The ACGT ethical and legal requirements

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ABSTRACT:

This deliverable contains an analysis of the relevant ethical and legal requirements for ACGT.

The first part of this document analyzes the ethical requirements regarding clinico-genomic research within the ACGT architecture, especially with regard to informed consent and disclosure of research results. In order to protect patients' autonomy and their right to self-determination – the most basic principles to be respected in the context of medical research involving patients – the informed consent for participation in ACGT has to react in an appropriate manner to these challenges. In ethical terms, a tiered consent offering to donors the possibility to authorize a broader or more restricted range of research to be done with their samples and data and time frame they may be used for research would be preferable. However, this model is difficult to handle in practice. Therefore, a model of consent referring to a purpose of intermediate scope (clinico-genomic research on cancer) in the context of a specific structure or project (ACGT) is proposed, which is within the limits of ethical as well as legal considerations. Concerning the disclosure of research results, it is widely agreed that general research results must accessible for research subjects regardless of the inalienable right of the patients to access his or her personal data. Since clinico-genomic research may also yield individually relevant results, it is additionally recommended that ACGT provides the technical and organizational means for individual feedback processes of such results.

The second part analyzes the legal requirements, particularly with regard to data protection and privacy. The goal to be achieved is to establish a structure where the competing aims of modern genetic research and the data protection needs of the

participating patients can be met. Genetic data is very sensitive data which differs from "normal" data in a crucial point: it cannot be anonymized completely and therefore falls under special requirements for data processing. In order to get as many data protection operations within ACGT outside the scope of the Data Protection Directive as possible, it is recommended to establish a Data Protection Architecture within the ACGT framework, which comprises a double pseudonymization procedure, the establishment of an ACGT Data Protection Board as central data controller and a Trusted Third Party.

Furthermore we analyze the impact of the Directive 2000/31/EC on E - commerce on ACGT. This analyzsis concerns the relationship between ACGT / physicians and researchers, dealing with service provider, users, contract by electronic means, etc. in the context of ACGT.

KEYWORD LIST: Data Protection, Informed Consent, Access To Information, Feedback Of Individually Relevant Research Results, Anonymization

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List of Contributors (authors)

- M. Arning (UHANN)
- B. Clearhout (Custodix)
- S. Castille (Custodix)
- N. Forgó (UHANN)
- N. Graf (USAAR)
- J. Herveg (FUNDP)
- D. Kafetzopoulos (FORTH)
- R. Kollek (UH)
- T. Krügel (UHANN)
- I. Petersen (UH)
- Y. Poullet (FUNDP)
- Cécile de Terwangne (FUNDP)
- J.-M. Van Gyseghem (FUNDP)

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Executive Summary

This deliverable contains an analysis of the relevant ethical and legal requirements for ACGT.

In part 1 of the deliverable the ethical requirements for ACGT are examined. Ethical debate regarding the involvement of patients has a long tradition. In the context of medical research involving patients, the ethical principle of autonomy is generally recognized as one of the most basic principles. Derived from autonomy, the doctrine of informed consent has been widely acknowledged. However, clinico-genetic research addresses new questions, because data are collected and used not only for specific research questions, but also for future research projects which cannot be defined at the time consent is requested. Furthermore, research results may be obtained which could be important for individual patients or groups of individuals (e.g. family members). Facing these new demands, doubts have been raised concerning the applicability of the doctrine of informed consent in its current form. Even though most scholars still maintain the informed consent as an instrument to implement the principle of autonomy, the form and scope of consent in clinico-genetic research is controversially discussed. At stake are three models of consent: the specified consent restricted to concrete research questions; the blanket consent allowing unlimited future research; and the tiered consent arranging different levels of authorisation in the consent procedure. In ethical terms, a tiered consent offering to donors the possibility to authorize a broader or more restricted range of research to be done with their samples and data would be preferable. However, this model is difficult to handle in practice. Therefore, a model of tiered consent referring to a purpose of intermediate scope (clinico-genomic research on cancer) in the context of a specific structure or project (ACGT) is proposed, which is within the limits of ethical as well as legal considerations.

Since clinico-genomic research may yield individually important research results, the question whether and under what circumstances which data should or must be fed back to patients concerned has to be discussed. It is widely acknowledged that general study findings must be accessible for patients involved. Furthermore, anybody has the right to access personal data stored about him or her. But the right to access such data, which is based on ethical principle as well as on legal provision, is a passive one. Therefore, the implementation of this right requires an organisational structure that is suitable to reply to donors' requests. Additionally, it is recommended that ACGT provides the technical and organizational means for individual feedback processes of such results initiated by the investigator. The only way to enable investigator driven individual feedback processes – and to allow individual donors to withdraw consent – is the pseudonymization of data. Therefore, the process of feeding back individually relevant data requires technical mechanisms to guarantee data retrieval by those donors who ask for an individual feedback. Nevertheless, it is controversially discussed what kind of data can be fed back since the relevance of data is not easy to define. From an ethical point of view it is, therefore, recommended to give the patients the option to decide about feedback of personal data.

Part 2 analyses the legal requirements to be fulfilled for lawfully establishing an integrated Clinico-Genomic ICT environment employing data extracted from human tissues. Special emphasis is laid on the issues of data protection and privacy.

The starting point of the analysis is the European Data Protection Directive 95/46 EC, which introduces rules applicable to every processing of personal data and sensitive data on a European level. As every EU Member State has to implement the regulations of the Data Protection Directive into national law, for an EU- wide project like ACGT, this Directive is the common legal basis for all participating states.

Furthermore, the relevant sections of the Directive on Electronic Commerce 2000/31/EC are analysed.

As genetic data is very sensitive data, which holds information not only about the data subject itself but also about his or her relatives, possible diseases, etc., the processing of this kind of data is only possible under special requirements.

The data protection structure to be established for ACGT has to find a balance for the two competing aims of modern genetic research and the data protection needs of the participating patients. In order to comply with current data protection legislation, it is recommended in this deliverable to (de-facto) anonymize as much of the patient's genetic data as possible.

Furthermore a data protection framework has to be set up for ACGT, which consists mainly of three parts. First, an ACGT Data Protection Board has to be implemented. It will be the central data controller within ACGT as well as a legal body able to conduct contracts regarding data protection on behalf of ACGT. Second, a Trusted Third Party is needed in this data protection framework, which is responsible for the pseudonymization of the patient's genetic data and which will also be the keeper of the pseudonymization key to re-identify the patient concerned. Therefore the patient's genetic data is de-facto anonymous for users and participants of ACGT not having the link. Third, contracts between all participating hospitals, research units or other users of the genetic data and ACGT must be concluded in order to ensure confidentiality, data security and compliance with data protection legislation.

For the unlikely case that we will have in some situations personal data anyway, we are confident of still being in line with data protection regulations as we will of course have (also for ethical reasons) informed consents for the data processing from the patients (see D10.1). An explicit informed consent is a major possibility foreseen by the Directive to make the processing of sensitive personal data legal (see Art. 8 para 2 lit a).

1 INTRODUCTION

In the field of genetic research science has made an enormous progress over the last years. This development produces great impact to data protection.

Genetic data of a human being provides information about his parentage, his ethnic descent, about genetic predispositions to complex diseases that are not caused by single genetic reasons and possibly about cure-methods - just to mention some possibilities of use. The recent discoveries include genes that seem to influence whether an individual is overweight, has a gift for dance or will be addicted to cigarettes.[1] The DNA can be procured easily without knowledge of the affected person by means of every nuclear-containing body cell, for example of a lost hair or a cell of the oral mucosa in the toothbrush, and can be pulled up for the answer of any genetic question. Genetic data even provides information about relatives of the data subject and therefore can have significant effect on the family over several generations and in certain cases on the whole group to which the data subject belongs.[2] As genetic information is unique and distinguishes the data subject from other individuals, concerns grow that genetic information could become a modern tool of discrimination. People worry that gene tests and genetic profiling could be used to keep them deemed at genetic risk of certain diseases or conditions from getting jobs and health insurance.[3] Therefore ethic committees and data protection legislation have created strict regulations for the processing of this sensitive data.

ACGT aims to deliver to the cancer research community an integrated Clinico-Genomic ICT environment enabled by a powerful Grid infrastructure. The technological platform will be validated in concrete setting of advanced clinical trials on cancer. Hence pilot trials have been selected based on the presence of clear research objectives, raising the need to integrate data at all levels of the human being (molecular, tissue, organ, patient, disease, individuals, group of individuals). Since ACGT promotes the principle of open access, thus enabling the gradual creation of a European Biomedical Grid on Cancer, the project plans to introduce additional clinical trials during its lifecycle.

The objective of ACGT is to obtain a better understanding of the optimal adjuvant therapy for the individual patient through translational research. In the area of adjuvant systemic therapy for cancer the three most important tasks can be defined as follows:

assessment of risk for metastasis (prognosis);

assignment of differential risk to different groups of patients (patient stratification);

selection of treatment for the individual patient (individualized therapy).

[1] The New York Times selected for SZ. June 26, 2006, p. 1.
[2] Article 29 Data Protection Working Party, Working Document on Genetic Data, http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf, [FN] p. 4.
[3] Wellbrock, MedR 2003, p. 77.

Research pertinent to these tasks will be performed on tumour and blood samples collected from patients involved in pilot trials. Such biomaterials are, on the one hand, valuable resources for biomedical research. On the other hand, they are part of the donor's body. Therefore collection and use of such samples in research is regulated on the international level and in many cases by national law.

One of the essential preconditions for establishing an integrated Clinico-Genomic ICT environment employing data extracted from human tissues therefore is that all research done in this context involving human subjects conforms to existing legal and ethical requirements. In addition, new ethical and legal challenges coming along with such an integrated Clinico-Genomic ICT-environment have to be identified and met with appropriate measures.

2 ETHICAL REQUIREMENTS

2.1 INTRODUCTION

ACGT aims to deliver to the cancer research community a European Biomedical Grid infrastructure, integrating clinical, biomedical, and genomic information on cancer. Since implementation into clinical and scientific practice is envisioned, it is required that this infrastructure mimics conditions and demands of standard clinical trials as closely as possible, and – at the same time – meets the needs of the research community. Therefore the technological platform will be designed and generated in the concrete setting of advanced clinical trials.

In order to assemble and to prove the Grid's structure, several preconditions have to be fulfilled beyond technical requirements. First of all, patients affected by a specific disease (in this case: different kinds of cancer) are needed who volunteer to take part in the ACGT clinico-genomic trials. Secondly, genomic data are needed in addition to socio-demographic and clinical data of these patients. Consequently, samples of tumour and blood have to be collected and analyzed from patients involved in trials which are or become part of the ACGT project.

Such biomaterials are, on the one hand, valuable resources for biomedical research. On the other hand, they are part of the donor's body. At least as long as such samples can be traced back to the donor, they are carrier of sensitive information and therefore protected by personality rights in general. Therefore, one basic prerequisite for establishing an integrated clinico-genomic Grid infrastructure is that all tissue-based research, data collection, processing and storage conforms to existing ethical and legal requirements.

However, no consistent legislation exists within the EU. Collection and use of tissue samples and genetic/genomic data in research is regulated on the international and European level and, in many cases, by national law. Hence, to ensure compliance of ACGT with all relevant legal and ethical provisions, in-depth knowledge of existing legislation is essential, but not sufficient. In addition, it is necessary to analyze clinico-genomic research from the ethical perspective in order to identify new ethical issues emerging in the context of such research, and to draw conclusions with respect to points to be considered in the design of the Grid's infrastructure.

Ethical debate concerned with the involvement of patients in clinical trial has a long tradition. Among the principles which have been identified as being applicable to clinical research, are the principles of autonomy, beneficence, nonmaleficence, and justice. It is generally accepted that autonomy is one of the most basic principles to be respected in the context of medical research involving patients. This does not only apply to clinical research, but also to research involving data and biological material (cells, tissues, DNA) collected from patients. Derived from the principle of autonomy is the doctrine of informed consent. This doctrine has been widely acknowledged in bioethical discourse as well as clinical research.

However, with the establishment of clinico-genomic and biobank research new questions arise. In the context of the ACGT structure, for instance,

- data are collected and planned to be collected and used not only for specific, predetermined research questions, but also for future research projects which cannot be defined at the time consent is requested;

- results may be obtained which could be of possible importance for individual patients or specific groups of patients.

In such cases the questions arise, whether consent can be given in advance to future, still unknown research projects, and whether and under what circumstances which data should or must be fed back to patients concerned (and their doctors) in order to enhance their treatment and to avoid harm. These and other questions have to be addressed and analyzed. This chapter will discuss what aspects ACGT has to take into consideration from an ethical perspective in order to protect the patients' right of autonomy and self-determination and, therefore, to pave the way for ethically designed research settings.

The approach chosen here is not one of normative, but of empirical ethics. The outcome of normative reasoning depends to a great extent on the ethical framework chosen. Since ACGT is a pluralistic research network it cannot be presumed that all partners share the same moral preferences and refer to the same ethical frameworks. Hence, referring to selected frameworks only would be an undue predefinition of ethical positions. For this reason we concentrate on reviewing and summarizing the current ethical literature pertinent to clinico-genomic research, biobank-research and related activities. The aim of such an approach is to identify current positions on the questions outlined above and to find out on what issues consensus is reached and where dissent remains.

2.2 INFORMED CONSENT

In the core of the doctrine stands the principle that any preventive, diagnostic or therapeutic medical intervention as well as scientific research involving human subjects is only acceptable with the prior, free and informed consent of the person concerned, based on adequate information. Furthermore, consent should, where appropriate, be expressed and may be withdrawn by the person concerned at any time and for any reason without disadvantage or prejudice.

Even though the doctrine is globally recognized,[4] informed consent as a condition *sine qua non* for regular and experimental medical interventions is a relatively new phenomenon. It was not before the Nuremberg Code in 1947, that the moral duty of physicians and researchers to obtain consent became more widely recognized. In 1964, the doctrine of informed consent for medical treatment and research became adopted by the General Assembly of the World Medical Association in Helsinki (World Medical Association 1964). The principles of the World Medical Association have been revised and

[4] The importance given to this doctrine today is reflected by the fact that virtually all international agreements on ethical and legal standards in medicine and biomedical research endorse the requirement of consent or informed consent. Examples of international instruments that list informed consent as one of the key principles of biomedical research are: World Medical Association 1964; Council of Europe 1997, 2005; Council for International Organizations of Medical Sciences (CIOMS) 2002; UNESCO 1997, 2003, 2005. For the historical background see D10.1, pp.7.

amended several times. In its current wording, the paragraph on informed consent reads as follows:

„In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing."[5]

This paragraph names the main components of informed consent: comprehensive information, explicit (written) consent to participate in research, and the right to withdraw this consent at any time. In addition, consent must be given on a voluntary basis; the person must be able and free to give consent without coercion or deception. In other words: "Any risk associated with a research protocol must be accepted on a voluntary basis".[6]

2.2.1 Ethical foundations of the doctrine of informed consent

Today, the doctrine of informed consent has been widely accepted in both clinical practice and (bio-)medical research. However, despite broad acceptance, considerable lack of clarity exists when it comes to the question of how the doctrine can or should be applied in practice and in various contexts of application.

2.2.1.1 General aspects

As part of human rights, the doctrine of informed consent represents an essential ethical and legal requirement for medical interventions that protects patients and their fundamental rights to integrity and self-determination. Generally, the requirement for informed consent refers to the principles of 'respect for persons' and 'respect for human dignity'. This means that one should not act against the wishes of human beings and respect their autonomy to consider options and make choices on their own.

However, the fundamental rights to integrity and self-determination are not the only justifications for requirement of informed consent. The duty to inform subjects about key aspects of a treatment or clinical trial can also be justified by the requirement of common decency or minimal respect which we owe others as human beings. Since most people do feel violated if others interfere their bodily integrity without consent, it can also be argued that the necessity to obtain consent is at least to a certain extent independent of social and cultural circumstances.

[5] WMA 2004, paragraph 22

[6] Hansson et al 2006, 267. A lucid summary of theoretical backgrounds for informed consent give Alderson and Goodey 1998. For a brief outline of the history of informed consent see Williams 2001 or, limited to the US, Press and Browner 1995.

2.2.1.2 Informed consent in tissue based research

Whereas ethical discourse focused on informed consent procedures concerning standard clinical research (e.g. drug trials) for a long time, current discussions focus on requirements for consent to tissue based research. In this context, it is widely accepted that the potential donor has to consent to blood or tissue removal. The duty of the investigator to inform the potential donor and ask for consent is primarily based on the ethical principle of respect for the person and her/his autonomy. Thus, the doctrine of informed consent is closely connected to the physician-patient-relationship. Donors provide investigators with 'raw material' to produce knowledge and, thereby, to advance in the treatment of diseases. As a result, informed consent is seen as "one part of honouring the contribution that the person is making to advancement of knowledge".[7] At the same time, to obtain informed consent expresses the recognition of patients' autonomy and his right to choose.[8] Trouet, for instance, underlines that a „source can be opposed to certain uses of his (anonymized) cells or tissues" and, therefore, the donors need to be informed about intended uses of the tissue as well as asked for consent.[9]

The concept of personal autonomy in tissue based research also comprises control over information obtained from tissue samples.[10] "Autonomy encompasses not just the right to self-determination about our bodies and how they are treated, but also to information about ourselves, our lifestyles, and our health."[11] In his investigation of the Australian Law concerning questions of the human body and of privacy of personal information, Alston emphasises that the issue of confidentiality is touched by using bodily samples as well as by using the information obtained from it in research.[12] According to Alston the legal protection of the individuals' right to have control over the own sample is conditional on the "modern significance of bodily samples as direct sources of personal information". From that perspective, biological samples constitute "an immediate source of personal information", a "virtual medical record".[13]

Other scholars draw attention to the importance of informed consent procedures to prioritize the interests of the present research subject in relation to future patients or the society as a whole. "By insisting on informed consent, the medical researcher is forced to acknowledge that the present research subject has a greater ethical claim than do future treatment possibilities."[14]

The importance of informed consent for tissue based research has not only been emphasised in the context of the physician-patient-relationship, but also in a broader sense: Consistently, its importance to build-up trust is highlighted in the discussion.[15] Trouet points out that informed consent is necessary even if the biological material has been anonymized. For him, "[p]atients want to have confidence in their doctors and this

[7] Clayton 2005, 15
[8] See Hansson et al 2006, Chen et al 2005, Clayton 2005, Pelias 2004
[9] Trouet 2004, 100
[10] See Sass 1998
[11] O'Brien and Chantler 2003, 36
[12] Alston emphasises the necessity to differentiate between the terms 'data' and 'information'; the distinction has been compared with that between 'raw material' and 'manufactured product' or between 'medium' and 'message'. See Alston 2005, 434. The perspective of human biological samples as raw material is shared by various authors, as, for example, Reymond et al 2002, 257.
[13] Alston 2005, 431
[14] Banks 2000, 549
[15] See for example Alston 2005, Trouet 2004, O'Brien and Chantler 2003, Clayton et al 1995

trust is violated when they discover that their biological materials are stored and used for other purposes without their knowledge".[16]

Most authors underline the importance of informed consent, but quite a few criticise how it is practiced in modern biomedical research. Although pretending to pay tribute to the principle of respect and autonomy, consent procedures in the research setting often have become a "convenient means of transferring responsibility for risk from the clinician or researcher to the informed patient".[17] In practice, informed consent is often considered as paperwork to be done, mainly for legal reasons.[18] O'Neill draws attention to the fact that "institutions and professionals increasingly see obtaining informed consent as protection against accusation, litigation, and compensation claims". She concludes that the growing importance of informed consent procedures is closely connected to formalisation processes in medical practice.[19] Informed consent, she cites a medical sociologist, has become "the modern clinical ritual of trust".[20]

Focusing on another aspect of practice, Sass criticises current informed consent procedures regarding their practicability. He states that the concept „has outlived its useful life in many areas of clinical research" and proposes that in the context of clinical trials and research the relation between patient and clinician, or researcher respectively, has to be understood as a contractual relationship.[21] Therefore, he wants to see the consent for tissue removal and usage as a contract between patient and clinician. Furthermore, according to Sass "the best protection and implementation of principles of privacy and confidentiality is to play decisions back to the patients".[22] According to this reading, informed consent does not serve as an instrument to ensure patients' autonomy but to avoid litigation and to solve questions of liability.

However, most scholars maintain the importance of informed consent as an instrument to implement the principle of autonomy. Some authors explicitly reject the idea of embedding consent to research uses of tissue samples and data into a contractual framework. Especially O'Neill underlines that consent can not be seen as sufficient justification for research activities: "Even if there is informed consent, we may judge surgery without medical purpose, medical practice by the unqualified, or unnecessarily risky treatment unacceptable and may think it wrong to use human tissues as commodities, as inputs to industrial processes, or as items for display."[23]

2.2.2 The scope of consent

According to international standards, informed consent is required for collecting, storing, and using human biological material such as tissue, blood, or DNA and data processed

[16] Trouet 2004, 100
[17] Alderson and Goodey 1998, 1314; see also Kottow 2004 and Case 2003
[18] Especially in the US-debate it has been repeatedly underlined that obtained informed consent serves as a legal protection tool. See O'Neill 2003, Alderson and Goodey 1998. Clayton et al underline that "obtaining informed consent also serves the interests of researchers by reducing the risk that subjects will pursue legal actions when their expectations about the research are not met. The possibility of unhappiness and even litigation later on may be greatly reduced by early disclosure, discussion, and the opportunity to refuse to participate". Clayton et al 1995,1787
[19] O'Neill 2003, 4. See also O'Neill 2004, 1134.
[20] Ibid, the author refers to Wolpe 1998.
[21] Sass 1998, 295
[22] Ibid, 292
[23] O'Neill 2003, 5

from tissue.[24] As discussed above, this requirement is based on the ethical principle of autonomy. In the European Union, a framework of data protection rules also obligates researchers to obtain consent to data processing and storage.

However, these general requirements are far from clear instructions how to deal with tissue collections or data processing in practice. Especially the issue of consent for future research purposes which cannot be clearly defined at the time consent is sought turns out to be difficult.

2.2.2.1 Models of consent

At stake are three different models of consent: 1) specified consent tailored to the aims and intentions of concrete research projects; 2) broad or blanket consent containing no restrictions with regard to future research, and 3) tiered consent arranging different levels of authorisation in the consent procedure.

2.2.2.1.1 Specified consent

The model of specified consent emerged together with the reverse model of general consent for future research ('broad' or 'blanket' consent) in the context of collecting human biological material. Specified consent is similar to the original doctrine of informed consent which is still practiced in many clinical trials, asking patients to consent to specific clinical trials comprising a limited number of therapeutic and diagnostic interventions and investigations. Basically, the concept of specified consent includes the obligation to inform potential study participants about the primary and secondary aims of the research project in question. They also have to be provided with information about potential risks and benefits of their participation and about their right to withdraw at any time.

Many scholars accept – at least in principle – the position proclaiming specified informed consent as an instrument to implement patient's autonomy. But serious objections have been made regarding the practicability of this model as well as its ethical value with respect to research with tissue samples. Although the argument that specified consent expresses respect for the donor of a sample has been affirmed, it is usually accompanied by concerns that fully implemented, it may be an impediment to research. "The argument would indeed be true if the process of obtaining specific consent did not jeopardise the amount and quality of research that can be done", conclude Hansen et al.[25]

Especially in biobank research or clinico-genomic research tissue or blood samples and processed data are usually collected for a multiplicity of (future) research projects of unknown character. In consequence, the efficiency of tissue based research on the one hand, and respect for confidentiality, autonomy and patients' rights in general on the other hand have been discussed as mutual excluding possibilities. Other authors have criticised this distinction as a rather utilitarian view which does not recognise the principle of patients' autonomy appropriately and is

[24] See Council of Europe 2006, chapter III, article 10, 2 and EU 2004, Annex A. In the Declaration of Helsinki (WMA 2004) research on human biological material is not specified, however, informed consent of the participant is required for any research involving human beings.
[25] Hansson et al 2006, 266

„dangerously reductive".[26] However, as far as tissue based research is concerned, there are some indications that 'amount and quality' of research could be seriously limited by a specified consent model. If operators of a tissue collection are requested to ask a multitude of tissue donors for specific consent for every new research project – possibly over a long period of time – the probability is high to lose a lot of volunteers and, thereby, data for research. In practice requests for reconsent were usually characterised by low response rates.[27] Although up to now only limited experience with reconsent exists, it has been attended by the concern that "the need for renewed consent for use of biobank material would reduce the number of participants available, possibly introducing selection bias and decreasing the scientific importance of the studies".[28] Tissue donors simply might not be concerned with or interested in reconsenting, they might have changed their contact data, or might be deceased.[29] Obtaining specified consent for every distinct protocol "would be contrary to the interest not only of society at large in medical progress but also to the interest of the individual research subject as well".[30]

The model of specified consent is not only impracticable with respect to future research. If specified consent for future research is required before tissue removal the potential donor have to be informed about conceivable research projects and also about imaginable possibilities and probabilities concerning the usage of the tissue. But complete information is hard to achieve, even in the context of standard clinical trials. This applies even more for future, yet unknown research projects. As O'Neill highlights, this demand cannot be met because "the descriptions to which consent is given are always incomplete. We can always add more detail".[31]

Quite a few authors are additionally concerned that the request for specified consent to an amount of research questions and projects might undermine the original idea of informed consent as a process that expresses respect for autonomy and enables the donor to exercise his or her right to self-determination. "Complex forms that request to consent to numerous, highly specific propositions may be reassuring for administrators (they protect against litigation), and may have their place in recruiting research subjects: yet they will backfire if patients or practitioners come to see requesting and giving consent as a matter of ticking boxes."[32] This appraisal is supported by the argument that the amount of issues regularly listed in consent forms may overstrain patients and, thereby, weaken the original meaning of informed consent.[33]

[26] O'Brien and Chantler 2003, 37. As outlined in paragraph 2.2.1/Ethical foundations of the doctrine of informed consent, O'Neill also draws attention to this change in the understanding of informed consent in clinical practice. See O'Neill 2003, 4
[27] See Hansson et al 2006, 266 f
[28] Ibid
[29] Referring to HIV-clinical research, De Montgolfier et al call attention to "the possibility of a number of the participants in the cohort dying". De Montgolfier et al 2002, 668
[30] Consortium on Pharmacogenetics 2002, 12
[31] O'Neill 2004, 1134
[32] O'Neill 2003, 6
[33] Fernandez et al, for instance, examined consent forms of 235 US-institutions; the length of the forms varied between 8 and 50 pages. Fernandez et al 2003a, 2906

2.2.2.1.2 Broad or blanket consent for future research

Albeit the model of specified consent has not been defined and named yet, it has a long tradition in clinical research. In contrast, the model of broad or blanket consent occurs quite recently in clinical practice. Indeed, it has only been discussed with respect to systematic collections of biological samples and genetic data. The model refers to the argument that „in the presence of an informed consent, use of samples beyond purpose might be a violation of the subject's rights."[34] Therefore, investigators are generally interested in keeping the definition of the field of research as broad as possible.

There is also empirical evidence available for patients' lack of interest for consent procedures.[35] Hence, advocates of a blanket consent concept emphasise its usefulness by referring to its efficiency in combining the interests of patients and investigators. Furthermore, it is often promoted by the argument that elaborate consent procedures are costly and time-consuming. Therefore, it would be more cost and time efficiently to simplify the procedure.

