform informed consent' means in practice the consent system of the country with the strictest regime. It can mean the loss of material from other countries, especially if this uniform model would be difficult to implement in their system. Here, it is submitted that it is best not to focus on uniform consent forms. It should be the responsibility of the PI that data or tissue become available according to legal and ethical standards applicable there. Admittedly this might be less convincing when explaining the ethics in a FP proposal than referring to the 'highest ethical standards' or international guidelines, recommendations and the like which sometimes set stricter standards for observational research than national legislations. Elsewhere, it has been suggested that democratic national legislation should count in European projects.[3]

Another reason for using uniform informed consent according to the 'highest standard' can be the fear that otherwise data or tissue cannot be exchanged between countries with different regimes. However, that fear is not correct as will be shown below.

3.3. *PET and the set-up of the project*

For the procedures mentioned in Section 3.1, two types of safeguards have to be met:

- The conditions under which data or tissues are available for research at the PI should follow the further logistics of data or tissue to B and the other steps in the chain of events.
- Adequate privacy protection for the donors starting at level B, hence already in the transfer of data from the PI to B.

Both safeguards are pretty self-evident. It will require the necessary procedural and technical measures to achieve them. These measures are usually referred to as 'privacy enhancing technologies' (PET).

When sending data to B, PET should always be used that make the data of the donors anonymised on that level. However, although fully anonymous data may provide useful statistics, it does not usually provide good research. In most studies, one wants to add new data about the donor from the PI or use the data from various sources at C.[44,45] Donor *x* should be uniquely distinguished for that purpose. Additional data should not be added to *x*2. This is done through a coding mechanism where the personal identifiers of the donor are replaced by an unique code number. At the level C or D, usually the data are also anonymised for the PI. The code to the PI is then held at B, though usually entered at the PI already together with a code number of the donor.

Anonymisation does not always lead to anonymous data in the sense of the Data Protection Directive. Whether data (and tissue) can be considered anonymous is extremely important for the set-up of the project. Anonymous data can always be used for research. The Data Protection Directive does not protect the more far reaching view of privacy mentioned, namely that one should be able to decide about what is being done with 'your' data even if there they have been made anonymous.

If data are not anonymous, they are personal data according to the Data Protection Directive. This has two consequences:

- In principle, consent is needed to use personal data for research. The Directive allows for exemptions on this principle. As already mentioned these have been implemented very differently throughout Europe. PET can be used in some countries to waive consent – though under very different conditions – but not in all.
- The controller–processor distinction will apply to the data-chain from the PI onwards.
- Here, the criteria for considering coded data as anonymous data in the sense of the Directive will first be discussed. After that a discussion will follow about the consequences for the data-chain if they are not.

4. Coded anonymous data

4.1. *Personal data versus anonymous data in general*

According to the Data Protection Directive (art. 2.b), personal data are 'any information relating to an identified or identifiable natural person ('data subject')'. An identifiable person is someone who can be identified, directly or indirectly by – in short – certain characteristics relating to that person. Recital 26 of the Directive gives a description of what determines whether a person can be identified: 'account should be given of all means likely to be used to identify the said person'.

'Likely to be used' refers to a contextual approach and a certain reasonableness test. Data which cannot be considered identifiable by one holder of the data, like a researcher, could be considered identifiable by another, like the police. However, as shown elsewhere, researchers are presumed by some Data Protection Authorities (DPA) using policing methods to re-identify,[3] even though researchers are not interested in persons as such but are interested in patterns of persons. This tendency towards a broad interpretation of the concept of personal data is defended in an Opinion of the so-called art. 29 Working Party on the concept of personal data.[46] This 'working party' has been established according to art. 29 of the Data Protection Directive and is composed of the members of the national DPA. It is argued that the broad interpretation is necessary to supervise the use of data. Anonymous data are 'free' and hence would escape the supervision of DPA. The Opinion argues that the Directive provides sufficient flexibility for less stringent regimes when processing data for research which have only a very remote chance of being re-identified, but must still be considered to be personal data because of this broad interpretation.

4.2. *Terminology of coding*

Coding means replacing the identifiers of the donor by a code number (CN). For the following discussion, we presume that insufficient indirect identifiers are then left to make the donor indirectly identifiable by those indirect identifiers.

Coding can be done 'one way' or 'two way'. With one-way coding it is always possible to translate the identifiers (ID) of the donor into the CN, but not the other way around. It is not possible to go back from the CN to the ID. With two-way coding the latter is possible. There are two 'keys' in that case. A key to translate the ID into the CN and a key to translate the CN back into the ID. See the list of abbreviations given below:

B	the database where data for the research project, usually only from the PI, are sent to
C	using the B for research questions
D	a database which is accessible under certain conditions to other parties than the PI and which shows which RD or tissue is available for research
ID	characteristics of the donor which make his or her unique identification directly possible, like full name, full birthdate, gender and address
CN	code-number which stands for the unique ID of the donor, but cannot reasonably be translated back to this ID by someone who is using this code-number, except in the case of two-way coding for the party who holds the key to this re-identification
MTA	Materials Transfer Agreement, the contract under which one researcher or research organisation is allowed to use tissue sent by another organisation.
PET	privacy enhancing technologies
PI	the research organisation which is participating from the start of the European research project, usually as a 'contractor' in the sense of FP programs.
RD	the data which are necessary to answer the research questions
TTP	Trusted Third Party
x	a particular donor