Drawing on results of an empirical survey, Wendler et al argue that the consent for new research that differs from the initially consented project or trial can be assumed if donors already did consent to the use of their sample for research purposes. In the survey the majority of respondents declared not to be in need of additional information to consent for further research with their samples.[36] Whereas this concept still relies on an initial informed consent based on the conventional understanding of informed consent, other authors propose to completely replace consent procedures in the context of tissue donation by a model of a simple binary choice. Chen et al, for example, do not see any problem to ask patients simply to consent to the use of their samples for future research or not. Their survey results suggest that this would be sufficient to meet the needs of research participants.[37] On the base of empirical data concerning attitudes of cancer patients, Pentz et al similarly recommend "to offer individuals a one-time binary choice." Although the authors found a certain "level of mistrust", especially regarding possible breaches of confidentiality, "none of these concerns appeared to keep individuals from consenting to having their samples used for research purposes." For tissue sampling in the clinical context, the British Medical Research Council (MRC) even goes further. It recommends having only one box on the consent form which should be ticked by the patient, or the health professional respectively, if the patient does not want his or her tissue to be used for future research. In practice, this 'opt-out' model would lead to presumed consent for future research using the sample: The council argues that the practice would make it easier for researchers in any case to handle stored samples with no consent record attached to them. It would than be reasonable "to assume that consent had been given for its use in research".[38]

In contrast to the rather functional argument regarding the meaning of consent expressed above, proponents of broad consent usually refer to the ethical principles of autonomy, self-determination and doing no harm. To justify a broad consent, the British Medical Research Council, for example, points out that consent procedures could overstrain patients. Requesting blanket consent from tissue donors would

[34] Reymond et al 2003, 353
[35] See Pentz et al 2006, Chen et al 2005 or O'Brien and Chantler 2003
[36] Wendler et al 2002b, 1460
[37] Chen et al 2005, 655
[38] MRC 2004, 3

spare patients as well as relatives with troublesome consent procedures and prevent from psychological harm.[39] A different reference to the principle of doing-no-harm is made by Wertz, who regards obtaining blanket consent for future research as acceptable as long as it is limited to diagnosis and treatment of diseases; it only should "exclude research related to reproduction, mental illness, violence, sexual orientation or other areas of behavioural genetics that are highly controversial", because research in these areas may produce greater than 'minimal' harm, especially to communities.[40]

Referring to patients' autonomy, Hansson et al bring forward the argument that "acceptance of broad consent and future consent implies a greater concern for autonomy than if such consents are prohibited".[41] The authors argue that full respect for patients' autonomy implies to provide them with any possibility of decision-making, including broad consent. To deprive patients of one form of consent would "interfere with self-determination" and thereby "disrespect autonomy". [42] Opining that detailed informed consent for all possible uses of stored tissue in the future "is overprotective of people's autonomy interests", Merz et al support a broad consent model for future research.[43] Although neglecting the legitimacy of blanket consent as far as identified tissue is concerned, in case of anonymized samples they consider it for this reason to be "acceptable".[44] O'Neill argues that broad consent complies with the ethical principles of autonomy and self-determination as long as patients "know they have access to extendable information and that they have given rescindable consent", because then they "have in effect a veto over what is done".[45]

These more or less pragmatic argumentations illuminate that blanket consent can – in the legal sense – hardly be accepted. As Caulfield et al point out, a one-time consent would indeed undoubtedly simplify the research process. However, in their eyes, blanket consent cannot be considered true consent. "Because blanket consents are necessarily vague, they are, by definition, far too general to have much legal weight."[46]

Then again, it seems to be almost impossible to apply the original concept of informed consent to future research projects. As O'Brien and Chantler emphasise, "we cannot meaningfully give consent to the use of our data in future research projects which not yet have been identified."[47] From this point of view – especially in genetic and genomic research – future uses of donated tissue samples as well as processed data scarcely may be anticipated. Because of "the speed of scientific development in the area of genetics and the vast spectrum of potential research hypothesis that may arise (…) there is no way to predict possible future uses of donated samples."[48] As Reymond et al conclude, „the traditional practice of

[39] Ibid
[40] Wertz 1999, 58
[41] Hansson et al 2006, 267
[42] Ibid. Hansson et al also criticise that in clinical settings 'double standards' have been applied; "given that ethics-review boards might grant biobank research without consent, it seems odd that participants themselves should not be allowed to give broad consent to future biobank research." Ibid, 268
[43] Merz et al 1997, 253
[44] See ibid, 254
[45] O'Neill 2003, 6
[46] Caulfield et al 2003, 3
[47] O'Brian and Chantler 2003, 39
[48] Caulfield et al 2003, 2

obtaining consent for unspecified future use of biological samples and data generated from clinical trials is no longer adequate for genetic research".[49]

2.2.2.1.3 Tiered consent models

Concerning the limitations of the two consent models discussed above, a lot of authors are committed to conceptualize a model of informed consent that avoids the shortcomings of specified and blanket consent. Some authors suggest abandoning the original doctrine of informed consent altogether and replacing it by the concept of authorisation instead.[50] However, O'Brien and Chantler emphasise that "moving away from 'consent' should not in any way be taken to imply a lesser need to give patients information and choices, and to respect their rights to privacy and autonomy".[51]

To overcome the uncertainties – especially regarding the apparently intractable problem of consent for future research –, models of tiered consent have been discussed. Such models give patients the opportunity to choose between various alternatives on different levels and thus legitimize the utilization of their tissue in a more or less restricted manner. This model seems to be more in accordance with the empirical findings mentioned above, as well as with the challenges of future tissue based research. As one of the first authors, Wertz suggested a model of choice between at least two alternatives regarding the particular issues: "The fairest approach may be a 'line-item' informed consent that would allow people to express their wishes about alternatives."[52]

Similarly Reymond et al propose to provide patients with information about different options „to help them understand clearly the nature of the decision they are about to make".[53] Alternatives could be: 1) generally refusing the use of their biological material, or 2) permitting only unidentified or unlinked use, or 3) permitting coded or identified use for one particular study only with no further contact, so that further studies are impossible, or 4) permitting coded or identified use for one particular study only with further contact permitted, so that further studies might be possible, or 5) permitting coded or identified use for any study relating to the condition for which the sample was originally collected with further contact allowed to seek permission for other types of studies, or finally 6) permitting coded use for any kind of future study.

Williams suggests a model of tiered consent which already has been exemplified by the US-National Heart Lung and Blood Institute.[54] According to his proposal, three levels of consent have to be recognised for 1) the current study, 2) goals broadly related to the area of the original study, and 3) goals unrelated to the area of the original study. In each level consent should be obtained for the use of the samples by the investigators and collaborators, for the recontact of donors and for the storage and reuse to accomplish the goals of further studies.

[49] Reymond et al 2003, 351
[50] See O'Brien and Chantler 2003, Caulfield et al 2003
[51] O'Brien and Chantler 2003, 39
[52] Wertz 1999, 57
[53] Reymond et al 2003, 353
[54] Williams 2001, 454

A different model of tiered consent is the step-by-step model proposed by Caulfield et al. According to this model, research participants choose at different moments the kind of consent they want to be asked for. As suggested above, an informed consent is obtained for the initial collection of patient's biological material and health information. For subsequent uses participants have to give a 'pre-authorisation'; this means they have to pre-specify uses for which they do or do not wish to be asked for consent in the future. They may choose to be contacted, for example, only in case of clinically relevant findings or, for instance, only if potential commercial applications are being derived. In this model, participants are allowed to give blanket consent for future research, but a broad consent "can only occur by the choice of the participant".[55] Thus, "each individual can specify in advance the extent of involvement in decision-making that is desired. This preserves aspects of autonomy, but neither restricts future uses as much as a full consent model, nor is it as permissive as the proposed blanket consent models."[56] However, in this approach the possibility to get informed about research results of clinical relevance is not taken into consideration. But Caulfield et al argue that biobank or genomic research often involves low penetrance genes. Therefore, "it is unlikely the research results will be of immediate clinical relevance to individual research participants."[57]

From a practical point of view, it is argued – similar to the discussion on specified consent – that reconsent is generally difficult to obtain.[58] Furthermore, bureaucratic obstacles are pointed out, especially the fact that participants have to be requested to inform the research institution, or the sponsor respectively, about any change of contact data. Last but not least, the costs for obtaining reconsent are also mentioned in the discussion.[59] Nevertheless, tiered consent models seem to serve as an alternative to specified and blanket consent in tissue based biomedical research.

2.2.2.1.4 Patients' and donors' perspectives

The question, whether required consent could overstrain patients, is repeatedly addressed in the discussion. This does not only apply to the extent of information given in consent forms, but also to the underlying concept of choice. Alderson and Goodey point out that the current focus on informed consent which is promoted by the concept may create severe problems in the clinical context. They ask if some options in medical and clinical settings, "although seeming to expand choice", rather "impose a tyranny of choice".[60] They conclude that choice „can be more onerous when people are uncertain how to choose among values and rules for choice making".[61]

Less vague, there is empirical evidence to suggest that consent processes may overstrain patients. Presenting findings of an empirical study on participants of clinical drug trials, Corrigan alludes to differences between patients' reaction: Generally, for patients with conditions of a mild and chronic nature the informed

[55] Caulfield et al 2003, 3
[56] Ibid
[57] Ibid, 2
[58] Main arguments regarding the issue of reconsent are discussed in paragraph 2.2.2.1.1/Specified consent. See also Hansson et al 2006, Case 2003, de Montgolfier et al 2002
[59] See Wertz 1999, 57
[60] Alderson and Goodey 1998, 1315
[61] Ibid

consent process "can open up the field of choice", she concludes.[62] But for most of the patients who were seriously ill "the experience of being invited to take part in clinical drug trials was burdensome".[63] Similarly, Gotay refers to a limited ability of seriously ill participants, particularly of cancer patients: „The anxiety associated with cancer diagnosis may cloud patients' ability to process information such as that found in consent forms."[64]

The latter argument is also highlighted by Wertz. She shows clearly that overstraining patients undermines the original idea of informed consent: Patients who do not take up easily or absorb information – for what reason ever – are impeded to exercise their right to autonomy and self-determination. Referring to the situation in the US she calls attention to the fact that "many people are unaware that they gave 'consent'".[65] For example, they do not realise that it is part of consent forms for surgery human that material left behind after the intervention becomes the property of the hospital unless the individual objects within a time frame. Those "'opt-out' procedures are very general", she notes, "and do not specify who will use the samples or for what research purposes or how long they will be stored".[66] Many people, she assumes, "may not notice the statements about possible research uses of samples, because they have more urgent matters at hand".[67]

However, the argument frequently brought forward that research information and consent were "peripheral issues" in a moment when seriously ill patients have to consider "their own future with a serious disease" is also criticised as a pragmatic one.[68] O'Brien and Chantler see it as a mere expression of a functionalist perspective on consent. This view is supported by Case who points out findings showing that researchers or medical professionals used the argument as a means to avoid that informed consent will become prescript in certain contexts.[69]

Nevertheless, to what extent consent procedures may be arduous to patients is still unclear, not only because empirical data concerning the issue remains rare. Results of a survey Kodish et al conducted provide an insight into differences which might exist between clinicians and parents of children with cancer. The interviews with 23 parents and 23 clinical researchers about the information given, the consent process, and its effects resulted in obvious disparities between investigators and patients concerning the question of distress and harm potentially caused by informed consent processes: Whereas ten parents declared to feel less anxious, eight parents felt more anxious. In the investigators' sample the relation was directly opposed: Whereas seven investigators believed that informed consent makes parents feel less anxious, eleven researchers thought the opposite would have been the case.[70] An even stronger disparity between the two interviewed groups can be noticed concerning the amount of information: Whereas eleven clinical researchers

[62] Corrigan 2003, 788
[63] Ibid
[64] Gotay 2001, 1097. That "clouded ability" motivated her to survey on healthy volunteers for assessing participants views on the adequacy of the consent process in clinical trials.
[65] Wertz 1999, 54. See also paragraph 2.2.2.2.2/The character of information provided in the consent process.
[66] Ibid
[67] Ibid
[68] O'Brien and Chantler 2003, 37
[69] Case 2003, 225. See also the discussion in paragraph 2.5.1.2/Community interests
[70] Kodish et al 1998, 2471, 2476, 2478. See also paragraph 2.2.2.2.3/Particularities of consent to research involving children

declared the amount of information given in the consent process being "too much", just three parents did so. A majority of fourteen parents found it "just right", five parents declared it to be "not enough", a statement which only two clinicians agreed to. As the authors conclude, data suggests that clinicians "underestimate how much information parents want to be given."[71]

Concerning the controversy discussion on consent to future research, empirical data suggest that potential donors do not mind the scope of consent. In a survey of 1200 tissue donors in Sweden, a big majority (920 donors) answered with 'yes' to the question whether they are "prepared to let the biobank and the regional research ethics committee decide on the use of your blood". Of those, 308 persons did affirm the phrase „I do not want any further information about new projects that involve my sample", whereas 446 patients „still appreciate information about projects involving my sample". Of the 130 donors who answered the opening question mentioned above with ‚no' or ‚do not know', 110 agreed with the statement „I want to assess and consent to or abstain from every project myself".[72] Interpreting their findings, the authors allude to the cultural specifity of the survey setting. Hence, the results might be specific for Sweden and not representative for other countries.

But the recent qualitative US-study of the views and attitudes of 26 breast cancer patients towards tissue or blood donation for research indirectly supports the presumption that consent for future research projects is not a matter of concern in patients' perspective. Regarding the use of stored tissue for studies that were not planned at the time consent was obtained, the 26 survey participants "generally had no concerns about this and many thought that it was a positive aspect of having donated samples".[73]

Furthermore, empirical data suggests that broad consent for future research is wide spread among patients.[74] In a survey enrolled by Chen et al, for example, more than 87 per cent of the examined "broad range of research participants" authorised future research on any condition whereas only 1,2 per cent of the participants authorised future research only if it is limited to the condition for which the sample actually was removed.[75] Interpreting the results of another survey among 504 tissue donors, Wendler et al summarise that "once consent for research purposes has been given, most respondents viewed additional consent for each type of research as unnecessary".[76] The authors conclude: "These data also suggest that individuals may not think it is necessary to specify which kind of research will be performed when obtaining biological samples initially."[77]

In this context, Pentz et al argue that altruism has a strong influence on decisions concerning research participation.[78] Results of their survey on cancer trial participants suggest that broad consent is widely accepted because altruism remains to be their central motivation for participation. According to the small and culturally unbalanced empirical base, patients apparently seem to have a lack of interest in the question regarding the scope of consent.

[71] Kodish et al, 1998, 2478
[72] Hoeyer et al 2005, 99
[73] Kaphingst et al 2006, 395
[74] See Pentz et al 2006, Kapp 2006, Chen et al 2005
[75] Chen et al 2005, 634
[76] Wendler et al 2002b, 1460
[77] Ibid, 1460
[78] Pentz et al 2006, 739

2.2.2.2 Informed consent and communication

Communication of information is an important aspect of informed consent. According to Beauchamp and Childress, communication is crucial for understanding.[79] Therefore, *informed* consent is not a single act. In fact, it comprises at least four main elements: 1) Provision of information (content, timing, setting, and the way it is communicated); 2) Comprehension; 3)Voluntariness; 4) Explicit declaration (written,or oral).

Thus, a sensitive issue in the context of informed consent is the question how to provide adequate information for decision-making, especially in tissue based research, and, in particular, if children are involved. Approaching this problem, two crucial arguments will be discussed: how to design consent to research as an ongoing process and how to deliver comprehensive and understandable information.

2.2.2.2.1 Consent as a process

Quite a few authors insist on understanding consent to research as "a process rather than an event".[80] But in practice the idea of consent as an ongoing process has not gained much acceptance.[81] "The process model is clearly an ideal, requiring great psychological and pedagogical skills from the physician", Press and Browner state.[82] Therefore, in practice usually "the event model" is realised.[83]

Nevertheless, a "need to see informed consent as an on-going process rather than a discrete act of choice that takes place in a given moment of time" is still postulated in the discussion.[84] Corrigan, for example, emphasises that the understanding of consent as a process facilitates the participants' right to withdraw consent. It "can open up the process of the trial itself, permitting the patient or healthy volunteer subjects to withdraw at any point during the study".[85] In this context Kodish highlights that attitudes of participants can change over time. [86] Referring to genetic research, Knoppers et al underline that ongoing communication with research participants is necessary "to recognise the importance of their altruistic contribution to the progress of research in the field of genetics".[87]

Furthermore, the problem how to adequately inform the research subjects can be approached. Concerning the handling of information some arguments support the idea of informed consent as an ongoing process. As mentioned above, O'Neill criticises the often ritualised understanding of informed consent.[88] Instead of

[79] Beauchamp and Childess 2001, 57 ff.
[80] Kodish et al 1998, 2479
[81] In the drafting of the UNESCO Universal Declaration on Bioethics and Human Rights the requirement for ongoing participation of the person in the provision of consent for medical diagnosis and treatment was proposed by the International Bioethics Committee of UNESCO, believing that giving consent is an interactive process in which the subject should take an active role from the beginning to the end of the research project. However, this procedural conception of informed consent was not fully supported by other bodies involved in the process and hence does not appear in the declaration endorsed by the General Assembly. See Kollek in the press.
[82] Press and Browner 1995, 10
[83] Ibid
[84] Corrigan 2003, 787
[85] Ibid, 788. For the issue of withdrawal see also paragraph 2.2.2.4/The right to withdraw consent
[86] Kodish et al 1998, 2479
[87] Knoppers et al 2006, 1
[88] See O'Neill 2003

providing research subjects with all information available before they consent, she proposes to give just some initial information concerning the general purposes of a trial and offer at the same time an easy access to further, more specified information. Although her first intention is "to give patients control over the amount of information they choose to receive", she also underlines that research participants need time "to absorb further information". [89]

Closely connected to the concept of consent as a process, the issue of communication between health professionals and research subjects in consent processes has been considered to be important. The meaning of verbal reflections and explications for an informed participation in clinical trials is underlined by various authors. "Verbal interaction with the researchers is a vital part of the consent process, especially as many people do not read the documents carefully".[90]

In interpreting the findings of her survey on healthy volunteers in cancer clinical trials, Gotay concludes that "continued communication also can enhance commitment to the study and ensure that the participants are full partners in the research process".[91] She states that compliance over a period of years can only be achieved by continued information about the study and its potential side effects and by the opportunity to ask questions "on an ongoing basis. Even the best consent form and intensive patient counselling at the beginning of the study are inadequate to accomplish this goal."[92] Although related to long-term prevention studies and to healthy volunteers, these consequences drawn from the analysis of survey results are valuable hints for the organization of the process of informed consent in clinico-genomic trials as well.

In this context, the general trust-building character of consent procedures is emphasised. To continue biomedical research, co-operation with patients is indispensable; it can only be achieved by a trust-based relationship between researchers, medical staff and potential research subjects.[93] As Williams expresses, an appropriate consent procedure "protects both research participants and the enterprise of research itself".[94] Alderson and Goodey strengthen the argument by underlining that especially from critical theory's point of view consent is basically seen as a protection tool for patients as well as an "essential constraint on the most powerful profession".[95] In this perception, informed consent is "not regarded as simple, one way medical information giving, but as an exchange of knowledge between doctor and patient so that together they can make more informed decisions".[96]

O'Brien and Chantler conclude: „People want to feel involved, not just in their care, but also in decisions about research and in helping others (...). Communications with patients about what is to happen to them, how information about them will be used, or even what will be done with samples taken from them, seems to be of universal benefit in the provision of care. Its value lies in fostering relationships of trust between doctors and those they care for."[97] Thus, „the focus must be in giving

[89] Ibid, 6
[90] Wertz 1999, 58. See also O'Brien and Chantler 2003, Kodish et al 1998
[91] Gotay 2001, 1099
[92] Ibid
[93] See Hansson 2005, or Williams 2001
[94] Williams 2001, 451
[95] Alderson and Goodey 1998, 1314
[96] Ibid
[97] O'Brien and Chantler 2003, 38

information, providing choice, and respecting patients' autonomy – not on completing the paperwork".[98]

2.2.2.2.2 The character of information

Referring to the principle of autonomy and respect for participants, authors regularly stress the importance of comprehensive and understandable information provided in the consent process. Jepson et al, for instance, underline that information has to be comprehensive, because its purpose is to enable a person "to choose freely between different options".[99] Similarly, Kottow highlights that information has to be complete. "The idea of informed decision-making is incompatible with incomplete knowledge."[100] De Montgolfier et al also emphasise the coherence between comprehensive and understandable information and conscious decision-making: "Not only must the information be truthful, clear, appropriate, complete and up to date", they summarise.[101] The aim has to be "that the patient has as complete an understanding as possible of the consequences of his or her decisions".[102]

However, in practice this concept of information is faced by a number of obstacles. For instance, Wertz points to an intrinsic inconsistency of the approach towards information. According to her, there is a "trade-off between accuracy and completeness of information on the one hand, and the likelihood that people will read and understand it, on the other".[103] Indeed, empirical findings suggest that patients usually lose rapidly sight of the information given in the consent process.[104] Wendler et al, for instance, found in their survey of 130 participants of longitudinal studies that a lot of information was forgotten after consent was given.[105] Similarly, a recent survey of 1200 tissue donors in Sweden resulted in 37 per cent of participants who could not remember whether having received any information at all.[106]

Understanding informed consent as an ongoing process is seen as a possibility to reduce the loss of information as well as the lack of understanding. If participants have the possibility to ask again and get information repeatedly, the problem might ease. Furthermore, as Gotay points out, „novel attempts to make the informed consent process more interactive (e.g. use of new technologies such as videodisks) may result in important information being retained longer".[107] However, since these proposals refer to trials with healthy volunteers, it remains debatable whether the approach would be efficient in clinical trials. As discussed above, in clinical research consent procedures generally have the potential to overstrain patients; in particular if severely ill patients have to understand complex information. As Bernstein summarises, "patients who have just been told they have a devastating condition (…) can hardly be expected to be in a psychological state of mind compatible with understanding all of the additional information the clinician investigator is about to

[98] Ibid, 39
[99] Jepson et al 2005, 193
[100] Kottow 2004, 568
[101] De Montgolfier et al 2002, 668
[102] Ibid
[103] Wertz 1999, 58
[104] See Hoeyer et al 2005, Dawson and Spencer 2005, Wendler et al 2002a
[105] See Wendler et al 2002a
[106] See Hoeyer et al 2005
[107] Gotay 2001, 1099

tell them concerning a clinical trial".[108] Therefore, he even argues that informed consent is "essentially impossible".[109] Although his paper deals with special questions of informed consent in clinical trials in surgery, his conclusion can be referred to the situation of severely ill tissue donors in general: "Given all the forces at play, some obvious and some not, it is exceedingly difficult to achieve full disclosure to surgical trial subjects, to ensure they are at full capacity to comprehend all the material important information, and to obtain a state of complete and unconditional voluntariness. It must simply be accepted that fully informed consent is rare and generally unattainable in most surgical clinical trials."[110]

To cope with this inconsistency, some authors entirely waive the demand for complete and comprehensive information. They rather address the criterion of appropriateness. For Hansson et al, for example, the content of information given depends on its relevance for the decision: "If the information covers all issues that are relevant for a person's choice, then that person's consent is appropriately informed."[111] However, the authors do not explain how to assess in clinical practice the relevance of particular information for patients' decisions. They only mention several studies assuming that "general information on these studies might be sufficient for the donor of the sample to make an informed decision."[112] More generally, they reckon that quality and content of information depend on the nature of research and the level of risk. "When there are more risks and high risks, information must be more detailed and the consent procedure more strict. For research that involves less risk for research participants, less strict information and consent procedures are appropriate."[113] Again, practical aspects of that approach, as the question who defines under which conditions the levels of risk, for example, remain open to discussion.

However, in this context it is indispensable to refer to possible paternalistic attitudes and their influence on the provision of information. Concerning the doctor-patient-relationship, Satin emphasises that consent might be given by patients as "an expression of blind faith in their physician's recommendations".[114] Similarly, Jepson et al see the danger of an "informed *compliance* rather than an informed *choice*".[115] The authors underline that the "provision of information may not be value free and may be used to direct choice".[116]

This point of view is supported by empirical findings. In the survey conducted by Bevan et al 38 per cent of patients who had consented to participate in clinical trials stated that their motivation was to comply with the doctors' request.[117] Interpreting her findings of a qualitative study on participants of clinical drug trials, Corrigan states that patients are looking for advice about the best treatment option and trying to get reassured about their condition by the doctor.[118] "In such a context, the

[108] Bernstein 2005, 271
[109] Ibid
[110] Ibid, 272
[111] Hansson et al 2006, 266. See also Jepson et al 2005
[112] Hansson et al 2006, 266
[113] Ibid
[114] Satin 2005, 293
[115] Jepson et al 2005, 193
[116] Ibid
[117] Bevan et al 1993, quoted by Corrigan 2003, 782
[118] See Corrigan 2003

request to consent can be interpreted as guidance to consent."[119] She underlines that the current model of informed consent "necessitates an equitable doctor-patient-relationship based on mutual participation", but this is very seldom to be found in practice. Contrariwise, "patients and doctors bring pre-existing norms and values to the clinical trial setting that shape their expectations and direct their behaviour".[120] Corrigan concludes that "there is a need for more socially nuanced concepts of freedom, autonomy and consent" and sees "a necessity to open up the debate about consent beyond the current polar opposition of autonomous decision-making and autocratic paternalism".[121]

2.2.2.2.3 Particularities of consent to research involving children

Obtaining informed consent is particularly challenging for research involving children and parents "because of the issue of competence".[122] The ethical challenge is posed by the fact that minors are – depending on age – either de facto or de jure not competent to give consent to research. Hence, the investigator must obtain informed consent from the parents, or legally authorized representatives respectively. In addition, because of different bodily conditions the risks of invasive clinical research might be more severe and might last longer for children and young persons than for adults.

For this latter reason, the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human subjects[123] first adopted in 1964 differentiates between research involving legally (or mentally) incompetent persons with and without therapeutic benefit. Research involving minors is ethically permitted only if the minors involved have direct (therapeutic) benefit and if the authorized representatives have given consent. The EU-directive on the implementation of good clinical practice in the conduct of clinical trials expands the permission for clinical trials on minors if "some direct benefit for *the group of patients* is obtained from the clinical trial".[124] Furthermore, the EU-directive states that the consent of the legal representatives must represent the minor's presumed will.[125]

Moreover, child's assent is necessary if possible. The World Medical Association, for instance, states a duty to gain assent: „When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative."[126] In order to form his/her own opinion, the minor needs according to his or her capacity of understanding information about the purpose and course of the trial, the possible risks and benefits, and implications of participation.[127]

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[119] Ibid, 782
[120] Ibid, 780
[121] Ibid, 771f.
[122] Dawson and Spencer 2005, 233
[123] WMA 2004
[124] EU 2001, Article 4(e), „Clinical trials on minors" (underline added)
[125] EU 2001, Article 4(a), "Clinical trials on minors"
[126] WMA 2004, paragraph 25, see also Directive 2001/20/EC, Article 4(c), "Clinical trials on minors"
[127] Dawson and Spencer discuss suitable formats for children, e.g. multimedia shows. Dawson and Spencer 2005, 234, see also Kurz 2003, 1280

According to empirical data[128] suggesting an unexpected capacity of children to participate in the process of informed consent, their involvement in decision-making has been growing within the last years. Guidelines in the United Kingdom even state: "The application of general principles indicates that, where children have sufficient understanding and intelligence to understand what is proposed, it is they and not their parents whose consent is required by law. (…) If the child is insufficiently mature to consent, then valid parental consent must be obtained."[129] Dawson and Spencer call attention to a possible disagreement between parents and child and conclude that "a parent cannot overrule a competent child's decision, but a clinician is unlikely to go ahead with research if either the child or the parent is reluctant".[130] From this follows that the investigator has to obey the minor's expressed will to refuse participation in, or to be withdrawn from, the clinical trial at any time.

However, the restrictions of research involving children have been criticised from different directions. At first, the distinction between basic research and therapeutic (or applied) research according to the World Medical Association Declaration of Helsinki, which demarcates ethically allowed from ethically prohibited research, is not always clear. As a result, minors are often excluded from clinical trials and, therefore, are generally discriminated regarding medical improvement in therapy. For example 80 per cent of the drugs currently given in paediatric therapy are not tested for children.[131] Accordingly, children generally have a higher risk in therapy, because they are treated with drugs that are not sufficiently tested for this patient group.[132]

In the US, the discussion is more focused on the evaluation of risks posed by clinical trials involving children. According to the guidelines of the US-Department of Health and Human Services (DHHS), which are implemented in the Food and Drug Act, "research not involving greater than minimal risk" is generally allowed[133], provided that parents have given consent. Minimal risks are given when "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests".[134] Similarly to this definition, the American Academy of Pediatrics describes minimal risks in research involving children for activities like physical examinations, venipunctures, or urine sample collections.[135]

Nevertheless, empirical data reveal that this approach does not prevent minors from risk and harm. Janofsky and Starfield published an US-survey asking heads of paediatric clinics to assess the risks of different clinical routines. In regard to distinct

[128] See for example Lohaus et al 2002, Alderson 1993

[129] Royal College of Paediatrics 2000, 5

[130] Dawson and Spencer 2005, 233

[131] Dahl and Wiesemann 2001, 88

[132] Clinical tests to get medical drugs for children approved are very costly. Additionally, paediatrics will prescribe medicines regardless of their status, because they do not have any alternative. As a result, pharmaceutical companies are generally not very ambitious in testing drugs on children. See Levine 1996.

[133] DHHS 2005, § 46.404, "Research not involving greater than minimal risk"

[134] Ibid, § 46.102 (i), „Definitions"

[135] AAP 1995, 286

age groups the clinicians were supposed to asses the risk of measures – for example venipunctures, intramuscular placebo injections, or skin biopsies – according to three risk categories: no risk or minimal risk, a minor increase over minimal risk, or greater than a minor increase over minimal risk.[136] The results of the survey have shown that clinicians haven't found a general consensus how risks are supposed to be rated.[137] Therefore, risks of distinct measures are assessed differently by practitioners according to their personal perception, empathy and experience.

The second major criticism against restrictions of research involving children is concerning the minor's assent. Though it is widely accepted that children have to be involved in the informed consent process according to their capacity of understanding, it remains unclear how to approach the capacity of minors appropriately.[138] Possible criteria are age, maturity, or psychological conditions of the child. Referring to empirical data, Leikin proposes that the capacity of understanding has two dimensions: understanding of their role within the research process as well as reasoning about research,[139] the latter requiring abstract thinking beyond personal experiences. Leikin states that only children from nine years on can reason about research,[140] whereas Lohaus et al conclude that children at the age of 12 are mature enough to give full assent.[141] In their German survey, the authors assess the capacity to consent of 140 children in third to eighth grade by approaching their concepts of illness. Other authors even claim that seven-year-old children are able to decide competently, especially if they have experience with chronic illness.[142]

In addition to maturity and age, psychological conditions might also have an important influence on the capacity to assent. An anxious child, for example, might approach the informed assent procedure differently from a self-confident child that is not afraid of posing questions at any time.[143] Since empirical data on children's capacity to consent are very limited, it finally remains to the discretion of the practitioner to assess the child's capacity.

However, as Dawson and Spencer highlight, "paediatrics is usually acute".[144] Especially in the context of clinical trials, the child is ill or was recently confronted with a serious diagnosis. Therefore, it may neither be capable to retain information nor to give consent to research activities. Consequently, consent to research

[136] The categories are based on the definition of minimal risk according to the DHHS.

[137] Arteriepunctures for 12-18-year-old, for example, were assessed by 24 per cent of the interviewees as no risk or minimal risk, by 55 per cent as a minor increase over minimal risk, and by 21 per cent as greater than a minor increase over minimal risk. Janosky and Starfield 1981, 844

[138] See for example the wording of the Convention on Human Rights and Biomedicine: "The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity. Council of Europe 1997, Article 6 (2), "Protection of persons not able to consent"

[139] Leikin 1993

[140] Ibid, see also Ondrusek et al 1998

[141] Lohaus et al 2002, 1503

[142] See for example Alderson 1993, Nicholson 1991

[143] See Dorn et al 1995

[144] Ibid

participation of children in clinical trials usually will be given by the parents, and not by the research subjects themselves.

Besides parental consent, research involving children creates some additional ethical questions to be taken into consideration, especially if it relates to genetic data or tissue samples. In this context, neither blanket consent nor consent to unlimited future use of data and samples is regarded as acceptable. At least when the child who donated the tissue matures and reaches legal capacity to consent, the principle of respect for the autonomy demands that the donor himself has to be informed and asked for consent. [145] For similar reasons Clayton et al underline that "genetic research involving children should also be structured in a way that allows the children to retain as many choices and opportunities as possible once they reach adulthood".[146]

In this context, some authors explicitly discuss a reconsent. Burke and Diekema, for instance, recommend inviting pediatric participants to reconsent when they become mature. "Without such reconsent, participants enrolled as children will be denied the opportunity for an independent decision regarding research participation based on the participant's own review of information about study procedures and goals."[147] The authors emphasise a moral obligation of researchers to provide participants within the process of reconsent not only with sufficient information about storing procedures and confidentiality protections, but also about future possibilities and potential risks of storing and processing genetic data.[148] Even though Burke and Diekema state that it is "cumbersome and costly", the authors propose to ask periodically for reconsent. This allows paediatric patients "to participate more fully in the assent and consent process as they grow older, and to provide a legally valid consent upon reaching the age of consent".[149]

A few authors draw particular attention to the case of cancer research involving children. Analysing the results of two empirical studies, Kodish et al state that "parents do perceive a sense of pressure and shortness of time to consent (…) and have difficulty making the consent decision".[150] Results of the survey allow an insight into possible reasons for these perceptions: First of all, the interviewed parents were overstrained because of the point in time they were asked to enrol their child in a clinical trial. Many parents interviewed by the authors refer to the 'state of shock' they were in shortly after diagnosis and criticize that the information and consent process have already been starting. As the authors summarise, "such devastating news initially may compromise parents' ability to make informed and independent judgements".[151] Similarly, Dawson and Spencer assume that cancer diagnosis may shock parents so that they may feel "confused or overwhelmed".[152] Nevertheless, empirical data concerning parents' attitudes towards the consent procedure as well as patients' compliance enhanced by continuous communication and information suggest that patients' ability to comprehend information and to stay involved is better than assumed.

[145] See Burke and Diekema 2006, 35
[146] Clayton et al 1995, 1792
[147] Burke and Diekema 2006, 36
[148] Ibid
[149] Ibid, 35
[150] Kodish et al 1998, 2468
[151] Ibid, 2479
[152] Dawson and Spencer 2005, 233

2.2.2.3 Issues to be consented to

Informed consent procedures consist of several steps. The first one is to ask the potential donor for volunteer participation and to provide him/her with information; the last one is to receive the signed consent form. In most cases, patient information is provided in a written form. This information is distinct from the consent form, which has to be signed by the patient, or the donor respectively. Patient information and consent form for tissue based research have to include general requirements that are regarded as standards of informed consent. However, to collect, store, and use data further considerations have to be taken into account to protect personal rights and to guarantee confidentiality appropriately.

2.2.2.3.1 General requirements

Because they are widely accepted and always part of the patient information, some issues can be regarded as standards of informed consent. These issues have to be mentioned and explained to the potential donor; they require the consent of the participant. Although most of the following points have been discussed already in more detail, they are listed here in brief to give an overview:

• The patient information has to include details of the main intentions of the tissue collection and the range of uses of data, and the timeframe of the storage.

• As far as interventions in order to obtain blood or tissue are necessary, it is important to provide the participant with information about the possible risks involved in such interventions.

• Potential donors have to be informed about measures token to protect their personal rights and to guarantee confidentiality. Duties to disclose information to third parties (as insurers or public authorities) have to be explained. Institutions that might have access to data stored about them have to be mentioned, as well as the extent of the access.

• Potential Donors have to be informed about their legal rights to withdraw consent at any time and to be disclosed of stored personal data and research results.[153]

2.2.2.3.2 Sharing data and information

Before consenting to tissue based research, donors have to be provided with information concerning institutions that might have access to the data. Reymond et al point out the failure of clearly established international frameworks for the protection of security, privacy, and confidentiality of tissue and data collections.[154] Since biomedical research is increasingly realised on a global level, but is at the same time subject to a variety of local and national – in part conflicting – regulations, consent to sample sharing might resolve the conflict of responsibility.[155]

[153] See Knoppers et al 2006, Fernandez 2003a, Merz et al 1997, Pelias 2004. The issue of feedback is discussed in detail in section 2.3/The right to know, the duty to inform, and the quality of feedback.
[154] For the European level see DIRECTIVE 2004/23/EC and DIRECTIVE 2006/86/EC.
[155] Reymond et al 2002, 264. They especially refer to the problem of intellectual property rights which are regularly defined by national laws.

In addition to practical arguments, the need for consent to share data and information is stressed by a variety of authors referring to personal rights like privacy and self-determination.[156] Following Alston, a "baseline privacy protection" requires an explanation of foreseeable or planned transfers of data to other institutions or organisations.[157] Clayton et al demand that consent for future research should comprise the possibility for potential tissue donors to select between different options concerning data sharing: They should be able to determine whether data will be shared with other researchers or not and, if affirmed, whether it may be shared with researchers inside or outside the institution that removes the sample.[158] The proposal corresponds with findings of a survey in the US enrolled by Pentz et al: Patients' willingness to donate their sample is slightly affected by the location where future research might occur. While a big majority broadly consents to the local use of their sample for research purposes, the consent is less likely to the use in the wider US, and least likely to the use in Europe.[159] However, conclusions concerning the scope of consent to data sharing in European research institutions can hardly be drawn from this study as long as patients' attitudes towards data sharing have not been studied yet in the context of the European health care systems.

2.2.2.3.3 Recontact

Connected to the issue of data sharing, the problem of recontact has been discussed in the context of tissue based research. Authors suggest addressing this topic in the initial consent form, and not in the frame of tiered consent models only.[160] Most of them agree that the issue has to be mentioned at least if the need for recontact is foreseeable. "Circumstances under which this will and will not occur should be carefully delineated at the time consent for the use of the samples is obtained", say for example Clayton et al.[161] This concern is stressed, because research subjects must be provided with the opportunity to refuse recontact. Furthermore, the possibility to feed back individual research results to patients necessitates consent of the donors. Therefore, the question of recontact will usually be part of the consent form.[162]

2.2.2.3.4 Commercial interests

It is supposed that the economic potential of research involving tissue samples has at least some implications for the consent procedure. Ashcroft even considers the issue so important that he suggests separating consent for research purposes from consent "for commercial use and exploitation".[163] Since usually commercial uses can hardly be put in concrete terms at the moment the tissue is removed, this proposal makes little sense. However, quite a few authors underline that potential donors

[156] See Merz et al 1997, Wertz 1999, Ashcroft 2000, Reymond et al 2002
[157] Alston 2005, 439
[158] Clayton et al 1995, 1794
[159] Pentz et al 2006, 736
[160] See Reymond et al 2003, and Merz et al 1997. In paragraph 2.2.2.1.3/Tiered consent, the issue is discussed in the context of tiered consent models.
[161] Clayton et al 1995, 1792
[162] Issues concerning the feedback of research results are discussed in section 2.3/The right to know, the duty to inform, and the quality of feedback.
[163] Ashcroft 2000, 410

have to be provided with information about possible commercial interests.[164] Reymond et al, for instance, recommend that "the issues of validation and patenting should be solved from the beginning, within the framework of the informed consent".[165] They emphasise the fact that "the subject – as provider of raw material – is the only member of the value chain who acts on an altruistic basis".

On the other hand, Reymond et al underline that the "transaction value" of the particular sample "that would have been trashed anyway" is considered – at least in Europe – as minimal".[166] Generally, in current biomedical research the limits between economic and medical interests are becoming increasingly blurred. Furthermore, the way a particular sample contributes to a publication, a patent, or a product, can hardly be assessed. Hence it is logically consistent that Reymond et al propose to inform the subject that he/she will not participate on potential commercial benefits arising from the research projects in question.

2.2.2.3.5 The timeframe of consent

Concerning future research involving tissue samples, the timeframe of consent is still an important issue in the bioethical debate. The question how long a given consent might be considered as valid has been discussed controversy. Sass underlines, as far as genetic research is concerned, the „sheer limitlessness of information which can be gathered".[167] In addition, in genetic research the availability of research material is basically unlimited as well. Wertz reminds another aspect of timeframe: Researchers might move and sources may die.[168]

Nevertheless, only a few authors address the issue explicitly. Hansson et al states that "consent should be regarded as valid until further notice".[169] Although recognising that "it would be regrettable to destroy material as precious as DNA, which could be useful in the light of new discoveries in the future", De Montgolfier et al argue for a restricted timeframe of consent.[170] "It appears desirable to limit the period of commitment, given the changing and uncertain nature of the consequences of patient's choices."[171] The authors refer to a DNA-databank project of HIV-infected patients, where samples will be stored for ten years after the closure of the cohort. For an extension of the storage period a new consent is required in this project, otherwise (if for any reasons consent is not accomplishable) the sample will be destroyed or completely anonymised.

2.2.2.4 The right to withdraw consent

The right to withdraw a given consent to research at any time is an inalienable right of individuals. Therefore, in the bioethical discussion the right to withdraw consent is evaluated as a fundamental right of research participants, or tissue donors

[164] See Clayton et al 1995, Reymond et al 2003
[165] Reymond et al 2003, 354
[166] Ibid
[167] Sass 1998, 290
[168] Wertz 1999, 55
[169] Hansson et al 2006, 269
[170] De Montgolfier et al 2002, 668
[171] Ibid

respectively.[172] Referring to the generally accepted prediction, Hansson et al state that "there should be a realistic opportunity for withdrawal of consent for those who have donated identifiable samples and data".[173]

However, concerning tissue samples, the definition of what is meant by a right to withdrawal differs significantly in the discussion. Hansson et al, for example, propose that the withdrawal of consent should be tantamount to the termination of processing personal data. It "does not imply a right to withdraw results that have already accumulated, rather it implies that new data cannot be obtained and that existing data must be maintained in an impersonalised form".[174]

To respond to the withdrawal of consent merely with the anonymization of the respective sample and data is criticised by Eriksson and Helgesson. They state that donors who withdraw their consent to research expect that their sample will be destroyed and both, sample and data, not be used anymore for research. Thus, anonymization is "hardly satisfactory", regarding the concept of autonomy; "the 'anonymization tool' does not do much moral work", they conclude.[175] On the other hand Eriksson and Helgesson argue that research subjects who wish to withdraw their consent have to provide "valid reasons" for changing their mind.[176] According to this perspective, the moral obligation to participate in biomedical research should not at all result in "mandatory inclusions" of data or samples, but "no one should take withdrawal from biobank research lightly".[177] The decision whether the reasons to withdraw are sufficient should be made „primarily by the researchers or biobank holders", the authors suggest. Concerns are supposed to be generally accepted if they are „genuine, deeply felt" and not based on misconceptions.[178]

Contrarily, the major position in the discussion on withdrawal in tissue based research demands respect for decisions made by tissue donors without reservation. Given that participation in research is an act of voluntariness, the right to refuse consent is indispensable. „Research subjects' reasons not to want their biological materials or information used in a study may be plausible or implausible, reasonable or unreasonable, in the view of the investigators. Nevertheless, the long established ethical principle of personal self-determination demands that every research subject be given an opportunity to decline to participate in any research project."[179] Sade underlines that "this principle is of critical importance; it should be sustained no matter how great the value (as perceived by the investigator or the research review committee) of the new knowledge [is] that might be obtained from such a study".[180]

Apart from challenging patients' autonomy, Eriksson and Helgesson's proposal miss empirical experiences in clinical practice. Hoeyer et al, for example, present study findings that the majority of the 1200 tissue donors who participated in their survey either was not aware of the possibility to withdraw consent (55,7 per cent) or even did not realise having consented at all (12,7 per cent).[181] However, Eriksson and Helgesson pose some practical reasons for the review of participant's reasons. This

[172] See for example Hansson et al 2006, O'Neill 2003
[173] Hansson et al 2006, 269
[174] Ibid
[175] Eriksson and Helgesson 2005, 1074
[176] Ibid, 1075
[177] Ibid, 1071
[178] Ibid
[179] Sade 2002, 1440
[180] ibid
[181] Hoeyer et al 2005, 98

would permit to avoid misconceptions insofar as they could be identified and subsequently cleared up. Furthermore, Eriksson and Helgesson propose to invite participants being part of the review process. Thereby, they can learn about different options, for example, anonymization, further research on existing identifiable material and/or data, or destruction of the sample.[182]

2.3 THE RIGHT TO KNOW, THE DUTY TO INFORM, AND THE QUALITY OF FEEDBACK

ACGT aims to identify genetic and other molecular components which are involved in cancer development and reaction to cancer treatment. Though genetic factors may increase the probability of disease development or adverse drug reactions, they do not cause them in the narrow sense of the term. Since the single risk factor is small, large numbers of tissue samples and data have to be stored and statistically analyzed.

This general research condition leads to comprehensively ethical considerations regarding the disclosure of data and information generated in research which allow tissue donors to get access to information about their individual data stored about him or her, general research findings, or research results that are of individual significance.

Therefore, the second ethical question which is not covered by specific legal provisions yet has to be addressed as follows: Under what circumstances are researchers required to actively give access to information? If at all, what kind of information do they have to feed back to patients? In the following chapters issues and arguments raised in bioethical discourse pertinent to these guiding questions will be identified, analyzed, and evaluated in its relevance for ACGT.

2.3.1 Access to personal information: a donor driven inquiry process

In the European context it is indisputable that everyone has the right to make inquiries about personal data which have been collected about him or her. Due to legal provisions, investigators are obliged to disclose such data on request. Data subjects have the right to be provided on request with information (1) about personal data stored about him or her, (2) about the origin of these data, and (3) about institutions or persons who have access to the data. Such claims can be made against any data processing body involved. Therefore, suitable mechanisms for granting access to personal stored data are required.

However, the legal duty to provide on request data subjects with information about stored personal data does not imply that they actually do understand what the data mean. Data is not the same like information, because information additionally includes contextual information which provides raw data with meaning: “Data is said to denote signs, patterns, characters or symbols which potentially represent some thing (a process or object) from the ‘real world’ and, through that representation, may communicate information about that

[182] Eriksson and Helgesson 2005, 1075

thing. The 'information' as such denotes the semantic content of the data communicated to a person."[183]

In the context of biomedical research the question arise whether researchers have to provide donors not only with raw data, but also with contextual information, since patients or tissue donors are usually not able to interpret genetic, molecular, or clinical data. Although such a duty is not codified in existing legal guidelines, it can very well be justified by the ethical principle of respect for the tissue donor because of the voluntariness, which guides the tissue donation. Thus, it may be postulated at least for the clinical context that investigators, or research sponsors respectively, are obliged to support patients in interpreting raw data if they are asked for. Such moral obligation could also be justified by the doctor-patient-relationship and by the principle of doing no harm. Since misinterpretation and misunderstanding might produce psychological distress, it may be an ethical obligation to give context information and to explain the importance and relevance of disclosed data to tissue donors to prevent harm.

2.3.2 Feedback of research results: an investigator driven disclosure process

Clearly different from a donor-driven inquiry process is what can be called an individual feedback process. When tissue-based research yields biostatistical results, which are of direct diagnostic or therapeutic relevance, it may be up the researchers to take the initiative to open an individual feedback process, i.e. a process by which donors who contributed to the research results and who have consented in advance to such a feedback, are approached and informed about the findings in general and asked whether they would be interested to get (or not to get) individual information.

More far-reaching is the question, whether researchers are legally obliged to *actively return* research results to persons concerned. According to a recently published analysis of eleven related legal and ethical documents from Europe, the US, and the international context seven of these documents propose criteria concerning individual feedback.[184] Four of them refer explicitly to genetic research. Other four documents, which only partially overlap with the ones just mentioned, point the right to know out to study participants. Three documents finally recommend that donors should have the right to choose whether they want to know or not. In sum, Renegar et al conclude that "there appears no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations in the US or the EU that research results have to be, in all circumstances, returned to study participants. However some guidelines advocate a proactive return of data in certain instances."[185]

Hence, according to currently available documents researchers seem not be legally obliged to offer individual feedback processes. In view of the possible importance and implications of this question for donors and researchers one has to ask, however, whether and under what circumstances an *ethical* obligation to offer such a process exists.

[183] Bygrave 2003, 2
[184] Renegar et al 2006
[185] Renegar et al 2006, 29

It might be difficult to argue that a *general obligation* exists to actively feedback research data to tissue donors. Nobody expects, for instance, the active feedback of traffic control video monitoring – these data are in most cases meaningless for the individual that might appear in one of those videos. A similar argument applies in the research context, when the implications of research data are not (yet) fully understood.

But when a research process yields clear findings being of actual or potential relevance for a person – e.g. his or her present or future health status – it is well possible to find valid arguments for a *specific obligation* to feeding back research results, especially when a tissue donor or patient explicitly stated his/her interest in participating in a feedback process in advance. The ethical principle to be applied here is the principle of avoiding harm: If a research process either intentionally or accidentally yields information that helps to avoid sickness or adverse drugs reactions, then the tissue donor must be enabled to use this information.

2.3.2.1 Informing about general research results

To fully understand the ethical challenges within the donor driven inquiry process, it is necessary to differentiate between the disclosure of general research results and the disclosure of research results of immediate or potential importance for a single individual.

2.3.2.1.1 Ethical foundations

In ethical discourse, it is widely accepted that research participants should have access to general research results.[186] Therefore, general research results of clinical studies or tissue based research should be made publicly available. The right of research participants, and especially of tissue donors, to be informed about such results is based on various ethical arguments. Zlotnik et al, for instance, underline the fundamental role of tissue donors for research. „The material means research subjects provide are more intimate and certainly no less crucial than financial resources (...). The request for an account of the outcome of research is correspondingly stronger – not weaker – for those who provide these most personal material means for research.“[187] Similarly, the American Society of Clinical Oncology underlines in its policy statement concerning genetic testing for cancer susceptibility the special interest of tissue donors in the research results. „Respect for the persons who are the sources of biologic materials for DNA research and their families necessitates recognition that these individuals have an interest in the studies that are performed on their tissues, even when the acquisition of the tissue takes place outside of the research.“[188]

In addition, the investigators' obligation to disclose general research results is actively derived from the fiduciary character of the relationship between researcher and donor. “The donor's involvement into research is limited to give the researcher control over a tissue sample. The research subject generally possesses neither the expertise nor the opportunity to monitor and supervise the researcher and his or her

[186] See Knoppers et al 2006, Pelias 2004, Fernandez 2003a
[187] Zlotnik et al 2005, 5
[188] ASCO 2003, 2405

use of that tissue sample."[189] Therefore, the disclosure of general research results has been pointed out as crucial to implement the principle of donor's autonomy. To accept donor's interest in research results "transcends the subject as a tissue or DNA donor and acknowledges the subject as an autonomous individual who may have ongoing interests in medical information that may be gleaned from his/her tissue donation in present as well as future research efforts."[190] As Shalowitz and Miller resume, "respect for participants' self-determination and a recognition of their integral role in research, underlies investigators' responsibilities to make aggregate research results available to participants."[191]

By making research results available, investigators, therefore, give account for their research activities. According to this perspective, authors underline that the given information on study results build up trust between researchers and donors. Shalowitz and Miller conclude that the disclosure of research results might improve the credibility of biomedical research in general. They emphasize that the provision of research results "will make the process of research more transparent and may increase participants' willingness to enrol, thereby facilitating future studies."[192] Similarly, Fernandez et al see "many tangible benefits to offering disclosure of research results to participants, both for individual participants and for the research as a whole."[193]

Consequently, there are some strong arguments for investigators' obligation to inform actively about general research results, or make them at least publicly available. According to the Helsinki Declaration, researchers as well as publishers are ethically obligated to publish research results. As outlined explicitly, the research results have to be publicly available regardless of their character. „In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available."[194] Above all, the publication of negative research results as falsifications of hypotheses, for instance, is ethically required to avoid unnecessary risks and harm. It has repeatedly been underlined that "unpublished data can lead to additional, redundant trials being performed, useless or even harmful interventions remaining in use and, ultimately, do not contribute to the growth of society's collective knowledge."[195] In the current scientific practice, negative research results are usually not published by researchers or sponsors, who finance the study. But in the last years several European institutions are engaged in establishing a study registry in order to overcome this problem.

2.3.2.1.2 Practical challenges of feedback processes regarding general research results

Generally, research results are made publicly available in scientific publications. However, Knoppers et al reviewing international guidelines and regulations concerning the feedback of research results clearly conclude that the traditional way

[189] Banks 2000, 578. See also Zlotnik et al 2005
[190] Pelias 2004, 4
[191] Shalowitz and Miller 2005, 738
[192] Shalowitz and Miller 2005, 740
[193] Fernandez et al 2003a, 2908
[194] WMA 2004, paragraph 27
[195] Knoppers et al 2006, 1173. See also Fernandez et al 2003a

of publishing research results in a scientific journal "is no longer ethically sufficient. The ethical principles of respect for the person, beneficence and justice obligate the researcher to offer results in a manner that is clear and understandable to the research participants."[196] The authors suggest that the communication with research participants can be a personal letter, news bulletin, newspaper article, website or a similar form.[197]

Sufficient and adequate information about the character of results *before* tissue removal is regarded as an indispensable prerequisite for patients' decision concerning tissue donation. Merz et al argue that investigators "should anticipate what information will likely be generated in the research and what will be done with that information."[198] Similarly, Clayton et al underline that patients should be informed about "what types of information they can expect to have provided by the investigators".[199]

The majority of authors state that no further information is required as far as general research results are concerned. However, tissue donors should be informed about possibilities how to be provided with information regarding general research results. Depending on the way how general research results are disseminated, it could be necessary to ask tissue donors for consent, especially if information is available by mail, or leaflet respectively.

Another important issue is the time chosen for disclosure of general research results. In this context Zlotnik et al highlight scientists' interest in publishing research results for the scientific community.[200] Scientific publication procedures normally discourage communication of research results prior to formal publication. Conflicts may emerge between scientists' interests to fulfil editor guidelines of scientific journals or claims of research sponsors and the donors' right to be provided with information about general research results as an act of accountability.[201] Knoppers et al resume that existing guidelines concerning feedback processes do not address "the timing of their communication".[202] If the issue is mentioned at all, it occurs in a generalised form. The Council of Europe guidelines regarding biomedical research, for instance, state that „conclusions of the research shall be made available to participants in reasonable time" after a study has been finished.[203] However, the term "reasonable" is not defined. As a "possible compromise" between conflicting interests, Fernandez et al suggest to disclose results "at the time of abstract publication; doing so also would help avoid the perception that research participants are the last to be informed of the results."[204]

[196] Knoppers et al 2006, 1173
[197] Knoppers et al 2006, 1173 refer to the draft of the European Federation of the International Epidemiology Association (IEA) that recommends: "It is advisable to publish the main results in a form that reaches the participants of the study and other interested members of the community where the study took place." IEA 2004, 7
[198] Merz et al 1997, 255
[199] Clayton et al. 1995, 1792
[200] Zlotnik et al 2005, 11
[201] The authors refer in particular to the Ingelfinger Rule of the New England Journal of Medicine (1974) and the International Committee of Medical Journal Editors guidelines (2001). See Zlotnik et al 2005, 11
[202] Knoppers et al 2006, 1174
[203] Council of Europe 2005, Article 28: Availability of results (1) and (2)
[204] Fernandez et al 2003a, 2907

2.3.2.2 Information about individually relevant research results

If biomedical research yields research results which are of indirect or direct diagnostic or therapeutic relevance for the tissue donor more question regarding the investigator driven disclosure process arise. In this situation it may be up the researcher to initiate an individual feedback process. This process by which donors who contributed to the research results and who have consented in advance to such a feedback are actively approached whether they would be interested to get (or not to get) individual information will be discussed to arrange such a feedback process within ACGT.

2.3.2.2.1 Ethical foundations

Basically, guidelines concerning the individual feedback process do not exist.[205] If at all, the issue has been mentioned in a generalised form. For example, the UNESCO Declaration on Human Genetic Data does not differentiate between general and individually important research results as a basis to decide about the feedback of research results.[206] But the guidelines of the Council for International Organisations of Medical Sciences (CIOMS) distinguish more precisely between "findings of the research in general" and "any finding" related to a "particular health status", at least as far as the wording is concerned.[207] The most detailed regulations concerning the feedback of biomedical research results have been made in the additional protocol to the Convention on Human Rights and Biomedicine, adopted in 2005. The protocol distinguishes not only between "access to information relevant to the participant arising from the research and to its overall results",[208] but it also explicitly states a duty to offer „information of relevance to the current or future health or quality of life of research participants".[209]

Beyond these precautious formulations in guidelines, the right to be informed about research results of individual relevance is strengthened by ethical arguments. Generally, patients have a right to be informed of any known facts that concern their current health status. The Council of Europe states, for instance, explicitly that "[e]veryone is entitled to know any information collected about his or her health".[210] This right to know, which is based on the ethical principles of autonomy and self-determination, also applies to information relevant to the person's health. Individuals should be able to get all available information that are or may become important for personal decision-making. Hence, the physician, who carries on special responsibility towards his/her patients, has a moral obligation to provide them with all relevant information collected about her or him.

In the context of the physician-patient-relationship another important ethical principle supports the necessity of feeding back individually relevant research results: the principle of doing no harm (nonmaleficience). Following this principle, medical researchers are obliged to inform patients or tissue donors about individual research

[205] See Fernandez 2003a or Knoppers et al 2006, who recently examined international guidelines concerning the question of feedback.
[206] See UNESCO 2003, 43, Article 10: The right to decide whether or not to be informed about research results
[207] CIOMS 2002, Guideline 5, Article 7: Obtaining informed consent: Essential information for prospective research subjects
[208] Council of Europe 2005, article 13, V.
[209] Council of Europe 2005, Article 27: Duty of care
[210] Council of Europe 1997, 4, Article10.2

results if disclosure can prevent harm.[211] Thereby Pelias points out that the meaning of preventing harm has changed in the context of modern biomedical research: "As the principle of personal autonomy has become entrenched in clinical medicine and biomedical research, the admonition to do no harm has acquired new meaning. What originally was the idea of doing nothing to cause a patient's condition to worsen has evolved to the idea of causing harm by failing to inform a patient or subject fully about treatment options or research expectations."[212] As Pelias argues, the extension of the principle of personal autonomy to the researcher-patient-relationship has had further consequences: The relationship between researchers and their research subjects continued to follow the principles of beneficence.[213] Hence, the duty to feedback individual research results is not only founded on the principles of nonmaleficience and autonomy, but also on the principle of beneficence. In conclusion, researchers as well as physicians are ethically obliged to provide patients, or research subjects respectively, with individually important information if this might benefit them[214].

2.3.2.2.2 What to feed back?

The underlying principle of beneficence does not answer the question what qualifies information as being beneficial for research subjects and, therefore, what kind of results should be fed back.

Crucial to this general discussion whether or not the feedback on individually relevant research results is generally obliged is the clinical relevance of such results. Conservative positions argue that only research results of proven clinical validity should be fed back to patients. This claim has the effect that incomplete evidence is withhold from donors. But even such "weak" evidence could nevertheless be a starting point for more thorough investigations and therefore relevant for donors. Other authors propose to feed back research results only if they have clinical relevance, *and* if effective therapies or strategies of prevention are available.[215] But this constraint regarding the feedback of individual research results has been criticized as paternalistic.[216] Referring to the importance of the principle of autonomy, paternalism is valued as an "essentially discarded concept", that is an antiquated remnant of a medicine where patients were rather objects than subjects.[217]

Beside the two fundamental positions – the obligation to generally give feedback on individually relevant research results and the obligation to give feedback only if the research results are clinically relevant and validated and if effective interventions are

[211] For further discussion of this principle see, for instance, Banks 2000
[212] Pelias 2004, 4
[213] Pelias 2004, 2
[214] See also Luttenberger et al 2006
[215] Recommendations of the US-American National Bioethics Advisory Commission (NBAC), for instance, are explicitly based on the "presumption that the disclosure of research results to subjects represents an exceptional circumstance." It should only occur when "the findings are scientifically valid and confirmed, the findings have significant implications for the subject's health concerns, *and* a course of action to ameliorate or treat these concerns is readily available". NBAC 1999, 9, recommendation 14
[216] See Banks 2000, Markman 2006
[217] Markman 2006, 1422

available – several authors suggest limiting the obligation of disclosure to clinically relevant results at all.

In this context, it is quite often stressed that research fundamentally differs from medical treatment. Merz et al, for instance, emphasise that medical research in general "is performed primarily to develop generalizable knowledge".[218] Referring to genetic research, Renegar et al underline that it is usually "undertaken to benefit society, not individuals."[219] Consequently, individual benefits, rights, or demands have to step behind the societal benefit of generalized knowledge. In the context of tissue based research, Kapp for example defines as "the chief role" of tissue donors "to serve as sources of needed data. This is a different situation than ordinarily occurs in clinical medicine, in which diagnostic or therapeutic interventions are suggested or carried out solely to benefit the current patient."[220]

But the current patient or research subject respectively, has always been differed from the future one. There are some reasons based on experiences with medical research to prioritise the current patient compared to the future one. As Banks underlines, "notwithstanding our obvious individual and social interests in medical research, however, there has been a remarkable reallocation of weight from the phantasmal future patient to present research subjects over the past several decades. In part, this reallocation of weight has been a consequence of revelations concerning military experiments conducted by the Nazis, the U.S. human radiation experiments, and North American medical studies such as Tuskegee".[221] In this context, Banks states that "informed consent has turned into a mechanism by which researchers explicitly limit their responsibilities to their research subjects". Risks and benefits are usually disclosed and limited concerns of medical researchers are explained. However, the author underlines that after consent is obtained "the ethical weight shifts back to the traditional darling of medical research – the phantasmal future patient".[222]

Following this argument, the claim to feed back individual research results only if they are clinically relevant can hardly be based on the difference between research and treatment. But one exception does exist: Individual study findings in basic research seem not be possible. As Knoppers et al underline, this is a contradiction in the wording. "Seemingly, returning individual basic research results is impossible and nonsensical as the very purpose of this type of research is not the production of individual but generalizable knowledge. Thus, in this context, the concept of individual research results is a scientific misnomer."[223] However, the authors do not discuss how to distinguish basic from applied research, an issue of growing importance in the context of pharmaco-genomic and -genetic research.[224]

Beside the rather normative provisos to deny the disclosure of individually important research results unless they are clinically valid and reliable, pragmatic arguments

[218] Merz et al 1997, 255
[219] Renegar et al 2006, 35. For a discussion of particularities concerning genetic research results see paragraph 2.3.2.2.3/Characteristics of genetic research results in the context of cancer trials
[220] Kapp 2006, 335
[221] Banks 2000, 548
[222] Banks 2000, 552
[223] Knoppers et al 2006, 1172
[224] Banks indirectly gives a definition describing the only situation in which the non-disclosure of individual research results might be justified: "There may be circumstances in which either the research is so preliminary or the research process is so novel or potentially inaccurate that the results of the research may be of dubious significance except as basic science." Banks 2000, 578

have been established. Merz et al call attention to the fact that "not all scientists agree on the magnitude of the risks or on the suggested limits on uses of research data". [225] According to this argument, it makes no sense to disclose research results as long as their clinical relevance and their importance for the patient are under discussion, because interpretation of data may change in the course of the validation process. Furthermore, Renegar et al point out that information quality is related to the circumstances of its production. "The clinical relevance of information is influenced by the conditions under which such information is generated and interpreted (…). [T]he standards to which laboratories are held will vary depending upon applicable laws and regulations. These operating standards will affect the credibility of the results and thus the risks and benefits of returning research results. It is important to emphasize that the clinical quality assurance measures in place at a laboratory do not imply clinical relevance."[226]

Although these rather pragmatic objections have been made to support the position that clinical relevance is one important prerequisite for the disclosure of individually important study findings towards patients, they can serve as well as an argument for an obligation to feedback individual research results irrespective of their character. Given that operating standards and clinical quality assurance measures can differ, they automatically affect the credibility of the results and the risks and benefits of feedback. If various interpretations of results and their importance exist, it can be argued for the same reasons that the only practicable way to appropriate feedback would be to wait for clinical reproducibility and validation. But on the other hand, even results which are not finally validated can be beneficial for the patient because they may be the starting point for more thorough medical examination of the individual.