Together with the CN research data (RD) are transferred to B. RD such as disease, date of birth, gender and environmental circumstances (where one lived, worked, etc.) can be indirectly identified as well. As already stated, it is assumed here that the aggregation level of these RD data is sufficiently high to make indirect identification impossible. Especially if one has an unique ID of the donor by a CN, it is possible to replace data which can function as identifying data and are necessary as RD by data on a higher level of abstraction, like year classification instead of full birth date.

Coding is always done at a point before the step where the coded data are used. For example, at the PI when data are transferred to B or at B before the use at C and so on.

'Double coding' should be distinguished from one-way or two-way coding. Double coding means that CN-1 is replaced by a CN-2 as an extra level of protection,[47] an additional PET. For example, when data are transferred from B to D, a new key might be employed. X's ID is then double coded. Additional aggregation of the RD might be employed here as well, namely to just those which are needed for queries in the more generally accessible database. This can be seen as an application of the 'minimal data use' principle which should guide PET. No more data should be used than are necessary for the methodology of the research project.

Single or double coding does not raise a principled discussion whether CN+RD are personal data or anonymous data. It can be a matter of practical assessment whether the CN (or the mechanism behind it) is sufficiently secure not to allow for translation back to the ID or whether the aggregation level of the RD is sufficient not to allow for indirect identification.

One-way or two-way coding does raise this principled discussion. With one-way coding data it will become anonymous at the next step, given that the conditions just mentioned are fulfilled. With two-way coding it is, in principle, possible to go back to the ID. Though not by the receiver of the CN+RD but by the sender, like the PI. Some data protection authorities (DPA) hold the view that if coded data can in principle be re-linked to the ID, even if not by the receiver of the CN+RD, they are always personal data. However, that view is not correct as will be shown below.

4.3. *Two-way coding can be anonymous*

In many projects one-way coding will be sufficient. One-way coding allows for additional batches of data to be sent from the PI to the B, where the additional RD will be added to each *x* to which they belong. Or that data from various sources, like hospitals and death registries can be merged at B, which, by using the same key to translate the ID into the CN, will end up at each *x* to which these data belong.

Sometimes this procedure will not be sufficient. At B only minimal RD are assembled and for certain projects one wants additional data about certain *x*'s of the PI. Or in the B–D construction the external researcher who is allowed to contact the PI, needs certain tissue. That usually can only be achieved if the PI can re-identify the donor. In these cases one will need two-way coding by the PI. Unless the PI would already have more one-way coded RD than are sent to B or there would be a separate tissuebank at the PI where the tissue is stored under a one-way coded CN. These situations are exceptional.

For the following two things have to be borne in mind. They are probably obvious to researchers, but, as it seems, sometimes not for DPA.

- Whether data are identifiable or not, the reference point is the holder of these data. So can that holder identify *x*? The aforementioned Opinion explicitly acknowledges this. So, irrespective of these being at some level in the data-chain they are identifiable. They are always identifiable at the start, otherwise the PI could not translate the ID into the CN.
- Uniquely distinguishing persons at the level of the holder of the data, as is necessary for research, does not mean identifying them. To group RD under *x* at B and not attach them to *x* – 2 can be done without knowing who *x* is. As it has already been said, researchers are interested in patterns, not persons. The Opinion (p. 16) is less clear about this when it states that when 'scattered pieces of information' are linked to one person, this means identification. That does not always need to be the case. It can also be a unique linking which can be achieved by PET using a CN without identification at the level of the holder of the data.

From the above it follows that if at some level in the data-chain identification is possible, this does not mean that the data are identifiable, hence personal data, at other levels. That all depends.

There is no principled difference between the following situations:

- The PI sends at point *t* RD of *x*'s under their CN to B, and at point *t* + 1 additional data about *x*'s under their CN. Additional RD are added to the existing RD under each *x* to which they refer to. One-way coding is used.
- The PI sends at point *t* RD of *x*'s under their CN to B. At point *t* + 1 additional data are needed at B, perhaps which had not been foreseen in the original dataset. The PI uses two-way coding to retrieve these additional RD and sends them under the CN to B.

The DPA which hold that two-way coded data are always personal data face a logical problem here.

However, it not only matters at what level the RD are re-identifiable, but also matters what use is made of them and the individual consequences for the donor. In the above examples, the RD were used to find patterns, scientific knowledge, hence generalisable hypotheses about all persons who hold certain characteristics for which the *x*'s of the research have served as mere examples.

If knowledge would be acquired specific to one *x* or more *x*'s and fed back to the PI to be added to the medical file of *x* using two-way coding, the situation is obviously different. That is not just observational research anymore. In that case it should be acknowledged that the data-chain is meant to acquire personal information about the donors. Though some levels will use anonymised RD, they cannot be considered to be anonymous data.