However, objections against the offer to disclose individual research results irrespective of their character usually refer to the aforementioned principle of doing no harm in the clinical context. But it is important to take into consideration that this principle has a dimension of liability which is presumably important for feed backing research results irrespective of their clinical relevance.

Reymond et al, for instance, highlight in their paper concerning the feedback of research results in gene expression studies that study findings might have direct influence on therapeutic or treatment decisions. If treatment fails, because it relies on false research results, these treatment decisions might result in liability proceedings in the future. Reymond et al conclude that "the investigators should be aware that claims against them might be expressed by the patient – in the future but on a retrospective basis".[227] Notwithstanding, fears of costly liability proceedings do not justify violations of research participants' autonomy. In this context Clayton et al emphasise, that there is no "look-back liability". [228] If implications of research results stay unclear or if effective interventions are not available, there will be no liability. Liability might rather occur, if results have not been disclosed. It might turn out that the not given information will be relevant for decisions concerning therapy as well as personal planning. On the other hand, Renegar et al enumerate different potential liability factors "from the perspective of the study sponsor generating research results in its laboratories". They call attention to the failure of experiences on that

[225] Merz et al 1997, 256. Moreover, for differences in interpreting the clinical importance of research findings see Renegar et al 2006.
[226] Renegar et al 2006, 32 f.
[227] Reymond et al 2003, 353
[228] See Clayton et al 1995

field. Thus, "whether the risk of liability proves to be a significant disincentive or whether this risk can be sufficiently managed are questions that will likely be answered only with more experience in providing research results to participants and observing how they are subsequently used".[229]

In the context of researcher-patient-relationship, Shalowitz and Miller highlight another important aspect. According to their critique, investigators become to "gatekeepers of research information relating to participants instead of offering participants the opportunity to determine what research information about themselves they wish to know".[230] The argument entails an aspect crucial to the discussion about the quality of research results: The disclosure of individual research results has to be *offered* as an *option*. Advocates of limited feedback as well as of generally feedback regarding individually important findings underline that research patients, or tissue donors respectively, should be provided with the *option* to be informed about individual research results.[231] In consequence the research subjects themselves decide whether or not they receive individually important research results. This requirement is based on the general principles of self-determination and autonomy that – as discussed above – currently govern biomedical research. Shalowitz and Miller add to this argumentation, that "the heart of the controversy surrounding disclosure of individual research results concerns the most appropriate manner of expressing respect for participants: limiting disclosure to those results that have established clinical utility vs. recognising a presumption that results should be made available to participants".[232]

Furthermore, a more practical argument becomes relevant. To delegate the decision about feedback to research participants seems to be a realistic response to the not solving conflicts concerning the quality of information to be disclosed. As Banks somehow pragmatically concludes, "the collateral obligations involved in not deciding not to disclose may be more onerous than placing the responsibility on the research subject to elect whether to receive the research results. Deciding not to disclose would require a much more cautious assessment of the meaning and validity of research results and a much more careful assessment of the consequences of those results to research subjects than medical researchers are used to providing."[233] Similarly, Renegar et al emphasise that, by obligating the investigators to decide about disclosure, „the nature of the data (significance, newness) to be generated will need prior consideration".[234] However, as we will see, investigators are not relieved from any responsibility concerning the quality and content of information given in an individual feedback process.

Since the different positions discussed in this section are based on different emphases of patients' autonomy, the discussion keeps on going. One solution to

[229] Renegar et al 2006, 30

[230] Shalowitz and Miller 2005, 738. In the discussion of their paper the authors emphasised that "investigators should not treat participants merely as patients by disclosing only clinically relevant information, because to do so would ignore their involvement as contributors to research." Shalowitz and Miller 2006, 37

[231] See on behalf of the first mentioned position Consortium on Pharmacogenetics 2002, on behalf of the second mentioned position Council of Europe 2005.

[232] Shalowitz and Miller 2006, 37

[233] Banks 2000, 567

[234] See Renegar et al 2006, 27. The authors refer to the legal situation in the US, where IC regulations in the common rule obligate researchers to provide participants with "significant new findings", if they „may relate to the subject's willingness to continue participation.

this controversy would be to refer to empirical data on patients' or tissue donors' perspectives on this issue. Such data concerning views and attitudes of patients towards feedback of research results and quality of individually important information to be provided would certainly help to clarify the demanding questions. However, empirical data on feedback of individual research results is rare. Available surveys from the US context do not refer directly to individual feedback, but to feedback of general research results.[235] Therefore, to arrange the feedback process concerning the disclosure of individual research results within ACGT, further particularities of genetic research have to be taken into consideration.

2.3.2.2.3 Characteristics of genetic research results in the context of cancer trials

Quite a few authors reflect on the particular character of genetic information. Analysing ethical guidelines in UK, Europe and on an international level (UNESCO, WHO, CIOMS etc.), Knoppers et al generally conclude that "an ethical duty to return individual genetic research results" exists, but is "subject to the existence of proof of validity, significance and benefit".[236] This is especially applicable if data comprise not only preliminary research results but relevant medical information like validated genetic disease predispositions: "If others know about genetic predispositions, there are no economic or even legal grounds (for example patent protection, intellectual property right, personal rights of third parties) to exclude data subjects from that knowledge".[237] But Renegar et al underline that "'genetic research results' is a broad category of information that includes validated and non validated, highly and poorly predictive, mostly probabilistic and sometimes deterministic data":[238] According to this definition, genetic research data are "by their very nature not individually identifiable, understandable or significant".[239] They are almost always characterised by a lack of independent replication and of established common interpretation among researchers and clinicians.

Therefore, disclosing genetic research results "could mislead participants to overestimate the significance of the results".[240] As Renegar et al emphasise, "even results that are widely recognised among geneticists do not necessarily lead to clear clinical interpretations (…) or practical implementation for patients". They conclude that these characteristics entail a "careful consideration in the risk/benefit assessment for returning results to subjects".[241]

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[235] Concerning findings of cancer research, for instance, Markman summarises that "limited existing data in the oncology literature appear to support the conclusion that the majority of cancer patients (…) would like to be given information about the trial when it is completed". Markman 2006, 1421 f.
[236] Knoppers et al 2006, 1170
[237] Weichert 2002, translated by R. Kollek
[238] Renegar et al. 2006, 31
[239] Knoppers et al. 2006, 1170
[240] Knoppers et al. 2006, 1170
[241] Renegar et al 2006, 31. A similar position was advocated for the first time by the WHO in its statement on genetic databases in 2003: Although genetic research data will usually remain of abstract significance, sometimes it might be valuable in the clinical setting. According to the WHO – as similar to the proposal of Knoppers et al 2006, 1174 –, some conditions should be met before a disclosure: "(a) The data have been instrumental in identifying a clear clinical benefit to identifiable individuals; (b) the disclosure of the data to the relevant individuals will avert or minimise significant

The conclusion particularly applies to genetic research results of a predictive character. Discussing ethical issues concerning DNA-banking in the context of HIV-research, de Montgolfier et al emphasise that respect for an individual's autonomy entails to formulate information about genetic predisposition in an exceedingly careful manner. They draw on the psychological challenge to give appropriate information in a counselling process, "calling into question the patient's pugnacity towards the disease, his or her compliance with preventive measures, and plans to procreate".[242]

In this context the American Society of Clinical Oncology (ASCO) states that tests for genetic variants that indicate a low or moderate risk for cancer susceptibility belong to clinical research, not treatment: „Genetic testing for these variants, including pharmacogenetic and pharmacogenomic testing, currently is in the realm of clinical research rather than standard clinical practice and requires consideration of informed consent and approval by relevant research oversight bodies."[243] Furthermore, it remains doubtful to strictly differentiate, for example, between cancer studies analyzing gene association and gene expression, since gene expression studies might reveal data about genetic traits and predispositions as well. ASCO underlines that "it is important to recognize that the distinction between studies assessing somatic alterations in abnormal tissue and those evaluating germline genetic variations is somewhat artifactual".[244]

Apart from implications of predictive genetic information another characteristic attribute of genetic research results is in the discussion. It is possible that "a result that has no clear clinical benefit at the time of the research will turn out to be very important to the participant at a later time".[245] This possibility is underlined as the very nature of genetic research results. In conclusion, the high uncertainties in the interpretation of genetic data define the preliminary character of decisions about their individual relevance categorically. As Renegar et al put it, the feedback of genetic research results „can involve both risks and benefits for the participants, and these can be expected to change over time".[246]

Concerning gene expression studies on cancer, Reymond et al raise the question whether the feedback of prognostic information is ethically justifiable or even demanded. The authors call particular attention to the usually uncertain character of gene expression information in cancer trials. "It is usually difficult or even impossible for the investigators to recognise in an early phase the future significance of novel research results."[247] Beyond the problem of liability mentioned above, the authors highlight that this kind of "early information" can provoke fear and anger because of its preliminary character. „To protect both the patient and the researcher", the authors recommend that any prospective gene expression study should define

harm to those individuals; (c) there is no indication that the individuals in question would prefer not to know." WHO 2003, 14, recommendation 8

[242] De Montgolfier et al 2002, 668

[243] ASCO 2003, 2399

[244] ASCO 2003, 2405

[245] Knoppers et al 2006, 1174. See also Renegar et al 2006, Reymond et al 2003, Banks 2000

[246] Renegar 2006, 30. Additionally, Renegar et al stress the influence of conditions under which "information is generated and interpreted". They especially refer to operating standards in laboratories and their relevance for the "credibility of the results and thus the risks and benefits of returning research results". Renegar et al 2006, 32 f.

[247] Reymond et al 2003, 353

"clearly as a specific research project that will have no influence on diagnosis or therapy of the particular subject".[248]

But as Markman illustrates, clinical research on cancer might yield, nevertheless, results of prognostic significance. In this context, the fear to harm patients by providing them with such uncertain results can increase paternalistic attitudes of physicians and lead to insufficient appraisal of patients' autonomy. Since patients could be harmed by being excluded from individual information such a paternalistic approach does not satisfy the ethical requirement of nonmaleficience. Rather, it should be analyzed, whether patient participation in the decision-making about which data should be fed back would be more satisfying. Since empirical data is limited, attitudes of cancer patients towards feedback processes of data should be further examined.[249]

Currently, only surveys regarding patients' general perspective on prognostic information about cancer are available. Although focusing on general clinical practice without explicitly relating to research settings, the recent survey of Miyata et al is interesting. The authors analyse answers of 246 participants regarding their attitudes towards diagnostic and prognostic information.[250] Concerning prognosis, the participants of the survey had to choose between the following options: non-disclosure, disclosure of general nature but not in detail, postponed full-disclosure, and immediate full-disclosure.[251] Miyata et al gather from their data that providing "general information on prognosis can satisfy the majority of patients' preferences". They conclude that "any disclosure policy should also try to acknowledge and meet patients' wishes of being informed together with their families and of being given information at a later time".[252]

2.3.2.2.4 To whom to feed back?

Not only cancer studies, but tissue based research in general may reveal data on germ line mutations that are of predictive nature for future diseases. For this reason, rights and interests of other family members concerning the disclosure of information will be ethically discussed in this paragraph.

As far as research involving human DNA is concerned, genetic information "is not only an individual, but also a family affair".[253] The familial dimension of genetic information has even provoked questioning of the term 'genetic privacy'. "It has been argued that genetic information cannot by its very nature be private and should therefore not be bound by the usual professional codes of respect for confidentiality

[248] Raymond et al 2003, 353

[249] Referring to the US, Markman highlights that "limited existing data in the oncology literature appear to support the conclusion that the majority of cancer patients who become research participants would like to be given information about the trial when it is completed". Markman 2006, 1421 f. Similarly, Fernandez et al point out that "subjects are increasingly vocal in expressing a right to see the information they helped to generate". Fernandez et al 2006, 1419

[250] The authors outline that "characteristics of the respondents may not be wholly representative of the general population". The survey was undertaken in an urban area of Japan; cultural differences, for example, may be supposed, so that answers of people in Europe would potentially differ from those collected in the survey. Miyata et al 2004, 5

[251] Miyata et al 2004, 2

[252] Miyata et al 2004, 5

[253] Andorno 2004, 437

(…), although, of course, a case can also be made for genetic information being regarded as the most private information of all".[254]

In view of these adverse positions it is not surprising that the discussion on rights and interests of family members concerning feedback processes is controversial. The dissent focuses on the intrinsic character of autonomy. Crucial to personal autonomy is – inter alia – a right *not* to know. Hence, patients, or research subjects respectively, have the right to decide whether or not they want to be provided with information concerning their current or future health status. If a subject refuses to be informed with predictive genetic information, his/her right of autonomy might conflict with the interests of genetic family members who want to know.

According to the majority in literature, individual rights generally outweigh those of relatives. But concerning the family's interests, a momentous exemption has been made. It is widely accepted that only the person who undergoes a procedure that yields personal genetic information of predictive character has to decide how to deal with the generated information and whether to communicate it to relatives or not. Nevertheless, under certain circumstances third parties might be grated a right to access personal information even in absence of research subjects' consent, as stated in various ethical guidelines and statements. "Where there is a high risk of having or transmitting a serious disorder and prevention or treatment is available, immediate relatives should have access to stored DNA for the purpose of learning their own status".[255] Similarly, the WHO recommends allowing disclosure of the data as far as it "will avert or minimise significant harm".[256] Here, the scope is even broader, since the text refers to "relevant individuals" and "third parties", and, therefore, not only to close family members.[257]

For physicians or health care providers in general, such exemptions may lead – at least hypothetically – to a conflict between their responsibility to avoid harm on the one hand, and their ethically founded duty to respect individual rights of self-determination and confidentiality on the other hand. The problem is that it is not clear what 'risk of serious harm' really means.[258] Parker and Lucassen point out that serious harm is always open to interpretation. The authors conclude that "the question of what constitutes 'serious' harm is likely to be an ethical question of continuing practical importance in clinical practice".[259]

Another starting point for the ethical debate concerning the balance between individual autonomy and informational interests of relatives is the right to know. It is reasonable to assume that family members have a right to know if genetic information reveals serious risks. This would open them the option to change their life plans, or eventually prevent or treat diseases.[260] This matter of fact can motivate relatives to ask for access to personal genetic information. However, it can also be

[254] Clarke et al 2005, 561. See also Andorno 2004
[255] HUGO Ethics Committee 1998, 2
[256] WHO 2003, 14, Rec.8 (b)
[257] WHO 2003, 13, Article 4.3. Similarly, the US-Common Rule notes that other persons' and common interests justify a breach of individuals' right to confidentiality as an exception. Referring to these wordings, Andorno briefly discusses the relation between the individuals' right not to know and public health interests. See Andorno 2004, 437
[258] According to Andorno, for instance, the risk of serious harm implies the availability of preventive or therapeutic measures. See Andorno 2004
[259] Parker and Lucassen 2003, 71
[260] See Andorno 2004

argued that relatives because of the right to know have the right to not be confronted with any information they probably do not want to know.[261]

According to the ongoing discussions, it can be stated that physicians are not obliged to provide family members with personal genetic information of their patient regardless of whether or not the affected patient has given consent. It has been argued that such a breach of confidentiality "may also compromise the autonomy of the patient's relatives, who may desire not to know genetic risks within family".[262]

De Montgolfier et al discuss the problem of confidentiality connected to predictive genetic information by referring to the very special case of HIV-infected patients. On the one hand, there are various reasons for patients to deny consent to disclose individual genetic research results towards relatives: Relationships to family members may be disturbed or patients may feel guilty or ashamed. On the other hand, the identification of, for example, "a predictive pharmaco-genetic factor may have consequences for other members of the family, taking the same drugs, or other drugs, prescribed for a completely different disease but acting on the same metabolic pathways".[263] The authors conclude that "the decision to share information should be left to the patient after he/she has been correctly informed by the physician about the interest of sharing a piece of information with particular relatives".[264] Similarly, the American Society of Clinical Oncology (ASCO) presumes that „the cancer care provider's obligations (if any) to at-risk relatives are best fulfilled by communication of familial risk to the person undergoing testing, emphasizing the importance of sharing this information with family members so that they may also benefit".[265]

However, the ASCO's recommendation grounds on the current state of genetic research on cancer. Since „in most adult-onset cancer syndromes, the disease probability and medical benefits associated with cancer genetic testing are still being defined", relatives are not supposed to be harmed seriously by a non-disclosure.[266] Contrarily, it seems more likely to increase emotional and psychological distress of healthy family members by providing them with genetic information concerning cancer predisposition. As already mentioned, only some genetic variants in cancer signify a moderate or high risk. Therefore, information about genetic predisposition in cancer is – in most cases – only moderately predictive and measures of prevention are rare or do simply not exist. Thus, it remains questionable, "whether the added information balances the risk of increased familial anxiety that may result".[267]

[261] See, for instance, Data Protection Working Party 2004, 8

[262] ASCO 2003, 2403. In its Declaration on Human Genetic Data the UNESCO even recommends "the right not to be informed should be extended to identify relatives who may be affected by the results". See UNESCO 2003, 43, Article 10. However, it has consistently been asked how patients' relatives can exercise this right, "if they probably even ignore that a family member has been tested". See Andorno 2004, 438

[263] De Montgolfier et al 2002, 670

[264] De Montgolfier et al 2002, 670

[265] ASCO 2003, 2403

[266] ASCO 2003, 2403

[267] Burke and Diekema 2006, S36. The authors refer to a concern unique to genetic research involving children: As an effect of knowing their child carries a genetic trait associated with a certain condition, parents may treat their children differently, for example, by 'medicalising' their child's life and becoming overprotective.

Although barely available, empirical data suggest that the issue of familial anxiety is very important for attitudes towards the disclosure of genetic information within the family. Clarke et al, for example, recorded in their empirical study experiences of genetic counsellors and clinical geneticists with nondisclosure in families.[268] Most frequently individuals explained their decision to withhold predictive genetic information with "the desire to avoid causing anxiety".[269] The authors conclude, in cancer families "affected individuals may be reluctant to raise anxieties in their healthy relatives in the absence of a clear practical benefit".[270]

2.3.2.2.5 Practical challenges of feedback processes regarding individual research results

Whereas the provision of general study results due to its impersonal character may be just a matter of adequate announcement, the feedback of individually relevant research results depends on the donor's informed consent. In bioethical discourse, there is a broad agreement that it is the donor and not the researcher who decides whether or not he or she wants to receive individually relevant research results.[271] If the issue is mentioned in ethical guidelines, the wording is unambiguous: Potential donors have to be informed about their rights within the consent process. "When human genetic data, human proteomic data or biological samples are collected for medical and scientific research purposes, the information provided at the time of consent should indicate that the person concerned has the right to decide whether or not to be informed of the results."[272]

Basically, a prior consent concerning individual research results is necessary to implement not only the right to know but also the right *not* to know.[273] As the Council of Europe emphasises in its guidelines concerning biomedical research, in communication of individually relevant information yielded by a research project "due care must be taken in order to protect confidentiality and to respect any wish of a participant not to receive such information".[274] Similarly, Knoppers et al point out that the implementation of the right not to know "depends on the informed consent process." Therefore, the question regarding feedback of individual research results "needs to be discussed before the research even begins. At that time, the participant can exercise a choice concerning possible future communication of research results".[275] Especially in the context of genetic research, consent has to be obtained

[268] The survey was carried out in 14 regional genetic services, 12 in the UK and two in Australia. Interestingly, the 65 cases of non-disclosure represented less then one per cent of all genetic clinical consultations during the ten month of study period.
[269] Clarke et al 2005, 559
[270] Clarke et al 2005, 560
[271] "The right of each individual to decide whether or not to be informed of the results of genetic examination and the resulting consequences should be respected." UNESCO 1997, 43, Art. 5c
[272] UNESCO 2003, 43, Article 10: The right to decide whether or not to be informed about research results
[273] See Reymond et al 2003, Fernandez 2003a, de Montgolfier et al 2002. After a controversial discussion in the 1990ies, nowadays it is widely accepted in the context of genetic research and diagnosis that the right not to know is regarded as an expression of autonomy. See Andorno 2004.
[274] Council of Europe 2005, Article 27: Duty of care. In article 10 of the European Convention on Human Rights and Biomedicine the right to be informed about "any information collected about his or her health" is accompanied by the clear statement that "wishes of individuals not to be so informed shall be observed". Council of Europe 1997, 4, Art.10.2
[275] Knoppers et al. 2006, 1173

at the very beginning to permit donors "to exercise a right not to know about genetic risks or predisposition to disease".[276]

Referring to the ethical principle of respect for patients' autonomy, several authors argue that donors should decide not only if they want to receive research results. "The prudent approach is to allow the research subject to elect what kind of information he or she wishes to receive, if at all."[277] As far as genetic research is concerned, Sass similarly argues that "health literate individuals will have to make autonomous choices about how they want to deal with the wealth of new genetic information".[278] Regarding the feedback of individual genetic research results, he suggests to supersede the current consent doctrine by a contract model to give patients individual options to choose „(a) for mandating disclosure of individual predictive, preventive, or therapeutic knowledge, (b) for refusal of all or some information, and (c) for postponing such a decision based on then existing individual circumstances or clinical results".[279]

In any case – whether participants generally consent to feedback or whether they consent to different levels of information – a number of scholars postulate that the consent given before the removal of tissue is only a preliminary one. For this reason it has been proposed that feedback of individually important research results should be organized as a tiered decision-making process. The first decision is supposed to be before the study begins. After being informed about the objectives and procedures of the study, participants, or tissue donors respectively, are asked if they want to get feedback of individually important research results at all. The second step of the decision-making process is supposed to be at the moment when research results are available which may be of relevance for specific individuals or groups of participants. At this point, donors who agreed on an individual feed back process should be informed and asked, whether they want to receive concrete results that may be relevant for them via their doctor. As Renegar et al highlight, such a "two-step-process for documenting the subject's decision to receive (or not to receive) results takes into account participants may change their minds during the course of the study".[280]

A tiered model of consent to feedback of genetic research findings meets not only the uncertainties in the interpretation of genetic research results. Another strong argument for a step-by-step-model arises from experiences with perceptions and understandings of informed consent procedures. There is empirical evidence that research participants usually do not remember the content of information or even do not recognise at all that they gave consent.[281] Wendler et al point out that the rapid oblivion of given information is a serious problem. "If subjects continue to forget the risks of disclosure (…) the provision of results could increase the risks of genetic research by increasing the information that subjects may disclose."[282] Therefore, if a second consent must be obtained at the time concrete genetic research results of

[276] Merz et al. 1997, 254
[277] Banks 2000, 580
[278] Sass 1998, 292
[279] Sass 1998, 295
[280] Renegar et al 2006, 35
[281] For a detailed discussion of research participants' loss of information during the consent process and opportunities offered by ongoing communication and tiered consent models to response adequately to this challenge see paragraph 2.2.2.2.2/The character of information given in the consent process.
[282] Wendler et al 2002a, 261

individual importance have become available, an additional occasion to provide patients with information and counselling will arise. Furthermore, questions concerning the feedback of research results of importance for relatives should explicitly be addressed within the consent process.

Generally, information about the feedback process given before tissue removal has to take into account various aspects. First of all, information about study results has to occur in an understandable and comprehensive manner. Shalowitz and Miller point for example out that understandability of results is important for participants to exercise their right to self-determination: At least if results "are to be meaningful and useful to participants' personal decision-making, they must be disclosed in a manner that is as understandable as possible." Furthermore, information should be as specific as possible, especially when patients are invited to choose between different types of feedback regarding individual research results.[283] As Reymond et al state referring to feedback processes within gene expression studies in the context of cancer trials, it has to be clearly addressed that results may be uncertain, that they might lack of significance, or that they may even be falsified in the ongoing research process.[284] Authors call also attention to the fact that it is usually very difficult to evaluate the clinical value of gene expression information. Additionally mentioned, information about genetic predisposition can cause fear. Altogether, the authors insist on informed consent to feed back genetic research results.

Referring to the ethical principle of doing no harm, Eriksson and Helgesson reflect on another important aspect of adequate information. Since the consent to feedback can raise unrealistic expectations, patients have to be informed about the possibility that research results may *not* have any individual benefit or importance. The authors see those expectations that can not be fulfilled as psychological harm.[285] Indeed, empirical data have shown that research subjects often expect a certain benefit in participating and that they perceive clinical trials "within the framework of curing".[286] Analysing interviews with participants of clinical drug trials, Corrigan, for instance, emphasises that all interviewed participants thought that the new drug on study "was likely to be an improvement on existing alternative drug treatment".[287] Similarly, a survey among 287 participants of cancer clinical trials in the US shows, for instance, "major deficiencies" how the purpose of the trial are understood: Although many of the respondents declared that they were satisfied with the consent process and understood given information, just a few were aware "of non-standard treatment, the potential for incremental risk or discomfort, the unproved nature of treatment, and the uncertainty of benefits to self".[288] Thus, the "therapeutic misconception" seems to be empirically confirmed.

As Kodish et al exemplify by the field of paediatric oncology, clinical investigators are exceptionally challenged, because they have to find a balance between their role as physicians and those as researchers. The authors conducted interviews with clinicians, or investigators respectively, in the context of clinical trials in children's cancer research. The big majority of the interviewees approached informed consent

[283] Options to be chosen could be: Feedback of results only, if they refer to prognostic information; feedback of results only, if they are predictive; feedback of results only, if prevention strategies already exist, etc.
[284] See Reymond et al 2003 or Pelias 2004
[285] Eriksson and Helgesson 2005, 1072
[286] Bamberg and Budwig 1992/93, quoted by Corrigan 2003, 782
[287] Corrigan 2003, 788
[288] Joffe et al 2001, 1775

discussions with parents, having the clear intention in mind to get consent for participation in the trial.[289] Kodish et al, therefore, insist in the distinction between "therapeutic research" and "research with the prospect of direct benefit", because "the terms investigators use have a significant impact on their own approach to research recruitment, and on the informed consent process itself".[290] As Joffe at al conclude, „research ethics rest on the realisation that the goals of advancing science or treatment, however noble, could conflict with the interests of present patients".[291] Thus, to avoid that research is equated with medical treatment or understood as part of it, tissue donors should be provided with sufficient as well as with unbiased as possible information about the character of expected results.

Indeed, it is repeatedly underlined that informed consent procedures may overstrain patients. Questions merely listed in consent forms, demanding information, and the complex issue in general might challenge the ability of patients to comprehend, in particular if they suffer from serious conditions like cancer. In the context of genetic research the complexity of information is a general problem, because genetic information is often not comprehensible by lay persons. Since genetic knowledge might simultaneously cause far-reaching social or psychological consequences, individual feedback processes should always be supplemented by medical consultation and genetic counselling.[292]

Additionally, counselling is endorsed by empirical data. In a recent qualitative study about attitudes of breast cancer patients towards tissue based research participants expressed concerns that individual results might be too difficult to understand.[293] As Shalowitz and Miller conclude, it might be necessary to use "established counselling methods to communicate complicated or uncertain results".[294] However, ethical guidelines do refer to the issue only indirectly. The Council of Europe, for instance, recommends that "information of relevance to the current or future health *or* quality of life" should be communicated "within the framework of health care or counselling".[295] The American Society of Clinical Oncology (ASCO) mentions pre- and post-test counselling only in the specific context of genetic testing on cancer to discuss possible risks and benefits of cancer early detection and prevention modalities.[296]

However, some intrinsic limits of genetic counselling have to be taken into account. As Van den Boer-van den Berg and Maat-Kievit state, "informing is not as value free as it sometimes seems to be, certainly not for the one who receives the information." Referring to genetic counselling in the case of Huntington 's disease, they make some general remarks concerning the counselling situation. "If a genetic counsellor thinks he/she ought to inform a couple of all findings, even if the findings are uninformative or difficult to interpret, he/she creates an environment in which decision 'to do' something with the test results seems wiser than ‚to do nothing'."[297]

Merz et al approach this problem by arguing for counselling provided *before* generating and processing information. The "potential for use of research

[289] Kodish et al 1998, 2470 and 2476 p
[290] Kodish et al 1998, 2468
[291] Joffe et al., 2001 1776
[292] Luttenberger et al 2006.
[293] Kaphingst 2006, 396
[294] Shalowitz and Miller 2005, 739
[295] Council of Europe 2005, article 27, Duty of care
[296] ASCO 2003, 2398
[297] Van den Boer-van den Berg and Maat-Kievit 2001, 41

information in the clinical management of patients" requires the need of "adequate counselling before developing information about the patients."[298] This argument is relevant in the context of genetic research. Here, the right to know as well as the right *not* to know require an adequate counselling about the character of possible future research results. As Williams concludes, professional counselling before participation in genetic research could sometimes be necessary to ensure that "the ramifications of participation in genetic research are properly disclosed and comprehended by each research participant".[299]

In the realm of informed consent concerning feedback of individually important research results it is necessary to highlight some issues concerning data protection and personal rights. First of all, potential tissue donors have to be informed that the re-identifiability of their personal data is mandatory for individual feedback processes.[300] Therefore, an important prerequisite for such a feedback process is that genetic data are not anonymized, but pseudonymized. This means that generated data can be linked back to a specific person by specified procedures. In order to protect rights and interests of donors, the feedback process itself must be designed such that in the course of such a process no unauthorized person may learn about the genetic constitution of a specific individual.

Interestingly, authors have not paid much attention to the question regarding *who* has to disclose research results towards patients. Referring to the ethical requirement to disclose individually relevant research results, Knoppers et al point out that "only a few guidelines at the international level specify with whom this duty lies."[301] In most cases the patient-physician-relationship is supposed to be an adequate social basis for the disclosure of sensitive information.[302] It is also emphasised that physicians are better qualified than researchers to translate research results to the participant. In conclusion, physicians of donors' choice should be involved in the transfer of information to the patient.[303]

To avoid that unauthorised persons access stored personal data, de Montgolfier et al organize their DNA-bank in a way that "only the physician responsible for the patient has the key to make the connection between a result and a patient".[304] Luttenberger et al, who describe the process of pseudonymization in the case of a German biobank,[305] propose that the donor and his/her physician should get access to individual genetic data only together before the donor's physician has proved to be entitled to trigger the individual feedback process. Therefore, according to this model, neither party alone can see these data.[306] Additionally, before individual data are forwarded to the physician of the requesting donor, the genetic data has been validated without connecting them to the personal data of the donor.

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[298] Merz et al 1997, 254

[299] Williams 2001, 451

[300] The information that identifiers will not be removed totally has to be given as well in regard to donor's right to withdraw consent to the use of a tissue sample. See paragraph 2.2.2.4/The right to withdraw consent

[301] Knoppers et al 2006, 1175

[302] See Andorno 2004

[303] See Knoppers et al 2006, Banks 2000

[304] De Montgolfier et al 2002, 669. The paper discusses issues of confidentiality, feedback and informed consent referring to a DNA-bank of HIV-patients in France.

[305] The case study is done in the context of Schering AG's GENOMatch Biobank. See Luttenberger et al 2006

[306] For the legal implementation to ACGT structure see part II/Legal requirements, see also D 11.1

Another important issue that has to be addressed is financial supply to organize the feedback process. As de Montgolfier et al point out, the return of research results "also has financial aspects, which have not received much attention to date" and propose that "a specific budget could be estimated at the beginning of a research project".[307] Another position argues that counselling, for instance, is not justifiable from an economic point of view. „Some object that the costs and burdens of disclosing study results to participants, including contacting participants and maintaining trained counsellors on staff, will tax already strained research budgets and make future studies more difficult."[308] Even patients occasionally express concerns regarding the research budget. In the aforementioned survey, examining the attitudes of breast cancer patients towards tissue based biomedical research, some participants put on record that the feedback of individual research results could constitute a "logistical burden" for research projects.[309] Hence, costs and therefore breadth of genetic counselling and disclosure have to be taken into consideration. Counselling may, for instance, be provided only when research results are available, or may be extended by additional counselling before the consent form is signed. Furthermore, the statement of costs should include costs arising from the dissemination of general research results, as for instance printing costs for leaflets or salaries for web-based services.

Principally, it has to be taken into account that counselling and disclosure always require special expertise, because researchers are normally not trained in communication to the general public. They "need to be alert for the moment when dissemination requirements go beyond their own expertise", states Zlotnik et al and ask for the engagement of educational and communication experts who can responsibly popularise and contextualise results.[310]

2.4 SUMMARY OF CONSOLIDATED ETHICAL REQUIREMENTS

ACGT aims to integrate clinical, biomedical, and genomic information on cancer to provide the cancer community a Grid infrastructure on a European level. In order to assemble and to prove the Grid's structure, several preconditions have to be fulfilled beyond technical requirements. Firstly, patients affected by cancer are needed who volunteer to take part in the ACGT-clinico-genomic trials. Secondly, genomic data of patients are needed in addition to socio-demographic and clinical data. Therefore, samples of tumour and blood have to be collected and analyzed from the involved patients.

The current ethical debate concerned with tissue based research has shown that new questions regarding the widely acknowledged doctrine of informed consent and the disclosure of research results arise. In the context of the ACGT structure, these questions have to be addressed and analyzed in order to protect patients' right of autonomy and self-determination – the most basic principles to be respected in the context of medical research involving patients.

[307] De Montgolfier et al 2002, 669
[308] Shalowitz and Miller 2005, 739 f. See also Banks 2000
[309] Kaphingst et al 2006, 396
[310] Zlotnik et al 2005, 11

2.4.1 Ethical requirements

Summarizing the ethical discussions presented in this paper, it is obvious that ACGT has to take several ethical requirements into account. According to this demanding assignment, the major challenges are to design (1) the informed consent process, (2) the donor driven inquiry process, and (3) the investigator driven feedback process of individually important study findings.

2.4.1.1 Summary: The informed consent process

The doctrine of informed consent is one of the well known elements of medical ethics and bioethics today. In ethical terms, the requirement for informed consent is based on the principles of respect for persons and respect for human dignity. Recognized as a condition *sine qua non* for any preventive, diagnostic or therapeutic medical interventions, the doctrine represents an essential ethical and legal requirement to protect patients' rights to integrity and self-determination.

In current clinical research, the doctrine of informed consent is also widely accepted and practiced. But with respect to tissue based or biobank research the discussion has changed remarkably. Doubts have been raised concerning the applicability of the doctrine in its current form. Some authors think that the established informed consent procedure is not sufficient to meet the challenges that arise from tissue based research, especially the uncertainty concerning future research projects as well as future outcomes. Questioning its applicability for tissue based research in general, others want to see the consent procedure designed as a contract between researcher and donor. Finally, informed consent has been criticized as a mere ritual. Clinicians and researchers often consider the informed consent process as paperwork to be done, mainly for legal reasons. According to this reading, current informed consent procedures do not serve as an instrument to ensure patients' autonomy but to avoid litigation and to solve questions of liability. However, despite such doubts, most scholars still maintain the informed consent as an instrument to implement the principle of autonomy. While this position is widely accepted, the debate on form and scope of consent in tissue based research is highly controversial.

The discussion on different models of consent (see paragraph 2.2.2.1/Models of consent) has shown that one of the major challenges is the question regarding the possible future uses of donated tissue samples. The practice of obtaining consent for unspecific future use of samples and data generated from clinical trials has been criticized as not being adequate for genetic research. But a convincing model of consent corresponding with patients' rights and, at the same time, enabling investigators to use tissue samples in the future still has to be found. The *specified consent*, restricted to concrete research questions and projects, fails to meet the interests of tissue based research; the *blanket consent*, allowing unlimited future research, fails to meet the general standards required by the current informed consent doctrine. Furthermore, blanket consent can hardly be regarded as legally sufficient for genetic and/or genomic research. *Tiered consent* arranging different levels of authorisation in the consent procedure has been proposed as able to provide an appropriate solution because if offers to donors the possibility to authorize a broader or more restricted range of research to be done with their samples and data and time frame they may be used for research. However, this model subdivides study subjects into different groups which have to be treated differently and therefore is difficult to handle in practice. Therefore, a model of consent referring to a *purpose of intermediate*

scope (clinico-genomic research on cancer) in the *context of a specific structure or project* (like ACGT) may be within the limits of ethical as well as legal considerations. This model also includes the necessity to ask for reconsent if the scope of consent (clinico-genomic research on cancer/ACGT project) will change.

Another question is whether to obtain informed consent should be understood as a one time action, or as an ongoing process. A number of well founded arguments have been introduced into the debate to take consent as a process not finished with the moment a tissue donor signs the consent form. Although some circumstances differ remarkable from tissue based research with adults, research involving children illustrates that ongoing communication is not only necessary, at least as far as genetic research is concerned, but possible as well. It may be assumed that the interest in ongoing communication about research is related to the severity of the disease the patient is suffering from. Because of the lack of empirical evidence, it remains a point of discussion whether consent as a process generally strains patients. To provide patients continuously with information concerning the research process, or to keep communication going respectively, might be seen as an expression of respect as well. Thereby, ongoing communication might facilitate obtaining consent for research. Furthermore, re-consent is crucial in the feed back process.

Objections against consent as an ongoing process are mainly based on unfavourable experiences with re-consent made in the US-health care system. Data on patients' attitudes towards such a model from different countries is limited. Therefore further investigation is needed in different cultural settings. The same is true for patients' apparent lack of interest in the question of consent. There is an urgent need to build an empirical basis for scholarly discussions as well as for practical solutions concerning patients' attitudes towards different models of consent in tissue based research in Europe.

As already mentioned the communication and decision-making process concerning research participation might distress patients with serious conditions in a way that they are unable to make an autonomous decision or even to understand the information provided in the consent process. This matter of fact poses particular challenges on the way information will be given to enable informed and conscious consents. In this context the right to withdraw consent is in the focus of the discussion. Although it is desirable to clear up or rather avoid misconceptions, it remains extremely questionable whether an obligation to present the objections for the personal decision to withdraw given consent is an appropriate way to reach these goals. Additionally, respect for research subjects' autonomy and self-determination do not permit to leave individual decisions concerning research participation up to the judgement of second or third parties. In consequence, donors must have the option to withdraw their consent without statement of grounds. Misconceptions about consent and withdrawl procedures must be avoided by appropriate information and communication.

2.4.1.2 Conclusions: How to design the informed consent process

Taking the fundamental concerns into account, ACGT should design the informed consent procedure by enhancing donors' autonomy as the main objective. In regard to the shortcomings of the specified, the blanket and the tiered consent models, the intermediate scope model seems to be the most appropriate solution to meet the complex challenges of donors' autonomy.

The intermediate scope model can be developed and tailored to the specific requirements of the ACGT-structure. This would mean to obtain the general consent to

participation together with the initial consent to feedback of research results not later than data will be transferred to ACGT, and to ask again for re-consent, when concrete study findings of potential individual relevance are available. Thereby, this consent procedure promotes an ongoing communication between clinician and patient over time.

Because of the projected Europe-wide cooperation within ACGT, it is furthermore indispensable to ask for sharing of data, information, and (potentially) tissue samples. To be clear and reliable about the scope of consent, the consent should be restricted to ACGT-projects only. Therefore, the timeframe and the group of researchers using data, or samples respectively, will be limited to the existence of ACGT as well. Fundamentally, the informed consent process including the patient information has to be consistent with each ACGT-project and -trial.

The discussion on the character of information (see paragraph 2.2.2.2.2/The character of information) has shown that the patient can only make independent decisions with adequate information provided in the consent process. Referring to the principle of autonomy and respect for participants, authors regularly stress the importance of comprehensive and understandable information. However, in practice this claim is faced by a number of obstacles. There is empirical evidence that patients usually lose rapidly sight of the information given in the consent process. Understanding informed consent as an ongoing process might reduce the loss of information as well as the lack of understanding.

The information and decision-making process concerning research participation might distress patients with serious conditions in a way that they are unable to make an autonomous decision or even to understand the information. This matter of fact poses particular challenges on the way information will be provided to enable informed and conscious consents. Regarding the presentation of information, the following aspects are important for possible donors to make their own decisions, whether or not they are willing to participate in ACGT-trials:

- *Be informed clearly:* The objectives, intention and range of research as well as the specific characteristics of the ACGT-structure have to be addressed and explained in a comprehensive and understandable way. Potential donors should be able to understand the kind of data that will be processed as well as the extent of projected data interchange.
- *Be aware of legal rights:* Furthermore, potential donors should be aware of their legal rights concerning the withdrawal of consent at any time as well as disclosure of stored data and information. In this context, it is indicated to explicitly refer to the general right to information based on the EU-directive of data protection. However, it is still open to discussion whether or not the right to access stored personal data also comprises the right to understand its relevance and importance. Thus, it is up to the research facility, if further information and explanation concerning stored personal data will be provided or not. From an ethical point of view, however, a mere disclosure of data without any explanation can hardly be supposed to be sufficient.
- *Be informed about consequences:* As far as the decision about the feedback of individual research results is concerned, it is important that potential donors understand the possible consequences of the disclosure. As discussed in this paper (see in particular paragraph 2.3.2.2.5/To whom to feed back?), the decision to feed back individual research results must be hold by the tissue donor, not the researcher or health care provider. Hence, information about possible consequences should be provided in a way that

enables potential donors to decide whether or not they want to be informed about individually important research results. Whether or not donor's relatives will be informed about study findings which may be of potential relevance for them individually has to be left to the donors discretion.

- *Be aware of counselling:* To meet the manifold information duties, it is advisable to offer adequate explanation and, if necessary, counselling within ACGT clinical trials before consent is obtained and during the whole research processes. Especially in the highly exploratory field of clinico-genomics an extended need for explanation and counselling can be assumed. Hence, expertise for explanation and should be provided in the context of ACGT clinical trials.

To facilitate potential donors' decision-making process regarding the participation in ACGT, the patient information should consider at least the following aspects:

- Information about the main intentions of ACGT and the range of possible uses of samples and data
- Information about measures token to protect donors' personal rights and to guarantee confidentiality
- Information concerning the right to withdraw consent at any time
- Information about donors' legal rights in regard to the disclosure of stored data and information
- Information concerning the feedback process of individual research results
- Contact information for donors to address inquiries
- Information about the timeframe of storage and consent

Beside the quality of information and its comprehensibility, it is indispensable to ensure that donors consent voluntarily and freely, that means without being constrained nor defrauded. Moreover, consent should be given explicitly. A pragmatic implementation of this demand is the written consent form.

Obtaining informed consent is particularly challenging for research involving children. Depending on age, minors are either de facto or de jure not competent of giving consent. Therefore, consent must be obtained from the parents, or legal authorized representatives respectively. But it is widely accepted, that children's assent is also necessary according to the minors' capacity. Therefore, minors as well as their parents have to be provided with information about the nature and course of the trial, the possible risks and benefits, and implications of participation. According to the minors' capacity of understanding, the information has to be formulated in a child-oriented manner. Nevertheless, the ethical debate (see paragraph 2.2.2.2.3/Particularities of consent to research involving children) has shown that no consensus exists how to appraise a child's capacity appropriately. Proposals concerning the age as stage of attained maturity are ranging from the age of seven to twelve years. Since empirical data on children's capacity are very limited, it finally remains to the discretion of the practitioner to assess the child's capacity to give assent.

Accordingly, it is recommended to give pediatric participants the option to reconsent when they become mature. In order that the grown up participants can make their independent decisions, researchers have to provide them with sufficient information about storing procedures and confidentiality protections, including potential risks of storing and processing data in the future. Therefore, an ongoing communication with

parents *and* children seems to be required to avoid coercion and involuntariness of minors.

Last but not least: Not only the donors, but also the users of the ACGT Grid structure have to be informed before getting access. Concerning the future of ACGT as a research structure involving several hospitals in Europe, users have to know what kind of limits the given informed consent puts on the use of samples and data. Furthermore, to achieve consistent ethical standards within ACGT, it is indispensable that investigators give an explicit consent as well. To participate in ACGT, hospitals and research institutions should declare in a written form that they will meet the requested standards of consent and information. Given the importance of ethical and legal aspects for the legitimacy of biomedical research, it is reasonable to demand a declaration regarding practical details how potentially participating institutions want to implement ethical standards required in ACGT.

2.4.1.3 Summary: Donor driven inquiry processes and investigator driven individual feedback processes

Since ACGT has been projected as a research structure involving hospitals and research institutions all over Europe, information flows within ACGT will reach a high degree of complexity. The design of data and information disclosure must not only take a variety of medical, ethical and legal aspects into account, but has also to include organisational and technical issues.

Comparatively easy to organise is only the disclosure of general study findings. In bioethical discourse (see paragraph 2.3.2.1/Informing about general research results), it is widely agreed that general research results must be accessible for research subjects. Public availability of study results not only makes the process of research more transparent, it also expresses respect for the research subject and his or her contribution to research. Especially in tissue based research donors usually have no other opportunity to be informed of what have been done with their tissue. By making study findings available, investigators brief donors on their activities using samples and data. Thus, the tissue donors participated in ACGT-projects should actively be offered summaries of research results.

However, there is no doubt in the ethical discussion (see paragraph 2.3.2.1.2/Practical challenges of feedback processes regarding general research results) that the traditional way of making study findings publicly available – the publication in a scientific journal – does not meet the demands posed by the complexity of current biomedical research objectives. Scientific discourse on the meaning of genetic information, for instance, is usually not easily comprehensible for lay persons. For this reason, scientific outcomes should be published as popularised summaries. Proposals in the literature how to disseminate general research results include personal letters, news bulletins or leaflets, printed or electronic newsletters, or other web based services.

Higher demands have to be made on data administration and data protection arising from the legal duty to disclose stored personal data on donor's request. As discussed in this paper (see paragraph 2.3.1/Access to personal information), anybody has the right to access personal data stored about him or her. The right to access such data, which is based on ethical principles as well as on legal provisions, is a passive one. Translated into the ACGT-structure and in one of the trials involved in the project, the implementation of this right requires an organisational structure that is suitable to reply to donors' requests for information about personal data stored about him or her.

The investigator initiated feedback of individually relevant research results can be called the greatest challenge for data administration and data protection within ACGT. First of all it requires that data will not be anonymized, but pseudonymized. It is the only way to enable feedback processes of individually important research results, and to allow individual donors to withdraw consent concerning the usage of their tissue sample and data. The process of feeding back individually relevant data also requires technical mechanisms to guarantee data retrieval by those donors who require an individual feedback. Moreover, precautionary measures have to be generated to avoid access of unauthorised persons to personal data.

In addition to organisational and technical questions several important ethical aspects of the issue needs to be considered. The first one is the type of data to feed back. Some researchers argue that only results of clinical relevance should be fed back. However, as discussed intensively (see paragraph 2.3.2.2.2/What to feed back?), the relevance of research results is not easy to define. Genetic research results are usually characterised by a lack of established common interpretation and independent validation. However, interpretation of preliminary study results may change as data become more reliable. Hence, statements about their individual relevance are always preliminary in character. Since such information could sometimes be helpful, but sometimes also harmful for patients, they could be harmed by being excluded from individual information as well as by being provided with it. Clinical relevance thus can not serve as a sole criterion to regulate the feedback of individual research results. Therefore, it is recommended to give patients the option to decide about feedback of personal data, especially in such a highly exploratory field as gene expression.

Furthermore, in new research areas like gene expression studies, or clinico-genomic research in general, it is difficult to draw the distinct line between fundamental and clinical research. In recent years, several approaches have been made to cope with the increasing lack of clarity regarding the traditional demarcations of clinical, fundamental, applied, or translational research. But attempts to reclaim traditional demarcations usually fail. The Consortium on Pharmacogenetics, for instance, suggests making the distinction between pharmacogenetic drug trials and hypothesis testing studies (see paragraph 2.3.2.2.2/What to feed back?). Whereas drug trials might produce results that are directly interesting and beneficial for the participant, hypothesis testing studies usually have no direct medical relevance for patients. However, this distinction may not always apply; in the context of ACGT individually relevant results are expected in the course of genomic research (see paragraph 2.3.2.2.3/Characteristics of genetic research results).

Another question is how to balance the individual's right of self-determination and the interests and rights of relatives. As far as genetic information on cancer susceptibility is concerned, individuals' right clearly supersede interests of family members. Since genetic research on cancer usually yields only moderate predictive results, it seems more likely to increase emotional and psychological distress by healthy family members providing them with research findings than by not disclosing them.

The specific challenges concerning the feedback of individual research results within ACGT can be pointed out as follows:

- *Individual cancer prognoses based on gene expression signatures are still uncertain*. These uncertainties may even grow, since different models to connect genomic data with clinical outcomes might give rise to different interpretations of available data. Uncertain prognoses because of genomic study findings may provoke fear and anger, possibly even for no reason. However, since gene expression information might have a direct influence on

therapeutic or treatment decisions individual feed back processes should be provided if clinically relevant and sensible.

- *Tissue based cancer research might reveal data of a predictive nature which may also be relevant for family members*. Since such data usually have a low predictive value, they are of little help for healthy family members and may even create emotional and psychological distress. However, in case of familial variants of cancer, where an increased risk within the family is already known, confidentiality has carefully to be protected towards the patient or tissue donor as well as towards his or her relatives. In these cases it should be up to the donor to inform family members of the possible relevance of his or her results for them. In principle, the issue of disclosing genetic information to family members has particularly to be discussed within the context of ACGT, because new aspects will probably arise in research as well as in clinical practice.
- *Research involving children has to protect their right not to know.* As far as children are involved in clinico-genomic pilot trials, their right to know as well as *not* to know has to be protected. At latest when children attain full age, they are entitled to be provided with information about personal study findings. At the same time, they are allowed to exercise their right *not* to know. For the latter reason research results should not be entered into medical records of children. Furthermore, in regard to children's informational rights the issue should be discussed whether individual study findings will remain re-identifiable without time limit, and, if at all, when such time limit should be set. In this context it has to be stressed that it is recommended to give pediatric participants the option to reconsent when they become mature. Within the reconsent procedure they have to be provided with sufficient information about storing procedures and confidentiality protections, including potential risks of storing and processing data in the future.

2.4.1.4 Conclusion: How to organize donor driven inquiry processes and investigator driven individual feedback processes

Since clinico-genomic research may yield individually relevant results, ACGT-structure must – from the ethical point of view – be able to actively offer such findings to patients.

Before patients consent to tissue donation for research, information about the general character of genetic research results has to be provided. That also includes information concerning the feedback of research results, the possible relevance of such results for the individual and his or her relatives, as well as the possibility that research results may *not* have any individual benefit or importance. Furthermore, potential donors have to be informed that re-identifiability of genetic data is necessary to give individual feedback at all.

The relevance of personal research results is not easily to approach. Therefore research teams, or operators within the ACGT-structure respectively, should carefully assess the relevance of the results they expect and inform donors' physicians at least briefly about their conclusions in regard to the quality of the findings for the individual donor.

Donors who have initially consented to participate in feed back processes should than be contacted by the doctor and asked whether or not he/she wants to receive results

which could be important for him/her. Since the donor's consent implements the principles of autonomy and self determination, which also comprise his/her right to know or *not* to know, he or she should have the option to consent again to disclosure when study findings are available.

To avoid that unauthorized persons access stored personal data, it is proposed that the donor and his/her physician of choice get access to individual genetic data only together before the donor's physician has proved to be entitled to trigger the individual feedback process. Furthermore, a careful arrangement of feedback processes includes the financial and logistical supply.

To ensure that donors understand the information provided, individual feedback processes should also be accompanied by counselling. From this follows that physicians of donors' choice should always be involved in the transfer of information to the patient.

Given the complexity of ethical aspects to be considered in regard to disclosure and feedback, the task to communicate information generated within the research structure to tissue donors should not be underestimated. In this context, it might be prudent to establish within the ACGT-structure a multilingual, internet-based information service for donors. The information service could be responsible for publication and dissemination of general study findings and other news concerning research activities within the network of ACGT. It could also be designed as an initial contact point for donors who look for more or specialized information that passes them on to other persons or places offering adequate expertise. Especially when more clinics and trials become involved in ACGT, it is advisable to integrate such a service into the architecture of ACGT.

Moreover, establishing such a web based service would initiate further, ongoing examination of ethical requirements, data protection measures and feedback processes within ACGT. The design of such processes could continually be revised and new challenges for patients' rights arising from future research activities could be approached more easily. Finally, beyond the obvious practical benefits of such a service, its establishment is an expression of respect for tissue donors' autonomy and altruism.

Generally, the ethical standards in ACGT need continuously be observed to ensure long-term adherence to existing ethical standards and to identify new ones, which have not been anticipated yet. Therefore, a continuous monitoring of existing tools and instruments for data protection as well as of the whole structure of information flows in regard to patients' rights and interests is prerequisite for patients' trust into ACGT.

However, to take patients concerns seriously, a better understanding of their perspectives is indispensable. Without patients who volunteer in clinical trials future clinico-genomic research is not possible. Some authors have expressed concerns that patients might be overstrained by the demands of such a project or not interested in research at all. Since these perceptions are usually derived from a small empirical basis of data mostly collected in the context of the US-health care system, it is necessary to assess views and attitudes of patients in Europe towards the feedback of research results as well as towards focus, scope and character of consent processes.

2.5 OUTLOOK: ETHICAL CHALLENGES IN THE EUROPEAN CONTEXT

There are some ethical challenges related to the perspective of ACGT as a research structure involving several clinics in different European countries. We address here in a generalised manner some of the issues we consider important in the European context and, therefore, to be discussed and related to the architecture of the ACGT project in time.

2.5.1.1 Revision of data protection and information flows

The extent of data interchange as well as the variety of access possibilities projected in ACGT requires the establishment of data protection tools and systems developed conscientiously and carefully. From the perspective of patients' rights, the structure of data and information flows is challenged by conflicting requirements: On the one hand confidentiality has to be protected, on the other hand stored information has to be accessible on request or even actively be disclosed.

Since until now only a few Grid structures have been built up for health research purposes, analysis of data protection tools and of systems regarding patients' rights is rare. In order to ensure long-term data protection and confidentiality, it seems therefore advisable to continuously revise existing tools and instruments as well as the structure of data interchange and information flows. Benkner et al, for example, refer to this argument. In their paper related to the European GEMSS-project they state that the security of the structure "must be periodically reviewed".[311] Since the ACGT structure is projected to be continuously enlarged within the next years, it would be farseeing not only to discuss the issue of regular revision process itself, but also to exchange views and experiences concerning its practical implementation.

Furthermore, Benkner et al propose to make patients "aware of the processing that will occur, and be able to review and correct the information held about them".[312] Hence, even if such an active participation of patients seems to be improbable in the review process, they must have the possibility to review and correct individual data and information. Hence, appropriate instruments must be implemented within the structure of ACGT to ensure the access to stored data and information on the review of security measures. EU-law guarantees a right to information about stored data. However, it remains an open question whether patients need to be actively informed about their right to access information stored about them. But it would be advisable to address the issue explicitly in the consent form.

2.5.1.2 Community interests

To ensure that patients' rights will be guaranteed in the long-term within the architecture of ACGT it is useful to be clear about possible implications that the administration of health care in Europe might have in the future concerning these

[311] Benkner et al 2005, 179. GEMSS stands for Grid-Enabled Medical Simulation Services (EU IST-project 2002 – 2005, www.gemss.de)
[312] Ibid

rights. At least, it is advisable to take structural tendencies of European health care policies into consideration.

Especially in countries with a state-run health care system, the law tends to prioritize community interests with possible adverse effects on privacy rights. In her analysis of recent regulations concerning research and consent in the UK, Case even sees a "fundamental change" regarding patients' rights to confidentiality, self-determination and autonomy.[313] Referring to the British law, she notes a distinction between physical and informational autonomy which made it possible to dispense from consent in research concerning information and data. Somewhat fatalist, she concludes with the assumption "that privacy will regularly be subordinated to community interests".[314]

However, societal interests have been discussed repeatedly in debates about tissue or blood donation for research purposes in the last years. Following the argument of the British Medical Council, for example, "in benefiting from the National Health Service, patients should be encouraged to give something back for the public good".[315] Similarly, the Swedish authors Eriksson and Helgesson point out that biobank research is a "public endeavour to promote the common good".[316] They even state a moral obligation to donate biological samples and to allow it to be used in future medical research. "If you expect to receive the best possible treatment, you ought to contribute to the processes by which such treatment is established. If you do not, you are a *free rider*", they summarise.[317]

A minority in the discussion argue that community interests are supposed to be superior to personal rights, by connecting the issue to the broader context of economical changes within European health care systems. To the same extent the necessity to cut expenditures grows, values as solidarity and society interests gain significance in public discussion. That is why the current concept of patient's autonomy and self-determination might be called in question by public health issues in the future.

Beyond these general considerations regarding changes of ethical priorities, there exist a concrete public health issue of ACGT's concern. Patients' rights of privacy, confidentiality and self-determination might be jeopardised in practice when it comes to the question of cancer or, more general, disease registries. Some years ago, for example, the British General Medical Council (GMC) prohibited almost conclusive the disclosure of patient details to cancer registries without expressed consent. In the discussion on the draft guidelines medical profession members asserted it would be impracticable to obtain express consent, because the consent procedure would overstrain cancer patients. The fear was "that cancer registries in the UK would collapse if informed consent were to be made a precondition to the communication of patient details".[318]

Many EU member states have been carried out cancer registries. The issue of registration is an important challenge for patients' informational autonomy. Therefore, it should be consequently discussed within ACGT how to deal with conceivable requests

[313] Case 2003, 215
[314] Ibid, 234
[315] MRC 2004, 4
[316] Eriksson and Helgesson 2005, 1075. For clinical research, Evans draws a similar conclusion: „By analogy with the paying of income tax, patients should not be allowed to ‚veto'' their social responsibility to take part in clinical research". Evans 2004, 198
[317] Ibid
[318] Case 2003, 225

for data transfers into national disease registries. For instance, the installation of registries regarding gene expression in cancer may be envisaged in the future.

3 LEGAL REQUIREMENTS

3.1 INTRODUCTION

Chapter 3 analyses the legal requirements to be fulfilled for lawfully establishing an integrated Clinico-Genomic ICT environment employing data extracted from human tissues.

We start with an in-depth analysis of the European Data Protection Directive 95/46 EC, which introduces rules applicable to every processing of personal data and sensitive data on a European level, which had to be transformed into national law by the Member States. The Directive sets out the rights of the data subject and control mechanisms, regulates the transfer of personal data into third countries and establishes general rules on the lawfulness of the processing of personal data.