Whether such individual feed-back is possible will very much depend on the nature and set-up of the research. For nearly all European projects using only data such individual feed-back is scientifically not possible. One will find patterns, but nothing specific about the donors. Hence, two-way coding at the PI will still generate anonymous data. For projects which use tissue alongside data, one could in theory find something specific to the donor, and hence the individual feed-back could sometimes be possible. In the section on tissue it will be argued that individual feed-back should usually be ruled out in the set-up of the project. In those cases, two-way coded tissue can still be considered to be anonymous tissue.

4.4. *It is not only about logic but about accountability and trust as well*

Some DPA might not be convinced by the fact that one-way or two-way coding is not logically different if individual feed-back is not possible. Additional arguments are used, as also can be seen in the Opinion of the art. 29 Working Party. They come down to the fear that two-way coding can be more easily 'cracked' by researchers at B, either by using hacking techniques or just a phone call from the researcher to the PI to be informed which person is behind a certain CN.

This challenge is harder to meet. It is not about logic and understanding the data-chain anymore but about (dis)trust. Regulatory authorities are built around distrust and lawyers thrive on it. However, one can also exaggerate. A basis of trust is necessary for economic prosperity[48] and as it seems for most other social values as well. A reasonable level of trust is even necessary for society to remain democratic. From a regulatory perspective a continuum of supervision exists to preclude breaches of the law. At one end of the continuum, expressing more distrust, one may see the arrangement where all the possibilities of breaches which very hypothetically might happen are eliminated by detailed standards set by the regulator and in order to act one needs the authorisation of this regulator. At the other end, expressing probably the most trust, there is no regulator at all but a free market and criminal and tort law as corrective mechanisms. The latter has been the basic principle of the 'law and economics' school in the US. It has severe limitations[49] and is certainly not the general principle put forward

here. However, placing everyone at the first end of the continuum would completely stall all economic and societal activities, stifle creativity and so on. There are middle positions such as relying on administrative and technical procedures from organisations to prevent possible breaches by that organisation and their staff. The organisation needs to make these procedures transparent. In the regulatory continuum adherence to these procedures can be organised in various ways, from regular inspections to self reporting and anything in between. Where on the continuum a certain activity should be situated will most of all depend on the 'risk' of that activity. Risk can be seen as the sum of the harm done and the chance that this harm will occur. Harm done by breaches of confidentiality of RD could be great, though – as it seems – less great, more incidental, than harm done by neglect in safety precautions in the food chain or disclosing personal identifiers for internet banking. The chances that such harm by observational research will occur are extremely remote. In spite of the rather massive flow of RD throughout Europe no breaches of confidentiality have ever been reported. Researchers, apart from lacking any personal interest to retrieve the ID of a certain x in the large database B of x's with CN+RD, are very well aware that the future of research in general and their career in particular depends on adhering to high standards of confidentiality. Hence, it is submitted that researchers and their institutions merit – in principle – a form of trust in the middle of the continuum and should not be regarded in the same way as companies who gather data for marketing purposes are, let alone as potential criminals.[50]

This contextual approach is not contrary to the Data Protection Directive. It even follows from Recital 26. Nevertheless, it is admitted that 'stupid trust'[10] will not be sufficient. The project should have transparent and accountable procedures about how it will uphold confidentiality. Next to the 'minimal data use' principle the 'minimal data access' principle will have to be employed to RD with a two-way coded CN, etc. 'Intelligent audits' as described by O'Neill[10] might be a complimentary safeguard. Under certain circumstances, the key to the CN could be held by a trusted third party (TTP). The TTP construction may have certain advantages for large databases where data are supplied from various PI. The TTP can then also provide the technical tools for coding and decoding under specific circumstances agreed beforehand in the protocol. However, the private companies which offer such tools are very expensive and the advantages of the TTP have to be weighed against the disadvantages, especially these additional costs. Mere lack of trust in confidentiality standards by researchers should be an insufficient reason for employing a TTP.

If safeguards mentioned are set in place, coded-anonymous data should be regarded, under the conditions described earlier, as anonymous data in the sense of the Directive.

The DPA will not be empty handed when data can be considered anonymous by these standards. It has a role in deciding whether they will be anonymous. That discretionary power must be used in a reasonable way, and, as has been discussed, based on a reasonable level of trust which, as past experiences show, is merited by researchers.

The DPA might also demand a role in reviewing the accountability of the research-organisations that the data have remained anonymous by these standards. The latter is indeed a modification of the system of the Directive. One data are declared 'anonymous', they are free to be used in whatever way. Hence, the tendency for a very high threshold before they are declared anonymous.

However, the 'flexibility' mentioned by the Opinion referred to, for using data for research which are anonymised but still personal data according to this high threshold, does not exist in many countries. Though this flexibility is embedded in the Directive, some countries have not chosen for a lighter regime for such data.[3,47] In others, that possible flexibility gives rise to much discussion.[18,51] In the Netherlands, in order to use such data for research the researcher has to meet many conditions. Bias is not a reason to waive consent; difficulties reaching all donors can be a reason. In that case, the researcher has to show that the patient has had a realistic opportunity to opt-out.[3,52] In the Dutch healthcare system, hospitals are autonomous on this point and due to sheer lack of interest many have not implemented this opt-out system. The next problem is that if they are still personal data the controller–processor system must be applied to the datachain. This may help for some aspects of dataflow through Europe, but it gives complications for others, especially in the context of observational research as will be shown below.

Hence, the pressing need to consider them anonymous if observational research is to continue. It will lessen the bias problem attached to consent procedures and will allow room for further observational research in Europe. On this special issue it has been suggested that the Data Protection Directive should be amended to enable population-based cancer registries.[53] This suggestion would then apply to registries of other diseases as well. Amending the Directive would be a lengthy and complicated process. It seems more fruitful to focus on a reasonable interpretation of the Directive as proposed here.

5. When the data are still personal data

5.1. *Controller–processor distinction*

Controller means 'the natural or legal person, public authority, agency or any other body which alone or jointly with others determines the purposes and means of the processing personal data'. 'Processor' means 'the natural or legal person, public authority, agency or any other body which processes personal data on behalf on the controller (without being subject to the direct authority of the controller)'. There is always a controller of personal data; there is not always a processor. The legislation of the country where the controller is based will be applicable when data are sent to a processor in another country. The controller–processor construction requires a written agreement between the two laying down the conditions under which the processor may process the personal data transmitted by the controller.

Using the controller–processor construction can help to solve two sorts of problems:

- As the legislation of the country of the PI will apply, complications that the country where B is based has another regime for using personal data for medical research will be avoided.

- The processor is not seen as a third party. Data processed by a processor are seen as data still under the responsibility of the controller.
- Hence, when data are sent by the PI to B acting as a processor, this will not be influenced by the conditions for which data may used for research at the PI. B can, within the terms of the contract, use these data as if it were the PI.

5.2. *Problems with this construction when merging at level C*

Within the controller–processor construction data at B will come from several PI. Each PI will be the controller for the set of data which it has transferred. As shown in Fig. 1, one could see this as columns of datasets next to each other. To complicate matters a little, for some of the columns the data will not be considered personal data, depending on the national legislation of the PI. The plan is of course that they will not remain separate columns but that they will be merged for the research, level C of Section 3.1.

In that case several new sets of RD will be created, depending on the research question. Depending on the circumstances – such as whether or not double one-way coding is employed to achieve these sets – they can still be considered personal data. If they are, at least to the background legislation of some of the PI, the question is who is the controller of these new datasets. Either the PI which contributed the data or the holder of B. In the latter case, the constituting data have been transferred to a third party after all. This must be allowed according to the background legislation of the PI. Hence, the conditions for using the data change. The holder will become the controller and the legislation of the country where it is based will apply to these datasets and subsequent steps.

If fully anonymous by all accounts cannot be achieved at level C, the best solution seems to be that the total of contributing PI remains the controllers. This must be reflected in the agreements which constitute B.

5.3. *The set-up will allow the personal data to be transferred to a third party for research*

The complications discussed in the previous section can be avoided if the RD+CN can be transferred to a third party for research. For studies using retrospective data that will depend on the national legislation of the PI and prospective European studies, this transfer could be embedded in the way the data are acquired. It has been argued not to focus too much on a 'uniform consent form' in this respect. Guidance could be given though. In this respect, it is worth noting that 'informed consent' is a phrase derived from medical care and clinical research but which is not used in the Data Protection Directive. If consent is needed in this context, 'explicit consent' suffices. That is a different concept, having a lower threshold for the information to be given.

6. Tissue

The use of tissue for research has not been regulated on the EU level. Regimes differ in various countries. Elsewhere, it is argued that a simple rule could be applicable for the exchange of tissue between countries with differing regimes.[3] That is that the legislation or deontological rules of the country of origin apply. One will see the resemblance with the controller–processor construction where the legislation of the country of origin is applicable as well. The problems with data discussed in Section 5.2 do not exist with tissue as tissue is not merged in the same way as data are. The results of the analyses of tissue are merged, but each sample remains a separate entity.

The materials transfer agreement (MTA), or the research contract in which this MTA is imbedded, usually carries many elements which one also sees in a controller–processor agreement. By analogy, the controller–processor construction can also be useful where countries have put restrictions on the export of tissue to protect their research infrastructure, sometimes under the guise of protecting their subjects. These restrictions are incompatible with the free trade principles within the EU, but it might be better to be pragmatic about it instead of challenging them in court. The controller–processor principle provides such a pragmatic solution.

The principle is applied by analogy for two reasons. It derived from the Data Protection Directive, and we have tissue here. But tissue is data as well. The more important second reason is that the tissue and accompanying data will usually be anonymous at the receiver, following from the analysis in Section 4.