Furthermore, the relevant sections of the Directive on Electronic Commerce 2000/31/EC are analyzed.

Under 3.3 the results of the abstract analysis are applied to the concrete project of ACGT.

As ACGT aims at the exchange of data, the data flows within ACGT are presented and explained. Genetic data of a patient will be collected and stored in a GRID-infrastructure, so that researchers participating in the project can access the patient's data for research purposes. For the success of the project and the acceptance of the patients it is crucial that the data flow is conducted lawfully.

The characteristics of genetic data with regard to data protection are assessed. Due to the fact, that they provide information not only about the data subject itself, but also about his or her relatives, possible diseases etc., genetic data is highly sensitive data, which can only be processed under special requirements. Importance is laid on the question of whether anonymous or pseudonymous data should be processed within the framework of ACGT, the dangers of possible de-anonymization and the legal question of whether additional knowledge is attributable to the data controller or not. Furthermore, the legal issues which arise from the inclusion of a trusted third party into the processing of data are discussed.

3.2 THEORETICAL ANALYSIS

3.2.1 European Data Protection Directive 95/46 EC

3.2.1.1 Genesis

The first pieces of legislation in the field of data protection were not enacted until the early 1970s. And the first important international instruments on data protection have been the OECD *Guidelines Governing the Protection of Privacy and Transborder Flows of Personal Data*[319], adopted by the OECD Council on 23.09.1980 and the CoE *Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data*[320], adopted by the CoE Committee of Ministers on 28.01.1981. But as those instruments haven't been binding for the Member States a large range of heterogenic regulations were adopted in the different countries and the internal market was affected increasingly.

Therefore the EC *Directive on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data* was adopted by the European Parliament and the Council on 24.10.1995. It is by far the most influential, comprehensive and complex international policy instrument, enacted to enshrine two of the oldest ambitions of the European integration project, namely the achievement of an Internal Market (in this case the free movement of personal information) and the protection of fundamental rights and freedoms of individuals and to create an equivalent standard of data protection. Member States of the EU were given until 24.10.1998 to bring their respective legal systems into conformity with the provisions of the Directive. At present, however, a large range of legal and quasi-legal instruments on data protection can be found.

In the Directive, both objectives are equally important. In legal terms, however, the existence of the Directive rests on Internal Market grounds. Legislation at the EU level was justified because differences in the way that Member States approached this issue impeded the free flow of personal data between the Member States. Its legal base was thus Article 100a (now Article 95) of the Treaty. However, the proclamation of the *Charter of Fundamental Rights of the European Union* by the European Parliament, the Council and the Commission in December 2000, and in particular Article 8 thereof has given added emphasis to the fundamental rights dimension of the Directive.

Art. 8 incorporates the right to privacy as an essential freedom and states that personal data must be processed fairly for specified purposes and on the basis of the consent of the data subject concerned or some other legitimate basis laid down by law. Moreover Article 8 constitutes everyone's right of access to data, which has been collected concerning him or her, and the right to have it rectified.

[319] http://ec.europa.eu/justice_home/fsj/privacy/instruments/oecdguideline_en.htm .
[320] http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm .

3.2.1.2 Scope of the Directive

To analyze whether research with genomic data has to be fulfilled under restrictions of the European Data Protection Directive 95/46/EC (Dir. 95/46/EC) initially the Directive has to be applicable.

3.2.1.2.1 Personal data

Article 3 (1) of Dir. 95/46/EC points out that the Directive is applicable only to the processing of "personal data".

"Personal data" is defined in Article 2 lit. a), covering any information relating to an identified or identifiable natural person, called "data subject". Further more an "identifiable person" is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

Therefore one can adhere to two cumulative conditions for data or information to be "personal": first, the data must relate to or concern a person; secondly, the data must facilitate the identification of such person. Although the first condition often will be embraced by the second as information will normally relate to or concern a person if it facilitates that person's identification. Therefore the main criterion appearing in these definitions is that of identifiability, i.e., the potential of information to enable identification of an individual.[321]

Data however, that does not refer to a natural person, is not subject to the processing-restrictions of the Directive. Accordingly data concerning objects as well as data not referring to a natural person anymore (anonymous data) is not covered by Dir. 95/46/EC.

3.2.1.2.1.1 Anonymous data

The Dir. 95/46/EC is not applicable to the processing of personal data that was rendered anonymous. Therefore it is of high importance to distinguish whether ACGT processes personal or anonymous data.

Whereas the first draft of the Dir. 95/46/EC included in Article 2 lit. b) a definition of anonymization, the Directive in its final version failed to do so.

The first draft of Dir. 95/46/EC defined anonymous data as personal data modified "*in such a way that the information they contain can no longer be associated with a specific individual or an individual capable of being determined except at the price of an excessive effort in terms of staff, expenditure and time*[322]". The "excessive effort" was cancelled in the final version. The only reference to anonymous data in the applicable Directive can be found in recital 26 of Dir. 95/46/EC. Recital 26 states that Dir. 95/46/EC shall not apply to data rendered anonymous in *such a way that the data subject is no longer identifiable*. The economic and social committee initially welcomed this change, for excluding the "excessive effort" would limit the scope of anonymous data and moreover the term "excessive effort" would

[321] Bygrave, Data Protection Law, p. 41 f..
[322] Proposal for a council directive concerning the protection of individuals in relation to the processing of personal data COM (90) 314.

be obsolete in the context of the rapid development in the information technology sector.[323]

The difference between these definitions is obvious: whereas the proposal takes "*an excessive effort in terms of staff, expenditure and time*" into consideration, the definition in recital 26 of Dir. 95/46/EC does not.

Therefore Dir. 95/46/EC considers data as anonymous only, if the data subject is no longer identifiable, i.e. the link that refers to the data subject is irrecoverably erased. Anyhow the German legislation for instance seized the suggestion of the proposal and, unlike the European legislation, implemented the "excessive effort" in its definition of anonymous data (§ 3 (6) of the Federal Data Protection Act (BDSG)).

Meanwhile the European perception regarding "anonymous data" seems to change. In 2003 the European Commission published its "*First report on the implementation of the Data Protection Directive*".[324] Referring to a document of the European Privacy Officers Forum (EPOF) from 2002[325] the Commission pointed out, the interpretation of certain provisions of Dir. 95/46/EC had to be reasonable and flexible. Whereas the EPOF stated that the definition of anonymization should be pragmatic and it should emphasise that the capability of identification must be subject to the reasonableness standard. EPOF pointed out that the German definition indeed would satisfy both requirements.

These statements give reason to assume that in the meantime the European Commission approves a definition of "anonymous data" that includes an "excessive effort". Therefore information concerning personal or material circumstances that can only with a *disproportionate amount of time, expense and labour* be attributed to an identified or identifiable individual is *de facto* anonymous data.

3.2.1.2.1.2 Pseudonymous data

In contrast to some national data protection regulations, Dir. 95/46/EC does not know the concept of "pseudonymous data". The German Federal Data Protection Act for example defines in section 3 para. (6a) pseudonymizing as "replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially difficult". Especially in a medical research project, the use of pseudonymous data can be very beneficial for the patient, because it is possible to re-identify the patient and to let him benefit from newly developed treatments. However, as stated above, in the European regulatory framework the concept of "pseudonymous data" does not exist.

3.2.1.2.2 Territorial application

The territorial scope of Directive 95/46/EC is clearly defined: The Directive is applicable, whenever personal data is processed within the European Union.

[323] Opinion of the economic and social committee on the proposal for a council decision in the field of information security, Official Journal C 159, 17/06/1991, p. 38.
[324] http://eur-lex.europa.eu/LexUriServ/site/en/com/2003/com2003_0265en01.pdf.
[325] http://www.html.dk/log/D25.pdf.

However, despite the supranational principles set up by the Directive, there is no common Europe wide regulation, because the Directive grants the Member States a certain discretion of how to transform the principles into national law. [326]

Further, the Directive was incorporated on 25.6.1999 into the 1992 *Agreement on the European Economic Area* (EEA) in such a way that States which are not Member of the EU but party to the EEA Agreement (ie. Norway, Iceland and Liechtenstein) are legally bound to bring their respective laws into conformity with the Directive, what they did.

3.2.1.3 Fair and lawful data processing

3.2.1.3.1 General

In Article 2 lit. a) Directive 95/46/EC defines personal data as any information relating to an identified or identifiable natural person. In Article 7 the exemptions from the general prohibition on processing personal data are listed. Summarizing the exemptions, it can be said that, according to Article 7, processing of personal data is permitted, if the data subject has given his or her consent, or if the processing occurs in his or her interest or in the public interest. However, the processing of personal data is limited by the fundamental rights and freedoms of the data subject. This also is reflected in the basic principle of *purpose specification*. The purposes for processing of personal data must be adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed. Personal data must not be further processed in a way incompatible with those purposes.

3.2.1.3.1.1 Requirement of a legal basis

In general under the Directive the processing of personal data is prohibited. However the processing may be lawful if certain preconditions are fulfilled.

Art. 7 (a) – (f) contains a catalogue of cases, in which Member States may permit the processing of personal data. According to this Art. 7 and to Recital (30) personal data may only be legitimately processed if the processing is carried out with the unambiguous and explicit consent of the data subject. Moreover data processing may also be legitimate in a number of further circumstances where consent may be implied, for example, if processing is needed to perform a contract between the data controller and the data subject or the data processing is necessary in order to protect the vital interests of the data subject.

Furthermore data processing may be lawful, without the explicit consent of the data subject concerned, on public interest grounds, such as where processing is necessary for compliance with a legal obligation to which the controller is subject to, or is necessary for the performance of a task carried in the public interest or exercise of official authority pursuant to Art. 7 (e).

Finally processing may be undertaken under Art. 7 (f), if processing is necessary for the purposes of the legitimate interests pursued by the controller or by the third

[326] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, Rn. 24.

party or parties to whom the data are disclosed, except where such interests are overridden by the interests for fundamental rights and freedoms of the data subject. However, if data is processed pursuant to Art. 7 (e) or (f) the data subject may, according to Art. 14, object to the processing of data pertaining to him (see below 3.2.1.5).

In addition the Directive states in Art. 8 that the processing of certain types of data which are regarded as especially sensitive for the data subject shall be subject to even more stringent controls than other personal data (see 3.2.1.3.2 sensitive data).

3.2.1.3.1.2 Technical and organizational measures

A security policy can be enforced mainly in two ways: Through technical measures (e.g. using firewalls and access control in applications) and through organizational measures (e.g. assigning responsibility for security of data in a clear way).

Because of the increased specialization of healthcare providers, and the increased complexity of care and research procedures, the size of the team of care or research providers that deal with one patient grows. Teams of ten to fifty are common. Consequently many people have increasing (potential) access to personal clinical information of a large number of patients and organizations rely less on trust. Therefore IT enforcement becomes essential. Besides, the increased use of IT makes technical measures to enforce the security policy unavoidable.

Accordingly Art. 17 requires, Member States shall provide that the controller must implement appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing. Having regard to the state of the art and the cost of their implementation, such measures shall ensure a level of security appropriate to the risks represented by the processing and the nature of the data to be protected.

In addition Recommendation R(97)5 of the Committee of Ministers to Member States "*on the Protection of Medical Data*"[327] provides some further guidance for healthcare providers. Recommendations have no legally binding character for the Member States, but are incentives for certain behaviour.

The text of the recommendation contains the following part:

9.1 Appropriate technical and organizational measures shall be taken to protect personal data - processed in accordance with this recommendation - against accidental or illegal destruction, accidental loss, as well as against unauthorised access, alteration, communication or any other form of processing. Such measures shall ensure an appropriate level of security taking account, on the one hand, of the technical state of the art and, on the other hand, of the sensitive nature of medical data and the evaluation of potential risks. These measures shall be reviewed periodically.

Such appropriate organizational measures to ensure the confidentiality, integrity and accuracy of processed data could be for example

[327] http://www1.umn.edu/humanrts/instree/coerecr97-5.html .

- to prevent unauthorised persons from gaining access to data processing systems with which personal data are processed or used (access control),
- to prevent data processing systems from being used without authorization (access control),
- to ensure that persons entitled to use a data processing system have access only to the data to which they have a right of access, and that personal data cannot be read, copied, modified or removed without authorization in the course of processing or use and after storage (access control),
- to ensure that personal data cannot be read, copied, modified or removed without authorization during electronic transmission or transport, and that it is possible to check and establish to which bodies the transfer of personal data by means of data transmission facilities is envisaged (transmission control),
- to ensure that it is possible to check and establish whether and by whom personal data have been input into data processing systems, modified or removed (input control),
- to ensure that, in the case of commissioned processing of personal data, the data are processed strictly in accordance with the instructions of the principal (job control),
- to ensure that personal data are protected from accidental destruction or loss (availability control),
- to ensure that data collected for different purposes can be processed separately.

Additionally in the field of data processing regarding genetic research it might be useful, if not essential, to integrate a Trusted Third Party.

A Trusted Third Party is a security authority that performs the security related functions and cryptography methods, in particular can ensures from an independent point of view the pseudonymization of the genetic data processed and transmitted within the research consortium via network (see detailed below under 3.3.2.4).

3.2.1.3.2 Sensitive data

The Directive 95/46/EC distinguishes between the type of certain data. Some data contain information that affects the privacy of a person more than other data. Therefore this special kind of data has to be protected more strictly because of its sensitive quality.

3.2.1.3.2.1 Definition

The Directive 95/46/EC defines sensitive data as special category of data in Art. 8 (1). This special category of data contains personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life. References to other sorts of data, that Member States regarded as sensitive had to be dropped from the lists in data protection laws in the EU as the list of data categories in Art. 8 of the

Directive is intended to be exhaustive[328]. Whether certain data has to be regarded as sensitive data has to be decides in each particular case. However, the special categories listed have in common that they bear the risk of discrimination to an extremely high degree and therefore have to be protected more strictly.

The processing of genetic data has given rise to several problems of data protection: First of all, as mentioned before, the high sensitivity of these data. Consequentially the European legislation added data concerning health, to which genetic data belongs, to the list of special categories of data in Article 8 (1).

3.2.1.3.2.2 Prohibition of data processing

The processing of this special category shall be prohibited by the Member States according to Art. 8 (1).

Prima facie there is no difference between the processing of sensitive data and other kind of personal data, as the processing of personal data shall also be prohibited by the Member States according to Art 6. (1) and Art. 7, unless the processing is permitted by law or by the data subject itself (see above 3.2.1.3.1.1).

But certain personal data contains information affecting the privacy of a data subject more than other data does. Therefore the Member States agreed on a better and stronger protection of this kind of personal data containing more sensitive information.[329]

Hence, the Directive introduces very strict exemptions in Art. 8 paras. 2, 3, 5. Only if these very strict conditions are fulfilled, the processing of sensitive personal data can be lawful. As these conditions are stricter than the conditions for a lawful processing of other personal data stated in Art. 7, sensitive personal data is better protected than other data, not revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life.

The Member States are also authorized to impose other exceptions than stated in Art. 8 para. 2, 3, 5, if the Member States obey the conditions introduces in Art. 8 para. 4.

The protection of sensitive data is not limited to the processing of personal data wholly or partly by automatic means.

Therefore the processing of sensitive personal data is not prohibited per se but complicated, as strict conditions are imposed by the Directive, under which the processing of sensitive personal data can be lawful.

3.2.1.3.2.3 Exceptions

The Directive states several exceptions to the prohibition of processing sensitive data in Art. 8 para. 2. Once the conditions of these exceptions are fulfilled the processing of sensitive data is no longer prohibited, as the processing of such data is permitted by law. In these cases the protection of the privacy of a data subject is less important than the purpose pursued by these exceptions.

[328] Bygrave, Data Protection Law, p. 69.
[329] OJ C/1992/311/p. 30.

The exceptions stated in Art. 8 para. 2 are (simplified):

- explicit consent by the data subject
- processing is necessary for purposes in the field of employment law
- processing is necessary to protect the vital interests of the data subjects
- processing is carried out by a foundation, an association or another non-profit-seeking body
- processing of data made public by the data subject
- processing of data necessary for the assertion of claims

Exceptions concerning the processing of data for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment are ruled in Art. 8 (3).

Art. 8 (4) gives Member States a broad scope to lay down exemptions in addition to those laid down in Art. 8 para. 2 either by national law or by decision of the supervisory authority. Member States are authorized to deviate from the prohibition on processing sensitive data where important reasons of public interest ,so justify in areas such as public health, social protection, scientific research and government statistics, are affected. However also in these cases Member States must provide specific and suitable safeguards to protect the fundamental rights and the privacy of individuals.

This exception as well as the one stated in Art 8 para. 3 might be corresponding to the data processing within ACGT. This will be analysed carefully below under 3.3.2.1.1.

Finally Art. 8 para. 5 states another exemption from the prohibition of processing sensitive data for data about criminal offences and similar issues. Those derogations provided for in para. 5 as well as para. 4 from the data processing-prohibition stated in para. 1 have to be notified to the Commission.

3.2.1.4 Duties of the data controller

According to Art. 2 lit. d) data controller shall mean 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 of personal data; where the purposes and means of processing are determined by national or Community laws or regulations, the data controller or the specific criteria for his nomination may be designated by national or Community law.

According to Art. 6 para. 2 the data controller has the duty to ensure that personal data are processed fairly and lawfully. Consequently the controller has to safeguard that personal data are only collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes. Moreover the data controller has to warrant that the data are not excessive in relation to the purposes for which they are collected and/or further processed. Further every reasonable step must be taken by the data controller to ensure that data, which are inaccurate or incomplete, having regard to the purposes for which they were collected or for which they are further processed, are erased or rectified.

Likewise the data controller has to make sure that the data are kept in a form, which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed.

Pursuant to Art. 17 the data controller must implement appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing.

Since it is the data controller who is liable for the legality of data processing and the fulfillment of the obligations towards the national data protection authority and the data subjects, it is essential that the data controller is always identifiable.

According to this Art. 10 and 11 state that the data controller must provide a data subject from whom data relating to himself are collected the identity of the controller and of his representative.

Furthermore Art. 12 states that the data controller has to provide every data subject information about the processing of his or her data.

According to Art. 23 if the data controller fails to fulfill his duties in accordance with the Directive and thus fails to respect the rights of data subjects any person who has suffered damage as a result of an unlawful processing operation or of any act incompatible with the national provisions adopted pursuant to the Directive is entitled to receive compensation from the data controller for the damage suffered. However the data controller may be exempted from this liability, in whole or in part, if he proves that he is not responsible for the event giving rise to the damage.

3.2.1.5 Rights of the data subject

The processing of personal data affects the privacy of the data subject. Therefore the data subject has to be granted special rights in order to enable him or her to protect his or her privacy. These rights are introduced in Art. 10-12 and 14 of the Directive, whereas Art. 13 states exemptions and restrictions of the data subjects' rights introduced in Art. 10-12.

3.2.1.5.1 Information in cases of collection of data from the data subject

The Data Protection Directive distinguishes between two situations of data collection: Art. 10 deals with data collection from the data subject himself; Art. 11 deals with information duties, when data has not been obtained from the data subject.

According to recital (38), the principles of fair data processing require, that the data subject must be in a position to learn of the existence of a processing operation and, where data are collected from him or her, must be given accurate and full information, bearing in mind the circumstances of the collection. The data subject should be able to assess the situation and make his or her decision on reasonable grounds.

Data collection is defined as the collection of information with a certain aim. It can be the immediate taking notice of information, storage on a data carrier or the reception of a data carrier with the possibility of using the information. Not in the scope of the

definition is the situation that the data controller gets the information without asking for it. Data is neither collected from the data subject if he or she does not know about the data collection or he or she cannot avoid the data collection.[330]

As data collection depends on a decision of the data subject, he or she has to be informed if the collection is compulsory or not. This aims at protecting the data subject from disclosing information under the wrong assumption that the disclosure is compulsory or that a refusal could have disadvantageous consequences. Therefore, the principles of fair data processing require information whenever it is doubtful whether the said person assesses the situation correctly.[331]

The Data Protection Directive does not set up requirements concerning form and procedure of the information duties. It only requires the said person to receive the information from the data controller or his representative at the instigation of the data controller. The data controller can make use of his own staff or third parties. Oral information is possible, but for practical reasons, written information, usually on the data collection forms, is most common, as it enables the data controller to produce written evidence that the information process was correct. The data subject must be informed when data is collected, even if the storage of the data concerned takes place later.

As the Data Protection Directive aims at making sure that the person concerned is informed, the duty to inform the said person does not apply, if the person already has got the information. It does not depend on how and in which form the person got the information, as long as he or she received it close to the time of decision making, so that the information received will be a part of the decision making process.[332]

Art. 10 lit. a) states that the data subject has to be informed about the identity of the data controller and of his representative. This requires information about at least name and address, under which correspondence can be delivered. The information must be precise enough for the data subject to make use of his right to information and correction without difficulties, either in writing or personally. If a third party is involved in the data processing, its name and address have to be published as well.

Moreover, the data subject has to be informed about the purposes of the processing for which the data is intended. It can only be the legitimate purposes enumerated in Art. 6 Data Protection Directive. The data subject must be informed about all intended purposes. This information enables the data subject to assess, if the data collected meets the intended purposes and can be collected lawfully.

Furthermore, the data subject has to be given further information in so far as it is necessary, having regard to the specific circumstances in which the data are collected, to guarantee fair processing in respect of the data subject.

Information is necessary, if the said person needs it to assess correctly possible consequences of his or her taking part in the data collection process and to make an informed decision. Further information is generally required, if data processing results in acquiring knowledge about other categories of data, e.g. by interpretation of psychological tests or analysis of blood or tissue samples.[333]

[330] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 180/181.
[331] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 180, 184.
[332] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 181/182.
[333] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 183/184.

The recipient of the data collected is of special importance, if the data is collected especially for his purposes, e.g. credit information services. In general, information about the category to which the recipient of the data belongs, is sufficient.[334]

3.2.1.5.2 Information where the data have not been obtained from the data subject

In contrast to Art. 10, Art. 11 Data Protection Directive applies, when data is not collected from the data subject him- or herself. Nevertheless, the data subject has to be informed and the information requirements set up by Art. 11 are nearly identical to those set up by Art. 10.

The most important difference is the point of time when the information duties apply: Art. 10 requires that the information duties are fulfilled at the time when the data is collected from the data subject.[335] In contrast to this, according to the wording of Art. 11, *the data controller or his representative must at the time of undertaking the recording of personal data or if a disclosure to a third party is envisaged, no later than the time when the data are first disclosed provide the data subject with […] information.* Whenever it is planned to pass the data obtained on to a third party, the information duties only have to be met, when the data is actually passed on. If the data obtained are stored without being passed on to a third party, the data subject has to be informed at the time of undertaking the recording. In both cases, the data subject must be informed in close time to the operation in question.[336]

The scope of the word "obtain" comprises the collection of data as it is defined for Art. 10. It applies to all cases of "collection" apart from those where data is collected from the data subject himself. The most important cases of application of Art. 11 are those where data is requested from another person or institution, the calling up of data which is held ready by another person or the collection of data without the said person being able make a decision about or to influence the collection, e.g. visual or audible recording or any other form of registration of characteristics, activities or behaviour of the person concerned.[337]

As the data subject does not take part in the data collection, he or she has to be informed about the categories of data to be processed. Neither does the data controller have the duty to inform the data subject about the data collection being compulsory or not.[338]

Art. 11 para. 2 states that the information duties of para. 1 do not apply where, in particular for processing for statistical purposes or for the purposes of historical or scientific research, the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law.

"Disproportionate effort" does not mean the absolute effort, but the effort in relation the data subject's interest to be informed. The information interest of the third person is valued higher if the data processing enhances the risk of misuse of the data. The data subject must be given the possibility to protect him- or herself by

[334] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 183/184.
[335] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 180.
[336] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 183.
[337] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 186/187.
[338] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 187.

making use of his or her rights. If the data concerned will only be used for statistical purposes or if there are effective safeguards against data processing with a link to the person concerned, a lesser effort can be seen as disproportionate. The Data Protection Directive mentions the examples of statistical purposes or purposes of historical or scientific research.

Information duties neither do apply if it is impossible to inform the data subject. In principle, the data controller has to inform the data subject, but the Data Protection Directive does not impose the duty on him or her, neither has he or she the right, to collect data especially for information purposes, as new risks for the data subject would result from the additional data collection.

Neither is there a duty to inform the data subject, if recording or disclosure is expressively laid down by law, because in this case, the data subject knows or can easily get to know the content of the regulation.[339]

3.2.1.5.3 Right of access

Art. 12 Data Protection Directive is the central provision, which guarantees the data subject's legal safeguards. The heading "right of access" gives a misleading, because very limited idea of the contents of Art. 12.

Art. 12 does not only contain a right of access. Moreover, it comprises the right to rectification, erasure or blocking of data. The rights guaranteed by Art. 12 arise from the data subject's personal rights.[340]

Recital (41) emphasizes the importance of the right to access: *"Whereas any person must be able to exercise the right of access to data relating to him which are being processed, in order to verify in particular the accuracy of the data and the lawfulness of the processing; whereas, for the same reasons, every data subject must also have the right to know the logic involved in the automatic processing of data concerning him, at least in the case of the automated decisions referred to in Article 15 (1); […]."* The right of access is limited by trade secrets, intellectual property and in particular the copyright protecting the software, but, however, these considerations must not result in the data subject being refused all information. There must be a consideration in each individual case, which information can satisfy both, the right to intellectual property and the data subject's interest in the protection of his or her personal data.[341]

Art. 12 lit a), sub-para. 1 states the data subject's right and the data controller's duty to inform the data subject, if data with a link to the person concerned exists or not. All further information only has to be passed on to the data subject, if his or her personal data is processed. [342]

Sub-para. 2 states the data controller's duty to inform the data subject in an intelligible form about the data undergoing processing and of their source. "Data" means any information about the person concerned. "Intelligible" means that it depends on the intelligibility of the information from a typical data subject's point of view. Moreover, the data subject has to be provided with any available information

[339] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 187/188.
[340] Ehmann, Eugen / Helfrich, Marcus, EG-Datenschutzrichtlinie, 1999, pp. 173/174.
[341] Ehmann, Eugen / Helfrich, Marcus, EG-Datenschutzrichtlinie, 1999, pp. 175/176.
[342] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 193.

as to the source of the data processed. The Data Protection Directive requires not only information concerning the category of the source, but concrete information.[343]

Sub-para. 3 states the data controller's duty to pass on information concerning the knowledge of the logic involved in any automatic processing of data concerning him or her at least in the case of the automated decisions referred to in Art. 15 (1). The Data Protection Directive has a broader scope than Convention 108 of the council of Europe[344] and average European data protection legislation. The Data Protection Directive goes further than storage and single data processing operations (transfer, rectification, erasure) , but places the general term "processing" in the centre of the protection.[345]

3.2.1.5.4 Right of rectification, erasure or blocking

Art. 12 lit. b) grants the right to rectification, erasure or blocking of data the processing of which does not comply with the provisions of the Data Protection Directive, in particular because of the incomplete or inaccurate nature of the data.

"Rectification" aims at securing the objective correctness of the data concerned.

"Erasure" means that the data controller does not have personal data any longer. This can be achieved by destruction of the data medium, deletion of the information or removal of the link between the data and the person concerned, which makes the identification of the person concerned impossible. As a result, the data controller does not have personal data anymore.

"Blocking" means that the data controller does not entirely give up the data at his disposal, but that he defines, which parts of the data won't be used at all or not to a significant extent.[346]

Furthermore, Art. 12 lit. c) states that the data controller has to give notice to third parties to whom the data have been disclosed of any rectification, erasure or blocking carried out in compliance with (b), unless this proves impossible or involves a disproportionate effort.

3.2.1.5.5 Exemptions and restrictions

Art. 13 lists, in which cases Member States may adopt legislative measures to restrict the scope of the obligations and rights provided by Art. 6 (1) (principles relating to data quality); 10, 11(1) (information to be given to the data subject); 12 (right to access, rectification, erasure or blocking) and 21 (publication of processing operations).

The Data Protection Directive allows exemptions and restrictions, but it does not impose an obligation on the Member States. The Directive does not allow exemptions and restrictions in further cases than in those listed in Art. 13.

Art. 13 para. 1 lists the following cases: national security; defense; public security; criminal prosecution; economic or financial interests of a Member State; monitoring,

[343] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, p. 194.
[344] http://conventions.coe.int/Treaty/en/Treaties/Html/108.htm .
[345] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 194/195.
[346] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 197/198.

inspection or regulatory functions connected; the protection of the data subject or the rights and freedoms of others.[347]

Art. 13 para. 2 opens a further possibility to restrict the rights of the persons concerned: scientific research and statistics. Based on scientific methods, the aim of scientific research is to investigate phenomena and to acquire new knowledge, as well as to correct and to integrate previous knowledge. It is based on gathering observable, empirical, measurable evidence, subject to the principles of reasoning. The aim of scientific research and of statistics is not to generate information concerning an individual.

But there are some differences to para. 1:

First, para. 2 only refers to the rights safeguarded by Art. 12, but not to the collection of data. Secondly, an exemption is only lawful, if there are "adequate legal safeguards, in particular that the data are not used for taking measures or decisions regarding any particular individual". Furthermore, the Directive requires, that the data concerned is "processed solely for purposes of scientific research" and are no longer kept in a personal form than it is "necessary for the sole purpose of creating statistics". "Adequate legal safeguards" could be the restriction to certain fields of scientific research, the exclusion of sensitive data, anonymization and regulations concerning the civil and criminal liability of the data processor and his employees.[348]

3.2.1.5.6 Right to object

The right to object to the use of personal data concerns the use of personal data from the time of its collection, up to the time of its destruction, and also includes its disclosure to third parties for this purpose. The right to object enables a data subject to ensure that his or her data are not processed as soon as he or she claims legitimate interests or overriding rights and freedoms, which overweigh the interests of the controller in processing his or her data.