The latter seems at first glance at odds with the Council of Europe (CoE) Recommendations on the use of human tissue for research.[54] Contrary to the EU, the CoE is competent to address ethics as such. In these Recommendations 'coded-anonymised tissue' has a special status with a special consent regime, in brief requiring a kind of multi-choice consent if the tissue is to be used for a broad range of research purposes. This regime is more strict than some countries where broad consent or even opt-out would be sufficient, and less strict than others, which require specific consent for each use of such tissue.[3]

The misconception in the discussion on linked-anonymised or two-way coded tissue is the idea that results in the tissue analyses of each individual sample will be fed back to the patient's file or at least to the sender of the tissue. There is considerable confusion about a possible obligation of individual feed-back to donors as proposed by some ethicists and lawyers. The present international guidelines do not seem to require this[55] or, like many authors on the subject, are ambiguous about what exactly is required and what kind of results we are talking about.[56] Individual feed-back could only make sense for the following types of results of research:

(a) General results which may have immediate clinical relevance for a group of donors or allow prediction of susceptibility to disease and methods for the prevention for a group of donors (sharing the characteristics found). Results will be fed-back to the treating physicians of those donors with these characteristics.
(b) Incidental findings when reviewing the tissue of a specific donor, which could have been found earlier with the existing techniques and state of the science but were missed then and which might have immediate clinical relevance for the donor concerned.

However, most large scale tissuebank projects have ruled out the individual feed-back of type a or type b results for good reason. One of those reasons for type a and b results is that the methods for analysing the tissue are usually aimed at finding statistical correlations and are too crude, not made under GLP conditions, to provide for individual predictions. Another reason for type a results is that those results are usually ambiguous and require further discussion and research about their clinical relevance.[55–57] Even if clinical relevance is clear, the added 'QUALY' (quality adjusted life years) or other side-aspects when offering this as a standard treatment or diagnostic test in health care might still be unclear and will need further debate. The most important reason against the feed-back of type a results is not found in the literature. That is, in the rare case a marker or any other research result would be found with direct clinical relevance and the balance would be positive on those 'QUALY' and other aspects, this result would have relevance to all patients having the correlation found, not just the donors. It should then be incorporated in clinical care for all those patients. It would be un-ethical to offer the new test only to those who donated the tissue (following from the first reason that an individual test would have to be performed anyhow). There are more arguments for non-individual feed-back (both for type a and b) such as simple logistics in large scale projects or the time-frame between the donation of the tissue and the results of research on it.

It has been suggested that reporting back incidental findings would re-establish the researcher–patient compact.[58] However, research on tissue would then become screening, without applying the WHO criteria for such screening[59] and the careful conditions of invitation the target group, informed consent, counselling for those found positive and quality control, which should justify such programmes.[60] In cancer research only a few cancers warrant screening.[53] Those genetic defects which warrant screening will be incorporated in neonatal screening, again based on weighing the pros and cons of such screening and embedded in a careful follow-up programme for those who have been found positive.[60] It would be both medically and ethically wrong to use observational research with large databases for individual screening on diseases. Again this argument cannot be found in the existing literature or international (ethical) guidelines and recommendations which seem to overlook well established principles of public health when discussing the newer topic of tissuebanking.

Neither is research on (residual) tissue meant for the individual review of earlier clinical diagnostics. That was not the condition under which tissue was made available for research by the PI. Furthermore, it is hard to see how the donor would have a right to such a review which would not have happened if there had not been this specific research project. One could conceive of very hypothetical cases where an incidental finding could prevent a life threatening event for the donor. In that case there is an obligation to warn the treating physician and, insofar as is possible, all codes should be broken for that purpose. However, such a case is very hypothetical indeed. Apart form all the other arguments mentioned before, the time-frame between the clinical procedure by which the tissue was taken and the moment of research means that such an incidental finding will nearly always come too late for the donor concerned. But if such a rare case would arise, where it is not too late to avoid a life threatening event, this will be the exception to the rule and should be treated as such.

Hence there are good reasons to construct a watershed between the clinical use of tissue and observational research on it. With such a watershed, tissue will be used coded anonymised for research. Such use can be considered anonymous under the conditions discussed in the previous paragraph.

This does not apply where there is a close link between patient and researcher who is also the patient's treating doctor or in some clinical trials.[52] In that case, there is no such watershed and we do not have the kind of anonymisation or large tissue-databases as is usually the case in European research projects.

No individual feed-back will usually be the rule and if two-way coding is only used as a research tool for requesting additional data, the tissue and accompanying data may considered to be anonymous at the level of the researcher. The sufficient safeguards to demonstrate this, mentioned in Section 4, apply here equally. If on the other hand, the safeguards do not exclude individual feed-back, the tissue and data are not anonymous. National legislation will then dictate which form of consent would be needed.

7. Additional remarks on good research governance

Good research governance, by analogy of 'good corporate governance', is about achieving a fair and transparent balance between the interests at stake. By research governance transparency in research projects can be achieved: how and why specific protocols have been selected, which stakeholders have been involved, how previously mentioned safeguards will work, are 'conflict of interests' policies in place, is data-sharing under researchers other than the PI possible and under what conditions,[61] how the results of research are disseminated, issues of intellectual property rights and how it will be guaranteed that the fruits of research will indeed benefit patients or the public at large in a solidarity-based European healthcare system. In the context of this governance, researchers should seek patient groups as their natural allies and stakeholders in research and try to include them in their European projects as has been the case already in some instances on a national or international scale.[38]

Valuable principles for research governance can be found in the UK Research Governance Framework for Health and Social Care.[62] However, the problems which this Framework has apparently given rise to,[63–65] are precisely an example of how it should not be done. To the problems reported by UK researchers can be added that the Framework cannot be applied outside the UK. Nevertheless, MTA from NHS trusts seem to require so. Apparently, it takes a certain kind of wisdom to understand that not all the principles are rules, that principles have to be balanced against other principles, that they will land in a complex reality which may differ from the virtual desk-top ideas about it and that professionals may have their own story to tell[66] about 'transcendent values'[67] embedded in their activities.

Research governance by analogy of corporate governance should be bottom-up and not be confounded with top down[68]

or 'governmental governance' as it is sometimes understood.[69] It should be applicable on an European scale, it should issue principles instead of a fixed framework and hence allow for sufficient flexibility in the diversity in national legislation and the specifics of a project, according to the 'comply or explain' principle.

For European projects research governance is at its infancy. It is there somehow, from the background of the PI and the inherent professional obligations of researchers. However, it has as yet not been sufficiently articulated for European projects. Reliance on the contract with the EC and additional agreements amongst the PI will not be sufficient for good research governance as that encompasses much more.

Developing principles for good research governance bottom up, with patient groups as natural allies of researchers, seems the way to go forward on the longer run. It may even become a yardstick against which national or international regulations can be measured. And without it, trust cannot be merited on the long run.

8. Concluding remarks

In this paper, a reasonable interpretation of the Data Protection Directive has been proposed, based on a realistic assessment of the risks of observational research and against the background of an ethics of citizenship and solidarity. The advantages of considering two-way coded data as anonymous data are numerous and risks are absent when research is carried out properly. Researchers have shown already that they are able to meet the obligations of confidentiality. Further transparency about the dataflow in (European) research projects and accountability for the PET used could additionally help to convince DPA of this reasonable interpretation. Direct contacts by researchers with the Working Party must be established as well. The discussion of its Report on personal data in this paper showed that at that European level misunderstandings exist about both the nature of observational research and the flexibility of national legislation in making such a research possible.

Until now it has proven difficult to draw attention at the European level to the specific problems of observational research.[b] The EMEA report[4] on the discussion of the clinical trials Directive was a refreshing read as for once problems with an European Directive were mentioned directly and not covered under a thick layer of rhetoric about the highest level of protection, achieving the Lisbon agenda, etc., as is usually the case. Something similar should be achieved for observational research. This paper might be helpful in setting the agenda for such a meeting. It has been proposed here that the possible solutions are less complicated than with the clinical trials Directive, a reasonable interpretation would be sufficient and the Directive does not need to be amended when that interpretation is followed.

In the longer run researchers should establish principles of good research governance for European projects, together with the other stakeholders, most of all interested patient groups. They have an interest as well that research continues, without 'paternalistic attitudes'[30] of ethicists and regulators. Such research governance could show that observational research will indeed come to the benefit of the solidarity-based European health care systems. Perhaps one of the ongoing FP projects could take the lead, even if this has not as yet not been identified as one of their 'milestones'.

[b] In 2006, at the biannual epidemiological congress a special workshop was held about the issues of European epidemiological research projects. All regulators, including all national DPA were invited; none came, except the invited speaker of the Italian DPA. The workshop was fruitful nevertheless because of the contacts amongst researchers established there. The paper on the problems in Estonia (nt...) was first discussed at this meeting.

Conflict of interest statement

Evert-Ben van Veen is director of MedLawconsult. MedLawconsult regularly counsels mostly academic researchers on regulatory and connected ethical issues of biomedical research, such as the projects mentioned in the acknowledgements.

Acknowledgements

Professor Jan Willem Coebergh was a great stimulus to write this article, professor Michel Coleman gave valuable advice on a earlier draft and so did two anonymous reviewers. This article is based on research which is 'translational' to the following projects which I counsel on regulatory affairs and ethical issues: COREON, a group of Dutch epidemiologists and Corese, the network of European epidemiologists on the issues mentioned; SURVEIL, an EC FP 6 NoE on better treatments for viral diseases (contract no: 503359); GENEPI – ENTB2, an EC FP 6/Euratom program to improve radiological cancer treatment by translational research on tissue through a virtual tissuebank (contract no.: FI6R-036437) The views expressed in this article are my sole responsibility.