Accordingly Art. 14 states the right of the data subject to object at any time on compelling legitimate grounds relating to his or her particular situation to the processing of data relating to him or her. In case of a justified objection, the processing instigated by the data controller may no longer involve those data.

Besides Art. 14 states the right to object to the processing of personal data relating to him or her which the data controller anticipates being processed for the purposes of direct marketing, or to be informed before personal data are disclosed for the first time to third parties or used on their behalf for the purposes of direct marketing, and to be expressly offered the right to object free of charge to such disclosures or uses.

In order to make the data subject aware of the existence of the right to object the Member States shall take necessary measures.

3.2.1.6 Transfer of personal data to third countries

The Transfer of personal data to third countries is ruled in Art 25 and 26 of Dir. 95/46/EC. Art 25 and 26 contain rules providing for restrictions to be put on the flow of personal data to countries without sufficient levels of data protection. The main aim of these rules is to hinder data controllers from avoiding the requirements of the Data

[347] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 201-209.
[348] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 210/211.

Protection Directive by shifting their data-processing operations to countries with more lenient requirements. Whereas Art. 25 specifies the principles of data transfer to third countries, derogations are listed in Art 26 Dir. 95/46/EC.

Third countries within the meaning of the Directive are countries which do not belong to the European Union (EU) or European Economic Area (EEA); accordingly Dir. 95/46/EC is not applicable in these countries (see above 3.2.1.2.2).

Art 25 (1) stipulates that data transfer *"may take place only if […] the third country in question ensures an adequate level of protection"*. And Art 25 (2) pointes out, that the adequacy of protection *"shall be assessed in the light of all circumstances surrounding a data transfer or set of data transfer operations […]"*. Such circumstances surrounding a data transfer for instance can be the *"nature of the data, the purpose and duration of the proposed processing operation or operations, the country of origin and country of final destination, the rules of law, both general and sectoral, in force in the third country in question and the professional rules and security measures which are complied with in that country"* (Art 25 (2)).

Moreover the Art 29 Data Protection Working Party has adopted a discussion document on the "*Transfers of Personal Data to Third Countries -Possible ways forward in assessing adequacy"* in 1997[349] and a working document concerning *"Transfers of personal data to third countries: Applying Articles 25 and 26 of the EU data protection directive"* in 1998[350] giving more detailed criteria for the consideration.

The assessment whether the respective third country ensures an adequate level of data protection lies firstly with the data controller who wishes to export the data and secondly with the national data protection authorities in the EU Member States.[351] Art 25 (6) enables the Commission to make determinations of adequacy which are binding on the Member States.

These decisions of the Commission involve

- a proposal from the Commission,
- an opinion of the group of the national data protection commissioners (Article 29 working party),
- an opinion of the Article 31 Management committee delivered by a qualified majority of Member States,
- a thirty-day right of scrutiny for the European Parliament, to check if the Commission has used its executing powers correctly. The European Parliament may, if it considers it appropriate, issue a recommendation and
- the adoption of the decision by the College of Commissioners.

The effect of such a decision is that personal data can flow from the EU Member States and three EEA member countries (Norway, Liechtenstein and Iceland) to that third country without any further safeguard being necessary. The Commission has so far recognized

[349] Art 29 Data Protection Working Party, 26.06.1997, Document XV D/5020/97 EN, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/1997/wp4_en.pdf .
[350] Art 29 Data Protection Working Party, Document XV D/5025/98 EN, available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/1998/wp12_en.pdf .
[351] Bygrave, Data Protection Law, p. 81.

- Switzerland,
- Canada,
- Argentina,
- Guernsey,
- Isle of Man and
- the US Department of Commerce's Safe harbour Privacy Principles

as providing adequate data protection.[352]

If the third country in question does not ensure an adequate level of protection, in accordance with Art 26 (1) a transfer or a set of transfers of personal data to those third countries may take place on condition that:

(a) the data subject has given his consent unambiguously to the proposed transfer; or

(b) the transfer is necessary for the performance of a contract between the data subject and the controller or the implementation of precontractual measures taken in response to the data subject's request; or

(c) the transfer is necessary for the conclusion or performance of a contract concluded in the interest of the data subject between the controller and a third party; or

(d) the transfer is necessary or legally required on important public interest grounds, or for the establishment, exercise or defense of legal claims; or

(e) the transfer is necessary in order to protect the vital interests of the data subject; or

(f) the transfer is made from a register which according to laws or regulations is intended to provide information to the public and which is open to consultation either by the public in general or by any person who can demonstrate legitimate interest, to the extent that the conditions laid down in law for consultation are fulfilled in the particular case.

A further derogation may take place if a Member State authorises the proposed transfer accompanied by *"adequate safeguards"* instigated by the data controller for protecting the privacy and other fundamental rights of the data subject (see Art 26 (2)). The Member State has to notify to the Commission and the other Member States of the authorizations it grants pursuant to Art 26 (2). Such safeguards may result from *appropriate contractual clauses*. The Commission stipulated standard contractual clauses that may be used to govern the transfer of personal data to third countries that do not offer an adequate level of protection.[353]

3.2.2 Directive on Electronic Commerce 2000/31/EC

"The purpose of the Directive on electronic commerce is to improve the legal security of such commerce in order to increase the confidence of Internet users. It sets up a stable legal framework by making information society services subject to the principles of the

[352] http://ec.europa.eu/justice_home/fsj/privacy/thridcountries/index_en.htm .
[353] See Model Contracts: http://ec.europa.eu/justice_home/fsj/privacy/modelcontracts/index_en.htm .

internal market (free circulation and freedom of establishment) and by introducing a limited number of harmonised measures."[354]

This Directive might be important because obviously, ACGT project deals with internet in relation with users. Going further, the project organizes services between several actors. The service consist in the exchange of information (data) between those actors who are physicians and researchers.

We have to consider that ACGT is part of the concept of E-health and is characterized by the use of Information and Communication Technologies and sets an infrastructure for the transmission of data through several actors.

The service given by ACGT is based on telematic infrastructures, notably the Internet or private telematic networks. The exploitation of these infrastructures in healthcare aims at improving the circulation of information to the benefit of all the actors of healthcare, such as practitioners, patients, researchers (from university, public or private research centres, pharmaceutical or medical devices industries, etc.), public or private bodies participating to the funding of healthcare and the quality control of healthcare services, etc. These telecommunication infrastructures provide the practitioners with the ability to collaborate through a network and to use, share or offer, special e-Health products (such as data) and services.[355]

We'll also to pay attention to the fact that ACGT project will probably (and certainly) continue over the year 2010 or will be followed by a similar project with a similar purpose or objective.The goal of this part 3.3.2 is to define if ACGT project and the actors enter the scope of the Directive 2000/31.

The first section will be a theoretical analysis to present the Directive 2000/31/EC while the second part will apply the Directive 2000/31/EC to the ACGT project.

3.2.2.1 Theoretical analysis

This part of the deliverable is quite different from the first one related to the Directive 95/46/EC. Actually, we'll deal - at this point - with providers and users who are not anymore the patients. This changes then the angle of view of the lecturer.

It also changes the level of the analysis. In fact, we'll be working at the level of the network and infrastructure as we'll see below and not at the level of the patient. That doesn't mean we don't care about the patient but he is at another level of the network.

This change of level doesn't mean we don't deal with data protection. Actually, the network or infrastructure is a component of the data protection matter.

[354] http://europa.eu/scadplus/leg/en/lvb/l24204.htm

[355] Y. Poullet and J. Herveg, Which Major Legal Concerns in Future e-Health ?, presentation at the e-Health and Health Policies, Synergies for Better Health in a Europe of Regions, Plenary Session : e-Health and New Social Dilemmas, to be published.

3.2.2.1.1 Scope of the Directive

The Directive 2000/31 covers all information society services which include services between companies (business to business), between companies themselves and consumers (business to user)and free services provided to recipients. It covers also other on-line services like databases.

The aim of this Directive is also to guaranty the transparency on the net.[356]

The article 1 of the Directive is relevant about its scope:

"1. This Directive seeks to contribute to the proper functioning of the internal market by ensuring the free movement of information society services between the Member States.

2. This Directive approximates, to the extent necessary for the achievement of the objective set out in paragraph 1, certain national provisions on information society services relating to the internal market, the establishment of service providers, commercial communications, electronic contracts, the liability of intermediaries, codes of conduct, out-of-court dispute settlements, court actions and cooperation between Member States.

3. This Directive complements Community law applicable to information society services without prejudice to the level of protection for, in particular, public health and consumer interests, as established by Community acts and national legislation implementing them in so far as this does not restrict the freedom to provide information society services."

The scope of the Directive is quite wide and it concerns all information society services even in sector which has a high level of protection as public health, etc…

We should pay attention to the fact that the Directive sets a minimum required to achieve its objective.

Thus the Recital 10 sets:

"In accordance with the principle of proportionality, the measures provided for in this Directive are strictly limited to the minimum needed to achieve the objective of the proper functioning of the internal market; where action at Community level is necessary, and in order to guarantee an area which is truly without internal frontiers as far as electronic commerce is concerned, the Directive must ensure a high level of protection of objectives of general interest, in particular the protection of minors and human dignity, consumer protection and the protection of public health; according to Article 152 of the Treaty, the protection of public health is an essential component of other Community policies."[357]

That means that national laws transposing the Directive can be less or more strict. This point is important when we'll have to confront the ACGT database to a national law.

[356] M. Dumoulin, Information et transparence sur les réseaux", in le commerce électronique européen sur les rails? Analyse et proposition de mise en œuvre de la directive sur le commerce électronique, Bruxelles, Bruylant, 2001, p. 95.

[357] We underline.

The article 5(1) of the Directive sets up some exceptions to its application which are not relevant in the ACGT project.

We also note that the Directive has no effect at all on measures taken at Community or national level, in the respect of Community law, in order to promote cultural and linguistic diversity and to ensure the defense of pluralism[358] and on private international law nor on the jurisdiction of Courts[359].

Attention must be paid to the fact that this Directive doesn't deal with personal data as mentioned in the Recital 14:

"The protection of individuals with regard to the processing of personal data is solely governed by Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data(19) and Directive 97/66/EC of the European Parliament and of the Council of 15 December 1997 concerning the processing of personal data and the protection of privacy in the telecommunications sector(20) which are fully applicable to information society services; these Directives already establish a Community legal framework in the field of personal data and therefore it is not necessary to cover this issue in this Directive in order to ensure the smooth functioning of the internal market, in particular the free movement of personal data between Member States; the implementation and application of this Directive should be made in full compliance with the principles relating to the protection of personal data, in particular as regards unsolicited commercial communication and the liability of intermediaries; this Directive cannot prevent the anonymous use of open networks such as the Internet."[360]

This point is very important because we see that this Directive may be a complementary regulation to the Directive 95/46/EC and won't ever take the place of it or be replaced by it. They may coexist. Therefore, we'll have to check the complementary measures which have to be taken to implement both Directives towards the ACGT project.

3.2.2.1.2 Internal market

As usually, the Directive settles principles towards the European internal market.

The article 3 describes the obligation of the Member States in respect of the free circulation in the internal market which we won't explain further in this delivrable.:

3.2.2.1.3 The information society service

First of all, we have to explain the concept of information society services which is defined by the Directive like *"any service, normally provided for remuneration, at a*

[358] Article 1.6 of the Directive.
[359] Article 1.4 of the Directive.
[360] We underline.

distance, by electronic means and at the individual request of a recipient of services"[361].

The clue words are:

The service must be provided **for remuneration**. It doesn't matter if the service is paid by the recipient himself or not. That means the payment can come from another source (advertising, etc.) than the recipient. We have to consider all activities are included in the concept of services (article 50 of the European treaty), except the ones made by the State in accordance with its social, cultural, etc. duties before they are opened to payment.

Recital 19 of Directive 98/48/EC of 20.07.1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations sets up:

"under Article 60[362] *of the Treaty as interpreted by the case-law of the Court of Justice, 'services` means those normally provided for remuneration; whereas that characteristic is absent in the case of activities which a State carries out without economic consideration in the context of its duties in particular in the social, cultural, educational and judicial fields; whereas national provisions concerning such activities are not covered by the definition given in Article 60 of the Treaty and therefore do not fall within the scope of this Directive"*

Article 50 of the European treaty sets:

*"*Services shall be considered to be 'services' within the meaning of this Treaty where they are normally provided for remuneration, in so far as they are not governed by the provisions relating to freedom of movement for goods, capital and persons.

'Services' shall in particular include:

(…)

(d) activities of the professions[363].

(…)"

We can set that all activities, excepted the ones done by the member state relating to its mission (i.e.: cultural, judicial, etc…), is likely to be a "service" on the sense of the article 50 of the Treaty.

To enter the scope of this directive 2000/31/EC, the service must also be provided **at distance** which means that the parties are not physically and simultaneously present.

The Annex V to the Directive 98/48/EC of 20 July 1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations give indications about the excluded services on the basis of the concept of "at distance":

"(…)

[361] Article 1(2) of Directive 98/48/EC of the European Parliament and the Council of 20.07.1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations.

[362] We should understand article 50 instead of article 60.

[363] This include the physician.

1. Services not provided "at a distance"

Services provided in the physical presence of the provider and the recipient, even if they involve the use of electronic devices:

(a) medical examinations or treatment at a doctor's surgery using electronic equipment where the patient is physically present;

(…)"

Furthermore, the service is made **by electronic means** which means *"the service is sent initially and received at its destination by means of electronic equipment for the processing (including digital compression) ad storage of data, and entirely transmitted, conveyed and received by wire, by radio, by optical means or by other electromagnetic means"*[364]. The supply consisting in material goods is excluded from the scope of the Directive even if it implies the use of electronic means (for example: train ticket, money, etc…).

By electronic means, the recital 18 includes only the online services and not the offline one. In the hypothesis of both services, the Directive will apply to, and only, the online one.

The Annex V to the Directive 98/48/EC of 20 July 1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations give indications about the excluded services on the basis of the concept of "by electronic means". For example, services having material content as rail tickets, banknote, etc…

It also excludes services which are not provided by electronic or inventory system as telefax services, voice telephony services, etc…

(…)

The service must be provided at the **individual request of a recipient of services** which means that the service is provided through the transmission of data on individual request.

The Annexe V to the Directive 98/48/EC of 20 July 1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations give indications about the excluded services on the basis of the concept of "by electronic means". That's excludes all services provided without individual request as television and radio.

3.2.2.1.4 Principles

One of the major principles put in place by the Directive is the one excluding prior authorization. That means the member states are not allowed to require a prior authorization or any other requirement having equivalent effect to pursuit the activity of an information society service in the member state.

The recital 23 sets up that *"provisions of the applicable law designated by rules of private international law must not restrict the freedom to provide information society*

[364] Article 1(2) of Directive 98/48/EC of the European Parliament and the Council of 20.07.1998 amending Directive 98/34/EC laying down a procedure for the provision of information in the field of technical standards and regulations.

services as established in this Directive" and is completed by the Recital 28 which states an exception to this principle for the postal services[365].

Another exception is added by the article 4(2) of the Directive.

Concerning the regulated profession as health on line, medicine on line, banking services on line, etc… in the surroundings of the commercial communications:

"1. Member States shall ensure that the use of commercial communications which are part of, or constitute, an information society service provided by a member of a regulated profession is permitted subject to compliance with the professional rules regarding, in particular, the independence, dignity and honour of the profession, professional secrecy and fairness towards clients and other members of the profession.

2. Without prejudice to the autonomy of professional bodies and associations, Member States and the Commission shall encourage professional associations and bodies to establish codes of conduct at Community level in order to determine the types of information that can be given for the purposes of commercial communication in conformity with the rules referred to in paragraph 1

3. When drawing up proposals for Community initiatives which may become necessary to ensure the proper functioning of the Internal Market with regard to the information referred to in paragraph 2, the Commission shall take due account of codes of conduct applicable at Community level and shall act in close cooperation with the relevant professional associations and bodies.

4. This Directive shall apply in addition to Community Directives concerning access to, and the exercise of, activities of the regulated professions."

3.2.2.1.5 Service provider

The Directive defines the service provider as *"any natural or legal person providing an information society service"*[366].

The definition is very broad since it includes all person dealing with commercial activity (by commercial activity, we have to understand service for payment in the sense of the article 50 of the European treaty and the interpretation given by the European court of justice[367]. Cfr. above).

In the sense of the article 50 of the European treaty, a physician has a "commercial" activity.

The duties towards the recipient are mainly informational.

The Directive sets also the principle that the provider must be established. This criteria of establishment must be analyze on qualitative, real and economical stability criteria.

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[365] *"The Member States' obligation not to subject access to the activity of an information society service provider to prior authorisation does not concern postal services covered by Directive 97/67/EC of the European Parliament and of the Council of 15 December 1997 on common rules for the development of the internal market of Community postal services and the improvement of quality of service(23) consisting of the physical delivery of a printed electronic mail message and does not affect voluntary accreditation systems, in particular for providers of electronic signature certification service."*

[366] Article 2(b) of the Directive.

[367] Arrest ECJ dd. 27.09.1998.

This concept of establishment is well set by the Recital 19:

"The place at which a service provider is established should be determined in conformity with the case-law of the Court of Justice according to which the concept of establishment involves the actual pursuit of an economic activity through a fixed establishment for an indefinite period; this requirement is also fulfilled where a company is constituted for a given period; the place of establishment of a company providing services via an Internet website is not the place at which the technology supporting its website is located or the place at which its website is accessible but the place where it pursues its economic activity; in cases where a provider has several places of establishment it is important to determine from which place of establishment the service concerned is provided; in cases where it is difficult to determine from which of several places of establishment a given service is provided, this is the place where the provider has the centre of his activities relating to this particular service."

3.2.2.1.5.1 General information

Article 5 specifies the kind of general information which is:

"In addition to other information requirements established by Community law, Member States shall ensure that the service provider shall render easily, directly and permanently accessible to the recipients of the service and competent authorities, at least the following information:

(a) the name of the service provider;

(b) the geographic address at which the service provider is established;

(c) the details of the service provider, including his electronic mail address, which allow him to be contacted rapidly and communicated with in a direct and effective manner;

(d) where the service provider is registered in a trade or similar public register, the trade register in which the service provider is entered and his registration number, or equivalent means of identification in that register;

(e) where the activity is subject to an authorisation scheme, the particulars of the relevant supervisory authority;

(f) as concerns the regulated professions:

- any professional body or similar institution with which the service provider is registered,

- the professional title and the Member State where it has been granted,

- a reference to the applicable professional rules in the Member State of establishment and the means to access them;

(g) where the service provider undertakes an activity that is subject to VAT, the identification number referred to in Article 22(1) of the sixth Council Directive 77/388/EEC of 17 May 1977 on the harmonisation of the laws of the Member States relating to turnover taxes - Common system of value added tax: uniform basis of assessment(29)."

Besides the general information, the Directive makes provisions for several more precise services as commercial communications, contracts concluded by electronic means.

3.2.2.1.5.2 Information related with the commercial communication

In case of commercial communication, the service provider has to give information to the recipient.

By commercial communication, we understand "any form of communications designed to promote, directly or indirectly, the goods, services or image of a company, organisation or person pursuing a commercial, industrial or craft activity or exercising a regulated profession"[368].

These following points are not included in this definition as set by the article 6:

"- information allowing direct access to the activity of the company, organisation or person, in particular a domain name or an electronic-mail address,

- communications relating to the goods, services or image of the company, organisation or person compiled in an independent manner, particularly when this is without financial consideration;"

The content of the delivered information is described as:

"(a) the commercial communication shall be clearly identifiable as such;

(b) the natural or legal person on whose behalf the commercial communication is made shall be clearly identifiable;

(…) [369]

3.2.2.1.5.3 Information related to contracts concluded by electronic means

In case of contracts concluded by electronic means, the information to be provided consists in:

"In addition to other information requirements established by Community law, Member States shall ensure, except when otherwise agreed by parties who are not consumers, that at least the following information is given by the service provider clearly, comprehensibly and unambiguously and prior to the order being placed by the recipient of the service: (a) the different technical steps to follow to conclude the contract;

(b) whether or not the concluded contract will be filed by the service provider and whether it will be accessible;

(c) the technical means for identifying and correcting input errors prior to the placing of the order;

(d) the languages offered for the conclusion of the contract."[370]

[368] Article 1(f) of the Directive.
[369] Article 6 of the Directive.
[370] Article 10 of the Directive.

3.2.2.1.5.4 Recipient of the service

The Directive defines the recipient of the service as *"any natural or legal person who, for professional ends or otherwise, uses an information society service, in particular for the purposes of seeking information or making it accessible"*[371].

Recital 20 specifies:

"The definition of "recipient of a service" covers all types of usage of information society services, both by persons who provide information on open networks such as the Internet and by persons who seek information on the Internet for private or professional reasons"[372]

A *contrario*, if we are in a "private" network accessible only to the members of the legal entity, we should be out of the scope of this Directive 2000/31/EC.

3.2.2.1.6 Liability of intermediary service providers

Another objective of this Directive 2000/31/EC is to reduce the liability of some actors working in the information society. Those actors, called intermediary service providers, will have to fit in categories to get to benefit from this reduction of liability.

Recital 40 exposes that:

"Both existing and emerging disparities in Member States' legislation and case-law concerning liability of service providers acting as intermediaries prevent the smooth functioning of the internal market, in particular by impairing the development of cross-border services and producing distortions of competition; service providers have a duty to act, under certain circumstances, with a view to preventing or stopping illegal activities; this Directive should constitute the appropriate basis for the development of rapid and reliable procedures for removing and disabling access to illegal information; such mechanisms could be developed on the basis of voluntary agreements between all parties concerned and should be encouraged by Member States; it is in the interest of all parties involved in the provision of information society services to adopt and implement such procedures; the provisions of this Directive relating to liability should not preclude the development and effective operation, by the different interested parties, of technical systems of protection and identification and of technical surveillance instruments made possible by digital technology within the limits laid down by Directives 95/46/EC and 97/66/EC"

The exemptions from liability established in this Directive cover only cases where the activity of the information society service provider is limited to the technical process of operating and giving access to a communication network over which information made available by third parties is transmitted or temporarily stored, for the sole purpose of making the transmission more efficient; this activity is of a mere technical, automatic and passive nature, which implies that the information society service provider has neither knowledge of nor control over the information which is transmitted or stored (recital 42).

A service provider can benefit from the exemptions for "mere conduit" and for "caching" when he is in no way involved with the information transmitted. This

[371] Article 2(d) of the Directive.

[372] We underline.

requires among other things that he does not modify the information that he transmits. This requirement does not cover manipulations of a technical nature that take place in the course of the transmission as they do not alter the integrity of the information contained in the transmission (recital 43).

A service provider who deliberately collaborates with one of the recipients of his service in order to undertake illegal acts goes beyond the activities of "mere conduit" or "caching" and as a result cannot benefit from the liability exemptions established for these activities (recital 44).

The limitations of the liability of intermediary service providers set in this Directive do not affect the possibility of injunctions of different kinds. Such injunctions can in particular consist of orders by courts or administrative authorities requiring the termination or prevention of any infringement, including the removal of illegal information or the disabling of access to it (recital 45).

In order to benefit from a limitation of liability, the provider of an information society service, consisting of the storage of information, upon obtaining actual knowledge or awareness of illegal activities has to act expeditiously to remove or to disable access to the information concerned. The removal or disabling of access has to be undertaken in the observance of the principle of freedom of expression and of procedures established for this purpose at national level. This Directive does not affect Member States' possibility of establishing specific requirements that must be fulfilled expeditiously prior to the removal or disabling of information (recital 46).

Hence the following regulations have been adopted.

3.2.2.1.6.1 "Mere conduit" – Principle: "No liability for the service provider"

Where an information society service is provided that consists of the transmission in a communication network of information provided by a recipient of the service, or the provision of access to a communication network, Member States shall ensure that the service provider is not liable for the information transmitted, on condition that the provider (art. 12, 1) :

"(a)does not initiate the transmission;

(b) does not select the receiver of the transmission; and

(c) does not select or modify the information contained in the transmission."

The acts of transmission and of provision of access referred to in article 12.1. include the automatic, intermediate and transient storage of the information transmitted in so far as this takes place for the sole purpose of carrying out the transmission in the communication network, and provided that the information is not stored for any period longer than is reasonably necessary for the transmission (art. 12, 2).

This Article shall not affect the possibility for a court or administrative authority, in accordance with Member States' legal systems, of requiring the service provider to terminate or prevent an infringement (art. 12, 3).

3.2.2.1.6.2 "Caching"

Where an information society service is provided that consists of the transmission in a communication network of information provided by a recipient of the service, Member States shall ensure that the service provider is not liable for the automatic,

intermediate and temporary storage of that information, performed for the sole purpose of making more efficient the information's onward transmission to other recipients of the service upon their request, on condition that (art. 13, 1) :

"(a) the provider does not modify the information;

(b) the provider complies with conditions on access to the information;

(c) the provider complies with rules regarding the updating of the information, specified in a manner widely recognised and used by industry;

(d) the provider does not interfere with the lawful use of technology, widely recognised and used by industry, to obtain data on the use of the information; and

(e) the provider acts expeditiously to remove or to disable access to the information it has stored upon obtaining actual knowledge of the fact that the information at the initial source of the transmission has been removed from the network, or access to it has been disabled, or that a court or an administrative authority has ordered such removal or disablement."

Article 13 shall not affect the possibility for a court or administrative authority, in accordance with Member States' legal systems, of requiring the service provider to terminate or prevent an infringement (art. 13, 2).

3.2.2.1.6.3 "Hosting"

Where an information society service is provided that consists of the storage of information provided by a recipient of the service, Member States shall ensure that the service provider is not liable for the information stored at the request of a recipient of the service, on condition that (art. 14, 1) :

"(a) the provider does not have actual knowledge of illegal activity or information and, as regards claims for damages, is not aware of facts or circumstances from which the illegal activity or information is apparent; or

(b) the provider, upon obtaining such knowledge or awareness, acts expeditiously to remove or to disable access to the information."

Article 14.1. of the Directive shall not apply when the recipient of the service is acting under the authority or the control of the provider (art. 14, 2).

Article 14 of the Directive shall not affect the possibility for a court or administrative authority, in accordance with Member States' legal systems, of requiring the service provider to terminate or prevent an infringement, nor does it affect the possibility for Member States of establishing procedures governing the removal or disabling of access to information (art. 14, 3).

3.2.2.1.6.4 No general obligation to monitor

Member States shall not impose a general obligation on providers, when providing the services covered by Articles 12 (mere conduit), 13 (caching) and 14 (hosting), to monitor the information that they transmit or store, nor a general obligation actively to seek facts or circumstances indicating illegal activity (art. 15, 1).

Member States may establish obligations for information society service providers promptly to inform the competent public authorities of alleged illegal activities undertaken or information provided by recipients of their service or obligations to

communicate to the competent authorities, at their request, information enabling the identification of recipients of their service with whom they have storage agreements (art. 15, 2).

Recital 48 specifies that this Directive does not affect the possibility for Member States of requiring service providers, who host information provided by recipients of their service, to apply duties of care, which can reasonably be expected from them and which are specified by national law, in order to detect and prevent certain types of illegal activities.

3.2.2.1.7 Codes of conduct

The directive, in the article 16, advises the member States and the European Commission to encourage:

"(a) the drawing up of codes of conduct at Community level, by trade, professional and consumer associations or organisations, designed to contribute to the proper implementation of Articles 5 to 15;

(b) the voluntary transmission of draft codes of conduct at national or Community level to the Commission;

(c) the accessibility of these codes of conduct in the Community languages by electronic means;

(d) the communication to the Member States and the Commission, by trade, professional and consumer associations or organisations, of their assessment of the application of their codes of conduct and their impact upon practices, habits or customs relating to electronic commerce;

(e) the drawing up of codes of conduct regarding the protection of minors and human dignity.

2. Member States and the Commission shall encourage the involvement of associations or organisations representing consumers in the drafting and implementation of codes of conduct affecting their interests and drawn up in accordance with paragraph 1(a). Where appropriate, to take account of their specific needs, associations representing the visually impaired and disabled should be consulted."

3.2.2.1.8 Sanction

The article 20 sets that:

"Member States shall determine the sanctions applicable to infringements of national provisions adopted pursuant to this Directive and shall take all measures necessary to ensure that they are enforced. The sanctions they provide for shall be effective, proportionate and dissuasive."

The European community knows that without any dissuasive sanction, the new regulation won't have any chance to be respected. Starting from that principle, the Directive impose to the member States to adopt effective and dissuasive sanction having in mind that those measures must be proportionate.

For example, the sanctions go from 250,- € (x 4) to 20.000,€ (x 4) in Belgium. We have to admit that the consequence of a violation of the law in Belgium can be quite expensive.

3.2.2.2 Implications of the Directive on Electronic Commerce for ACGT

At this point and after having analyzed the Directive from a theoretical point of view, we need to pay attention to the applicability of the Directive in a project like ACGT.

This more practical analysis will consider that the ACGT project is created for a longer term than the length of the European contract itself and will continue after 2010. Even if it's not the ACGT project, it will be another one having the same purpose and finality. The objective of the European commission is to have a study over the European regulation involved in a huge European scientific GRID infrastructure like the one built up by the ACGT consortium.

By the terms "physician" and "researcher", we also understand hospital and university.

3.2.2.2.1 ACGT as information society service

In this part, we'll have to check whether the ACGT project will enter the scope of the Directive 2000/31/EC of 08.12.2000 on certain legal aspects of information society services, in particular electronic commerce, in the internal Market and, in case of positive answer, we'll have to point the duties and rights related to this directive.

Reminding the concept of the ACGT network, ACGT will create a database filled with data coming from both physician and researcher. The data won't be modified by ACGT by any processing. ACGT will have in charge all the access control and will give grants to the users. Having that in mind, we have to check whether ACGT is a society information service.

We also have to keep in mind that the ACGT database is a service based on telematic infrastructures, notably the Internet or private telematic networks. In consequences, ACGT offers a network or infrastructure to the physicians and researchers to achieve its goal.

We'll also have to pay attention to the fact that the ACGT project will continue over the year 2010 or will be followed by a similar project with a similar purpose or objective and finality.