REFERENCES

1. Easton DF, Deffenbauch AM, Pruss D, et al. A systematic genetic assessment of 1,433 sequence variants of unknown clinical significance in the BRCA1 and BRCA2 breast cancer-predisposition genes. *Am J Hum Genet* 2007;**81**(5):873–83.
2. Wacholder S, Chanock S, Garcia-Closas M, El Ghormli L, Rothman N. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. *J Natl Cancer Inst* 2004;**96**(6):434–42.
3. Van Veen EB, Riegman PH, Dinjens WN, et al. Regulatory and ethical issues on the exchange of residual tissue for research in Europe. *Eur J Cancer* 2006;**42**(17):2914–23.
4. European Commission/EMEA. Report of the conference held on 3 October 2007 on the operation of the clinical trials directive (2001/20/EC) and perspectives for the future.
5. Sheard L, Tompkins CNE, Wright NMJ, Adams CE. Non commercial trials of a medicinal product: can the survive the current process of research approval in the UK? *J Med Ethics* 2006;**32**:430–4.
6. Hearn J, Sullivan R. The impact of the 'Clinical Trials' directive on the cost and conduct of non-commercial cancer trials in the UK. *Eur J Cancer* 2007;**43**:8–13.

7. Carvalho FL. Regulation of clinical research and bioethics in Portugal. *Bioethics* 2007;**21**:290–302.
8. Bovenberg JA. *Property rights in blood, genes and data: naturally yours?* Leiden/Boston: Martinus Nijhoff; 2006.
9. <http://www.ukbiobank.ac.uk> [accessed 25.02.2006].
10. O'Neill O. Accountability, trust and informed consent in medical practice and research. *Clin Med* 2004;**4**(3):269–76.
11. Jacobsen SJ, Xia Z, Campion ME, et al. Potential effect of authorization bias on medical record research. *Mayo Clin Proc* 1999;**74**(4):330–8.
12. Woolf SH, Rothemich SF, Johnson RE, Marsland DW. Selection bias from requiring patients to give consent to examine data for health services research. *Arch Fam Med* 2000;**9**(10):1111–8.
13. Al-Shahi R, Vousden C, Warlow C. Scottisch Intracranial Vasculkar Malformation Study Steering Committee. Bias from requiring explicit consent from all participants in observational research: prospective, population based study. *BMJ* 2005;**331**(7522):942.
14. Jusilahti P, Salomaa V, Kuulasmaa K, et al. Total and cause specific mortality among participants and non-participants of population based surveys: a comprehensive follow-up of 54372 Finnish men and women. *J Epedimiol Commun Health* 2005;**59**:310–5.
15. Oosterhuis W, Coebergh JW, Van Veen EB. Tumour banks: well-guarded treasures in the interest of patients. *Nat Rev Cancer* 2003;**3**(1):73–7.
16. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. *Bioethics* 2006;**20**:24–36.
17. 95/46/EC.
18. Coleman MP, Evans BG, Barrett G. Confidentiality and the public interest in medical research – will we ever get it right? *Clin Med* 2003;**3**:219–28.
19. Beyleveld D, Townend D, Rouillé-Mirza S, Wright J. *Implementation of the Data Protection Directive in relation to medical research in Europe*. Aldershot/Burlington: Ashgate; 2004.
20. Roscam Abbing HDC, Boekrecensie MC. Ploem: Tussen privacy en wetenschapsvrijheid. *Tijdschr voor Gezondheidsrecht* 2006;**8**:632–40.
21. Ingelfinger JR, Drazen JM. Registry research and medical privacy. *New Engl J Med* 2004;**350**(14):1452–3.
22. Academy of Medical Sciences. Using personal data for public good: using health information in medical research; January 2006.
23. Editorial. Striking the right balance between privacy and public good. *The Lancet* 2006;**367**(9507):275.
24. Vandenbroucke JP. Geen voorafgaande 'informed consent' vereist bij wetenschappelijk onderzoek zonder risico of belasting. *Ned Tijdschr Geneeskd* 2006;**150**(11):616.
25. Barrett G, Cassell JA, Peacock JL, Coleman MP. National Cancer Registry. National survey of British public's views on use of identifiable medical data by the National Cancer Registry. *BMJ* 2006;**332**(7549):1068–72.
26. Wendler D. One time general consent for research on biological samples. *BMJ* 2006;**332**:544–7.
27. Kettis-Lindblad A, Ring L, Viberth E, Hansson MG. Perceptions of potential donors in the Swedish public towards information and consent procedures in relation to use of human tissue samples in biobanks: a population based study. *Scan J Public Health* 2007;**35**:148–56.
28. Hamilton S, Hepper J, Hanby A, Hewison J. Consent gained from patients after breast surgery for the use of surplus tissue in research: an exploration. *J Med Ethics* 2007;**33**:229–33.
29. Hoedemakers R, Gordijn B, Pijnenburg M. Solidarity and justice as guiding principles in genomics research. *Bioethics* 2007:342–50.
30. Knoppers BM. Biobanking: international norms. *J Law Med Ethics* 2005;**33**(1):7–14.
31. Swierstra T. *Slachtoffer of burger? Een essay over nader gebruik van lichaamsmateriaal ten behoeve van genomics onderzoek*. Groningen: Nederlandse Vereniging voor Bio-Ethiek; 2004.
32. Knoppers BM, Chadwick R. Human genetic research: emerging trends in ethics. *Nat Rev Genet* 2005;**6**(1):75–9.
33. Holm S. Not just autonomy: the principles of American biomedical ethics. In: Harris J, editor. *Bioethics*. Oxford: Oxford University Press; 2001.
34. Brassington E. John Harris' argument for a duty to research. *Bioethics* 2007:160–8.
35. Custers B. *The power of knowledge: ethical, legal and technological aspects of data mining and group profiling in epidemiology*. Nijmegen: WLP; 2004.
36. Draft CIOMS Guidelines for Epidemiological Research. <http://www.cioms.ch/070516april_epi_revisions.pdf> [accessed January 2008].
37. Hausman D. Protecting groups from genetic research. *Bioethics* 2008;**22**:157–65.
38. Borisch B. Tissue banking in a regulated environment – does this help the patient? Part 2-Patient views and expectations (including the Europa Donna Forum UK Position). *Pathobiology* 2007;**74**(4):223–6.
39. Rose N. *The politics of life itself: biomedicine, power and subjectivity in the twenty-first century*. Princeton/Oxford: Princeton Un. Press; 2007.
40. Brody BA. *The ethics of biomedical research: an international perspective*. New York/Oxford: Oxford University Press; 1998 [chapter 3].
41. Arnason V. Coding and consent: moral challenges of the database project in Iceland. *Bioethics* 2004;**18**:27–49.
42. Glantz L, Roche P, Annas GJ. Rules for donations to tissue banks-what next? *New Engl J Med* 2008;**358**(3):298–303.
43. Spinello RA. Property rights in genetic information. *Ethics Inform Technol* 2004;**6**(1):29–42.
44. Black N. Secondary use of personal data for health and health services research: why identifiable data are essential. *J Health Serv Res Policy* 2003;**8**(Suppl. 1):36–40.
45. Schmidt MK, Van Leeuwen FE, Klaren HM. Genetisch onderzoek met opgeslagen lichaamsmateriaal: een codderingsprocedure met optimal gebruik van informatie bij behoud van privacy. *Ned Tijdschr Geneesk* 2004;**148**(12):564–9.
46. http://ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm; June 2007 [accessed January 2008].
47. Emea. Position paper on terminology in pharmacogenetics. London: 2002 (EMEA/CPMP/3070/01).
48. Fukuyama F. *Trust, the social virtues and the creation of presperity*. New York: Free Press; 1995.
49. Sunstein CR. *Free markets and social justice*. Oxford, New York: Oxford University Press; 1997.
50. Rahu M, McKee M. Epidemiological research labelled as a violation of privacy: the case of Estonia. *Int J Epid* in press, doi:10.1093/ije/dyn022.
51. Iversen A, Liddell K, Fear N. Consent, confidentiality and the Data Protection Act. *Br Med J* 2006;**332**:165–9.
52. See section 5 of the Code of Conduct for health research which has been approved by the DPA for conformity with the applicable Dutch privacy legislation. This Code of Conduct can be found at <www.federa.org> [accessed 29.01.2008].
53. Gouveia J, Coleman MP, Haward R, et al. Improving cancer control in the European Union: Conclusions from the Lisbon round-table under Portugese EU Presidency, 2007. *Eur J Cancer* 2008;**44**:1457–62.
54. Council of Europe, Committee of Ministers. Recommendation Rec (2006) 4.

55. Renegar R, Webster CJ, Steurzebecher S. Returning genetic research to individuals: points-to-consider. *Bioethics* 2006;**20**:24–36.
56. Miller FA, Christensen R, Giacomini M, Robert JS. Duty to disclose what? Querying the putative obligation to return research results to participants. *J Med Ethics* 2008;**34**:210–3.
57. Code on the Proper Secondary Use of Tissue. Explanatory report. Rotterdam: FMWV; 2002.
58. Kohane IS, Mandl KD, Taylor PL, Holm IA, Nigrini DJ, Kunkel LM. Medicine reestablishing the researcher–patient compact. *Science* 2007;**316**(5826):836–7.
59. Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: World Health Organisation; 1968.
60. Gezondheidsraad. Neonatale screening. Den Haag; 2005.
61. <http://www.med.nyu.edu/spa/policies/nih/DataSharing.html>.
62. Department of Health, *Research governance framework for health and social care: second edition*, London, 2005. Available at http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4008777 [accessed 07.04.2008].
63. Editorial. Research governance: a barrier to ethical research? *Q J Med* 2004;**97**:113–4.
64. Editorial. Meeting the challanges of research governance. *Rheumatology* 2005;**44**:571–72.
65. Salman RA, Brock TM, Dennis MS. Research governance impediments to clinical trials: a retrospective survey. *J Roy Soc Med* 2007;**100**:101–4.
66. Campbell AV, McLean SAM, Guridge K, Harper H. Human tissue legislation: listening to the professionals. *J Med Ethics* 2008;**34**:104–8.
67. Friedson E. *Professionalism, the third logic*. Cambridge: Polity Press; 2001.
68. Kerrison S, McNally N, Pollock AM. United Kingdom research governance strategy. *BMJ* 2003;**327**:553–7.
69. As discussed in Gottweis H, Zatloukal K. Biobank governance: trends and perspectives. *Pathobiology* 2007;**74**(4):206–11.