Those two considerations have a deep consequence for ACGT. Actually, ACGT can be considered like an established entity as soon it has a legal personality (ethical/legal board) and is a main actor in the network it creates.

Starting from the criteria that ACGT is an established legal entity, we must check if ACGT is an “open network” (understanding it may concern more actors than the actual partners). As said before, one of the ACGT's purpose – and maybe of the European Commission – is to set a European database opened to researchers and physicians all over Europe. That means that the ACGT service will be available for other people than the partners of the legal entity and the use of the data will go out of the present consortium even if it will be under some conditions. We cannot say anymore that the network only exists for the members of the consortium. Obviously, the users fall within the definition of recipient of a service as described by the Recital

20[373] even if they need a username and a password to access the database[374]. In fact, the figure presented in D11.1 is showing a network open to other users than the members of the consortium..

3.2.2.2.1.1 ACGT as an information society service

As seen before, the clue words to define information society service are a service given by remuneration, at a distance, by electronic means and at the individual request of a recipient of services.

At a distance: Obviously the different parties dealing with ACGT services will never be physically or simultaneously present to contract. Therefore, ACGT fulfils this criteria.

By electronic means: The entire ACGT project is based on the Internet and Grid technology what means the service is provided by electronic means. All the transmissions of data will obviously be through the Internet. Therefore, ACGT fulfils this criteria.

At the individual request of a recipient of services: first of all, we shall define the recipient of services in the ACGT project. Actually there are two recipients. The first recipient will be the researcher when he will contract with ACGT for using the database for his research. Obviously, he will generate a service by his individual request. The second recipient will be the physician who will formulate an individual request to ACGT to get a feed back with the result of the research through ACGT's database. The individual request can occur at the beginning of the relation between the user and ACGT. It means the transmission of date to a user doesn't have to follow, at each time, a special request. The contract between ACGT and the user can provide that the information will be sent as soon there is an up date, for example.

Remuneration: by remuneration, we understand any form of retribution. We have to keep in mind that ACGT won't be self supporting and will need a financial support. In theory and from an economical point of view, the incomes can be provided by the users of the data base, advertisers, grants from State members or EC, etc…. It's a question of choice and the source doesn't matter because the concept of remuneration is very broad.

At the present time, the remuneration consists in European Commission's grant.

We therefore have to conclude that ACGT will get remuneration in the sense of the article 50 of the European treaty from a way or another. Then the services provided by ACGT for the researchers and the physician fulfil this criteria.

The consequence of this conclusion is that ACGT falls within the scope of the Directive and must respect the obligations of it in matter of information and other

[373] The Recital 20 explains that, if the service is allowed for the members of the legal entity, it can't be considered like a information society service. This Recital Internet as an example with the use of the word "such". As showed before, the service won't be available only for the members of ACGT consortium.

[374] For example, an hospital won't be a provider in the way of the Directive 2000/31/EC as long as the database will be accessible only to the physician of that hospital. As soon as the hospital is opening its database to other physicians, it can become a provider.

duties concerning the contracts concluded by electronic means[375] and commercial communication.

A way to go out of the scope of this Directive may consist in providing an off-line service excluding *de facto* all on-line services (see above), which obviously doesn't fit with the concept of the ACGT project.

3.2.2.2.1.2 Information needed and under which form

What kind of information is due by ACGT and to whom? The article 5 of the Directive sets up some minimal requirement in matter of information:

"1. In addition to other information requirements established by Community law, Member States shall ensure that the service provider shall render easily, directly and permanently accessible to the recipients of the service and competent authorities, at least the following information:

(a) the name of the service provider;

(b) the geographic address at which the service provider is established;

(c) the details of the service provider, including his electronic mail address, which allow him to be contacted rapidly and communicated with in a direct and effective manner;

(d) where the service provider is registered in a trade or similar public register, the trade register in which the service provider is entered and his registration number, or equivalent means of identification in that register;

(e) where the activity is subject to an authorisation scheme, the particulars of the relevant supervisory authority;

(f) as concerns the regulated professions:

- any professional body or similar institution with which the service provider is registered,

- the professional title and the Member State where it has been granted,

- a reference to the applicable professional rules in the Member State of establishment and the means to access them;

(g) where the service provider undertakes an activity that is subject to VAT, the identification number referred to in Article 22(1) of the sixth Council Directive 77/388/EEC of 17 May 1977 on the harmonisation of the laws of the Member States relating to turnover taxes - Common system of value added tax: uniform basis of assessment(29).

2. In addition to other information requirements established by Community law, Member States shall at least ensure that, where information society services refer to prices, these are to be indicated clearly and unambiguously and, in particular, must indicate whether they are inclusive of tax and delivery costs."[376]

The directive sets also that those information must be accessible by an easy, direct and permanent way in any case and in any service of the information society.

[375] Article 9 and following of the Directive 2000/31.

[376] Article 5 of the Directive 2000/31/EC.

3.2.2.2.1.3 Electronic contract - extra information –

We have to pay attention to the fact that extra information is required in some situation as in case of contract concluded by electronic means. Is ACGT concerned by this contractual matter? Indeed, there will be contractual links between ACGT and the researchers and between ACGT and the physicians concerning duties and right of the different parties. Those contracts will, certainly, be concluded by electronic means and between non consumer parties.[377] That means that the extra information set by the article 9 can be reduced to ashes if the parties give their agreement on this reduction. We have to be aware that those contracts are not the ones concerning the data protection! They concern a different level of the network!

Actually, the Directive sets:

"1. In addition to other information requirements established by Community law, Member States shall ensure, except when otherwise agreed by parties who are not consumers, that at least the following information is given by the service provider clearly, comprehensibly and unambiguously and prior to the order being placed by the recipient of the service:

(a) the different technical steps to follow to conclude the contract;

(b) whether or not the concluded contract will be filed by the service provider and whether it will be accessible;

(c) the technical means for identifying and correcting input errors prior to the placing of the order;

(d) the languages offered for the conclusion of the contract.

2. Member States shall ensure that, except when otherwise agreed by parties who are not consumers, the service provider indicates any relevant codes of conduct to which he subscribes and information on how those codes can be consulted electronically.

3. Contract terms and general conditions provided to the recipient must be made available in a way that allows him to store and reproduce them

4. Paragraphs 1 and 2 shall not apply to contracts concluded exclusively by exchange of electronic mail or by equivalent individual communications."[378]

In practice, the information given to the non consumer user can be reduced to ashes in the sense of the Directive 200/31/EC if there's an agreement between the parties. Within the framework of ACGT, this possible substantial reduction of information will facilitate the work of ACGT.

Actually this information is not required if the contract is concluded exclusively by exchange of electronic mail or by equivalent individual communications. The interpretation of this paragraph must be restrictive and concerns the process of the contract which is made entirely by Email or equivalent individual communication.

[377] Consumer is defined like "any natural person who is acting for purposes which are outside his or her trade, business or profession" (article 2(e) of the Directive.

[378] Article 10 of the Directive 2000/31/EC; we underline.

At the present time, the contracts will certainly be made by Email or by paper. Therefore, during this period of "no electronic contracts", ACGT won't have to execute the stipulation of the Directive 2000/31/EC concerning the contract concluded by electronic means.

3.2.2.2.1.4 Liability – intermediary service provider

We also should wonder about ACGT's liability. ACGT can also be considered as an intermediary service provider and benefit from the reduction of liability set by the Directive (see above). Will it only store the information from the providers to give the opportunity to the recipient to get it.

The question is to know who will be the service provider then. Actually, if ACGT is the intermediary service provider, someone else needs to be the service provider itself. Who will be? The only person likely to be this one could be the physician and/or the researcher. Can that be the case? We'll analyze that further on but we can already set that could be hardly feasible for them in terms of administration and so on.

Therefore, we have to consider that ACGT can't be a intermediary service provider even if the data base is build from data coming from an other party and is not modified by ACGT itself.

About the question of ACGT's liability, we'll have to return to the national regulations because the Directive 2000/31/EC doesn't deal with that issue.

Maybe this question will have to be analysed further on in a later stage of the project.

3.2.2.2.1.5 Commercial communication

A last point which is connected with the remuneration concerns the commercial communication. Is ACGT making commercial communication?

We have to remind the definition which is:

"any form of communication designed to promote, directly or indirectly, the goods, services or image of a company, organisation or person pursuing a commercial, industrial or craft activity or exercising a regulated profession."[379]

A way to get a source of remuneration for ACGT, could be to put advertising on his websites. If ACGT takes this solution, it has to be aware that it will be considered like a commercial communication and it will have to respect the articles 10 and following of the Directive 2000/31/EC (see above).

3.2.2.2.1.6 Sanction

This Deliverable can not deal with this point because the sanctions are set by the member states' legislations.

[379] Article 2 (f) of the Directive 2000/31/EC

3.2.2.2.2 Physicians and researchers as information society service

In this part of the document, we have to deal with the position and the functions of the physicians and researchers. Obviously, both physicians and researchers transfer information (data) to each of them through or with the collaboration of ACGT which gives the infrastructure (see above). The physician makes available some patient's data to the researcher through the ACGT data base and the researcher makes available the results of his research to the physician in charge of the patient again through the ACGT database. Therefore there's a kind of services given by each one.

We have to check again the clue words defining information society service which are service provided by remuneration, at a distance, by electronic means and at the individual request of a recipient of services.

- **Remuneration**: we remind that by remuneration, we understand any way of retribution. For sure the physician gets retribution from the patient and in some situation from Member States. The question is to determine what kind of remuneration is got by the physicians. Is it for therapeutic purpose to the patient or to give the service of furnishing the information to ACGT and the researchers. Giving an answer to this question is to resolve the question to know if he can be provider or not. Actually, if the physician doesn't get any remuneration for the service, he won't be considered like service provider because a criteria is missing.

  From another hand, if we consider that the physician gets remuneration for the service given to ACGT and the researcher, this first criteria is fulfilled and will have substantial consequences for him as we'll see further.

  The same question is put forward for the researcher. Actually, he often gets remuneration from Member States, EU, etc. Following the example of the physician, we can consider this remuneration is given for the research and not for the availability of some results for physician consisting in giving the results of the research to ACGT and the physician. On another hand, the remuneration can be considered in relation to the service given to those last one with the linked consequences. In fact, if we are in this last position, the researcher has to be considered like a service provider.

  At this point, we may consider that both physician and researcher don't get any remuneration for making available date through the infrastructure set by ACGT. Their remuneration is related to the therapeutic finality for the physician and a finality of research for the researcher. Therefore, they can not be considered under scope of the Directive 2000/31/EC.

  In consequence, it's not needed to analyse the other clue words and we won't do it.

3.2.2.2.3 Temporary conclusion

In terms of temporary conclusion, we certainly have to consider that ACGT will enter into contract with both physician and researcher as seen in D11.1.

Electronic contracts will be signed to set duties and rights of the different parties in their relationships. We must pay attention to the fact that the system will grow and the number of physicians and researchers will certainly increase (it's one of the purpose of the ACGT project). Sooner or later, those contracts will be made by electronic means and ACGT will have to give the information mentioned at the article 5 of the Directive. On the other hand, ACGT will be able to have agreement with the users to spare its obligation to provide the information mentioned at the article 10 because those users will never be consumers.

To be as flexible as possible, the suggestion consists in the creation of general terms document in a form which can be stored by the contractors and agreement forms.

The main purpose of the general terms is to set duties and rights of the parties as the secrecy, no use of the data outside of the purpose defined by the project, etc…

To have the grant from ACGT to access to the database, the user will have to sign the agreement form and, therefore, accept the general terms explained above. It obviously will be done by electronic means sooner or later.

3.3 DATA PROTECTION WITHIN ACGT

3.3.1 Data flows

ACGT aims at the exchange of data. Genetic data of a patient shall be collected and stored in a database so that a researcher participating in the project can do research with the patient's data. It is obvious that the dataflow is a crucial part for the success of ACGT. And only if this dataflow can be designed in a lawful and fair way this project can be a success and be accepted by the participating patients. So the lawfulness of the dataflow is a crucial factor for ACGT, if not THE crucial factor.

To ensure the compliance of the clinical trials within ACGT and the project itself with all relevant legal and ethical issues it is of high importance to identify, qualify (from a legal point of view) and structure the data flows that are produced during the patients' therapy in a first step. The clinical pilot trials are characterised by a multitude of data flows between different institutions.

The following figure gives an overview of the current practice, using the Nephroblastoma trial run by the University of Saarland, which is one of the trials within ACGT, as an example (GCCR: German Childhood Cancer Registry):

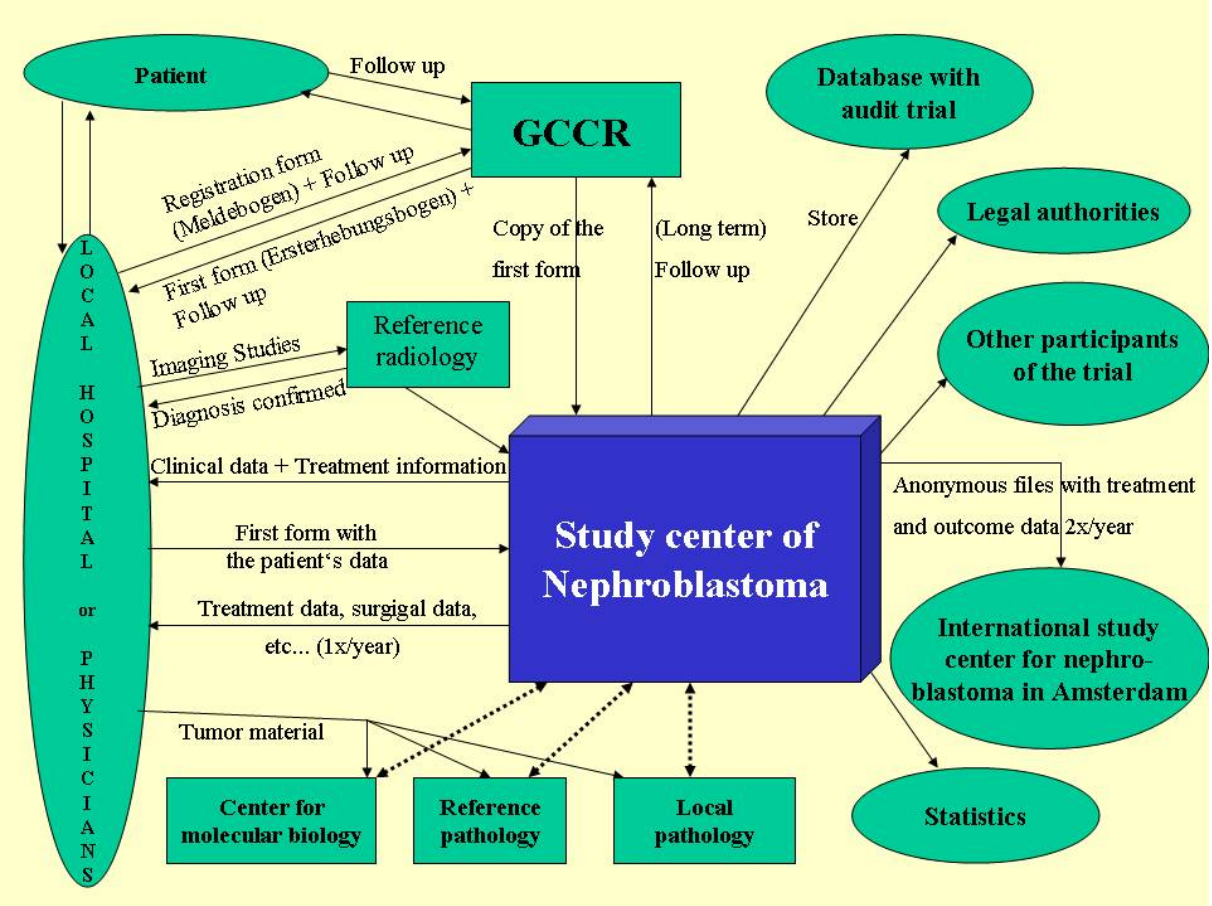

Figure 1: Data flows within ACGT

The figure shows the complexity of the data flows that occur in a trial like the Nephroblastoma trial. A lot of data processing, in particular data transmission, is needed to carry out such a trial.

The easiest way to run such a trial from a legal perspective would be to use only anonymous data, as the processing of anonymous data doesn't need a legal basis or an informed consent of the data subject, as anonymous data is not personal data and would therefore not fall under the scope of the Data Protection Directive.[380]

But the analysis of data flows shows that most of the data cannot be processed anonymously. As the identification of each patient has to be guaranteed in order to give one the best therapy, most of the data needed for such a trial has to be processed in a pseudonymous way. Rendering data pseudonymous means replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially difficult.

Based on the condition that pseudonymous data has to be treated as personal data and that each processing of personal data needs a basis of authorization[381], it will be

[380] See the more detailed explanation above under 3.2.1.2.
[381] See 3.2.1.3.1.1 and for sensitive data additionally 3.2.1.3.2.2.

necessary to process as little personal data as possible. Hence the data flows shown in *figure 1* have to be divided into data flows that need to be personalised, with the effect that data protection legislation is applicable for such a data processing, and into data flows that can be anonymous, therefore data protection legislation would not be applicable to the processing.

Most of the involved parties only process pseudonymous data without having the link to the individual. Therefore this kind of pseudonymous data could be treated as anonymous data for a data controller, who does not have the link to the individual and therefore does not know the particular data subject. The consequence would be that a data controller who does not have the link to a data subject would not need a basis of authorisation for the processing of that data, as this data would have to be qualified as anonymous data for the data controller and would therefore not fall under the scope of the Data Protection Directive.

That is why we analyze the meaning of the term “anonymous data” in the European context with the primary goal to classify some pseudonymous data as anonymous data, so that a basis of authorisation is no longer needed.

A further step will be to identify one or many data controllers within figure 1 above. The data controller is responsible for the lawfulness and fairness of the data processing. He can delegate the processing. But also in case that other bodies (third parties) are commissioned to collect, process or use personal data, the responsibility for compliance with the data protection provisions rests with the data controller. For the data transfer between the data controller and the data processor no basis of authorisation is needed. In other words the less data controller there are within ACGT, the easier it gets to process data within this project.

On the other hand it gets more difficult for the data controllers to ensure compliance with the legal framework of data protection, as he would be responsible for more actions and more data processing units. Therefore it is of vital importance to provide guidelines for the data controller and a reliable framework for the exchange of data within ACGT. That is why the data flow of ACGT has to be designed in a way that a data controller can comply with all the provisions in an easy way. If this framework gets too complex, no researchers (who are no data protection experts) would use ACGT. So the data flow design of ACGT has to keep this in mind and provide a data exchange ensuring that a researcher complies with all the data protection legislation, if he uses the ACGT platform according to the instructions.

Having this in mind, a new model for the data flow within ACGT was elaborated. This model will be explained and examined in detail in the following, especially its conditions, the exact implementation and the involved parties are analyzed.

3.3.2 Legitimate processing of genetic data (Directive 95/46 EC)

Genetic data is a very sensitive type of data. Therefore the legitimate processing of genetic data has to comply with quite strict regulation. But the processing of genetic data is a quite new phenomenon. So not all the questions regarding the legitimate processing of personal data have been answered yet. New problems arise, dealing especially with the questions when and under what conditions the processing of genetic data is lawful and

who is allowed to process this kind of data. These questions will be examined and answered in the following.

3.3.2.1 Genetic data

Genetic data is of very sensitive quality, if not the most sensitive data about a human being at all.

Genetic data contains a huge amount of information about the person the genetic data refers to. It provides information about his or her descent, ethnical origin, and, with a certain probability, also about future diseases and possibly about their healing chances and much more. Each individual's genetic data is unique and can contain information even of yet unborn blood relatives. Therefore each person can be identified reliably by its genetic data.

Genetic data encompasses all kind of data concerning the hereditary characteristics of an individual or the pattern of inheritance of such characteristics within a group of individuals, who are related to each other.

Due to the amount of information they carry concerning an individual's state of health, origins and descent, genetic data has to be classified as highly sensitive. Because of this highly sensitive quality genetic data has to be protected from a legal point of view as well as from an ethical point of view in a highly strict way, as the unlawful processing of genetic data would put the privacy of the data subject at high risk.

3.3.2.1.1 Special characteristics of genetic data with regard to data protection

The characteristic features of genetic data are their uniqueness and the highly sensitive quality of the information they contain. Consequently, European data protection legislation ranks data concerning health, such as genetic data[382], as data requiring special protection (see Art. 8 para. 1 Dir. 95/46/EC). Therefore, the processing of these kinds of data is subject to restrictions.

In general, the processing of genetic data is prohibited according to Art. 8 para 1 of the Directive. The processing may only be lawful, if the data subject has given it's explicit consent to the processing of it's genetic data (Art. 8 para 2 lit a) or one of the exemptions stated in Art. 8 paras 2-5 applies.

The regulation of the processing of personal data is based upon two main ideas. The first idea is that the economical, social, cultural and individual activities, with no public or private distinction, require in various extents the processing of information relative to natural persons. The second idea, intimately bound to the first one, is that natural persons must be protected against any infringement to their fundamental rights and freedoms that might arise from the processing of information relative to them. In other words, the processing of personal data is frequently needed for multiple good reasons. But, at the same time, the processing of personal data induces the danger to expose natural persons to grave risks of discriminations or

[382] See Working Document of the Art. 29 Data Protection Working Party: Working Document on Genetic Data, p. 5 (available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf)

infringements to their fundamental rights and freedoms. With respect to this and with this aim in view, the processing of personal data must comply with several rules expressing the balance between all the interests in presence. In this context Directive 95/46/EC aims to ensure the protection of fundamental rights and freedoms of natural persons (data subject), and in particular their right to privacy with respect to the processing of personal data[383]. This protection requires regulating the processing of personal data in order to prevent any infringement to the fundamental rights and freedoms of the data subject.

To be effective and coherent this regulation has to be built on the analysis of the risks capable to affect the fundamental rights and freedoms of the data subject. It is only possible to determine the conditions under which personal data can be processed in full respect of the fundamental rights and freedoms of data subjects when these risks are identified.

This risk assessment is particularly important since the recent evolutions of Information and Communication Technologies have multiplied the possibilities to process personal data and therefore increased the risks of infringement to the fundamental rights and freedoms of the data subject.

The use of a new technology such in ACGT project should naturally induce the assessment of the new risks attached to its implementation especially in healthcare regarding the protection of medical data.

The general principle is that the risk of infringement to the rights and freedoms of the data subject does not depend on the information content. But the risk depends on the purpose of the processing of personal data. In other words the potential or actual danger for the fundamental rights and freedoms of the data subject has to be assessed regarding the purpose of the processing of personal data.

But the principle is slightly – though not entirely – different for sensitive data[384]. It is commonly admitted that the sole content of these data already exposes the data subject to the risk of infringement of his or her fundamental rights and freedoms, whatever could be the purpose of the data processing. Put differently, any use of sensitive data is susceptible to create grave risks of discrimination for the data subject. Therefore sensitive data require a special protection taking into account their content and the purpose of their processing.

With this end in view the Directive has decided that "*data which are capable by their nature of infringing fundamental freedoms or privacy should not be processed* (…)"[385]. The ban on processing medical data is the special protection provided by the Directive to ensure the respect of the fundamental rights and freedoms of the data subject regarding the processing of his or her medical data.

Hence the ban on processing medical data should not be seen as opposed to the free movement of personal data. The ban on processing medical data is more a limit than an exception to the free movement of personal data. In fact the free movement of personal data can only be conceived in the full respect of the fundamental rights and freedoms of the data subject and this respect includes the ban on processing medical data.

[383] Directive 95/46/EC, art. 1.1.
[384] Usually, sensitive data are personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership and personal data concerning health or sex life.
[385] Directive 95/46/EC, recital 33.

Nevertheless the Directive grants permission to process medical data in seven hypotheses. In these ones the legitimacy of the processing of medical data (the balance between the interests in presence[386]) is formally presumed (cf. *infra* the necessity to really assess its legitimacy). This comes from the fact that, in principle, the situations described in these hypotheses should justify the processing of medical data, without prejudice for the other conditions ensuring the lawfulness of the data processing.

These exceptions to the ban on processing medical data must be restrictively interpreted.

The processing of medical data is strictly forbidden beyond these exceptions.

The first hypothesis granting permission to process medical data is the consent of the data subject (Art. 8 para. 2 lit. a). The data subject's consent is frequently presented as the natural base for the legitimacy of the processing of medical data. Therefore the probably most relevant exception for research purposes within ACGT is the "Explicit consent by the data subject to the processing of this data" (Art. 8 para. 2 lit. a).

However in the case of a scientific project it must be considered that to consent in advance to each individual operation performed upon the data is almost impossible as normally in the course of a project new research methods are developed which may demand other operations performed upon the data than the patient has consented to before. Also the cooperation with other scientists may require the extension of the consent. On the other hand it may be doubted whether a consent, which is worded too extensively still is valid.

In general such consent must be given in written or comparable form. Art. 8 para. 2 of the Directive does not state this explicitly. But according to Art. 7 lit. a) a data subject has to give his or her consent unambiguously even if only non-sensitive personal data is processed. So Art. 7 doesn't state the need of a written consent explicitly either. But as the consent has to be given in an unambiguous way, a written consent is regularly needed according to Art. 7 lit. a).

A fortiori, although it is not stated explicitly in Art 8 para. 2, the consent to a processing of sensitive personal data has to be given in a written way as well, as the processing of sensitive personal data effects the privacy of a data subject more than the processing of non-sensitive personal data. Therefore the level of protection of sensitive personal data has to be at least as high as the level of protection of non-sensitive personal data (see more detailed 3.3.2.7).

Another exception allowing for the processing of sensitive data is where "processing is necessary to protect the vital interests of the data subject or of another person where the data subject is physically or legally incapable of giving his consent"[387].

The notion of "vital interest" means expressly and exclusively the situation of an imminent danger to the life of a natural person. This covers the protection of the vital interests of the data subject but also of any other natural person. However in this last situation the Directive adds that the data subject must be physically or legally incapable of consenting to the processing of his or her medical data. It can not be deduced from this disposition that the data subject, physically or legally capable of consenting, could, without any consequence, refuse to authorize the processing of

[386] Cf. *infra* for the identification of these interests.
[387] Directive 95/46/EC, art. 8.2, c)

his or her medical data when the vital interests of another person are at stake. The qualification of this behaviour should be qualified under the applicable law. But for ACGT this exception is not applicable as patients participating in ACGT are not legally or physically incapable of consenting to the processing of their medical data.

Art. 8 para. 3 of the Directive states another possibly important exception for scientific research projects like ACGT. According to that the processing of sensitive personal data is permitted, if the processing of the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy.

Scientific research projects often aim to improve the treatment of (future) patients, so does ACGT. If a processing of sensitive data is required for the provision of treatment, this processing is permitted, if it is done by a health professional or another person subject to an obligation of secrecy described in the Directive.

But this exception only allows the processing of sensitive data if it is required for a concrete treatment of a concrete patient (data subject). Therefore scientific research projects aiming to improve the treatment of several patients in the future do not fall under that exception.

According to Art. 8 para. 4 Member States may lay down additional exemptions by national law or by decision of the supervisory authority for reasons of substantial public interest, subject to the provision of suitable safeguards.

So the Directive does not state exemptions from the prohibition of processing of sensitive data, but empowers the Member States to introduce national exemptions for reasons of substantial public interest and subject to the provision of suitable safeguards.

The disadvantage of that regulation for European scientific research projects is that it is the free choice of the Member States to introduce such exemptions in their national law. Furthermore the conditions for a processing of sensitive data because of a particular public interest can differ between the Member States, as the Directive empowers the Member States to introduce such regulation and does not harmonize it in detail. Therefore it is very difficult for European projects to comply with all the national regulation regarding the processing of sensitive personal data for reasons of substantial public interest.

Examples for a substantial public interest are introduced by Recital (34) of the Directive:

"(34) Whereas Member States must also be authorized, when justified by grounds of important public interest, to derogate from the prohibition on processing sensitive categories of data where important reasons of public interest so justify in areas such as public health and social protection - especially in order to ensure the quality and cost-effectiveness of the procedures used for settling claims for benefits and services in the health insurance system - scientific research and government statistics; whereas it is incumbent on them, however, to provide specific and suitable safeguards so as to protect the fundamental rights and the privacy of individuals;"

So, scientific research is mentioned explicitly in Recital (34) as a possible example for an important public interest. Member States can therefore introduce regulation permitting the processing of sensitive personal data for scientific research purposes

under the condition to provide specific and suitable safeguards so as to protect the fundamental rights and the privacy of individuals. As mentioned above, these exemptions introduced by the different Member States shall be notified to the Commission (Art. 8 para. 6). The exemptions can be introduced either as national law or by decision of the supervisory authority. But no Member State is forced to introduce such an exemption and also the exact definition of this exemption is up to the Member States. For a trans-European scientific research project like ACGT, this exemption is not very helpful either, as it can not be guaranteed that each Member State has introduced such an exemption. Besides, even if this exemption was introduced in each Member State the different national laws would not be harmonized very much. It would not be practicable to examine all the national exemptions of the Member States for scientific research and create the model of the data flow within ACGT according to common rules stated in each national law as the lowest common factor.

Furthermore the legitimacy of the processing of sensitive data is not complete when only formally fitting into one of these exceptions to the ban on processing sensitive data, even with the consent of the data subject. Indeed these exceptions are only hypotheses where the legitimacy of the data processing is formally assumed.

Now the legitimacy of the processing of sensitive data – the balance of the interests in presence – has to be really assessed.

First the interests in presence have to be identified. Are they only the interests of the data controller and of the data subject or should we also consider the interests of third concerned parties and of the whole society? In our view these two last categories of interests should be taken into account when evaluating the legitimacy of the processing of sensitive data.

Then the explicit and valid consent of the data subject presumes, until contrary proof, the existence of an acceptable balance between the interests in presence in the processing of his or her medical data. However, in this case, it is quite difficult to assume that the data subject has adequately taken into account interests other than one's own.

In any case the processing of medical data will not be legitimate if the balance between the interests in presence is not respected, even with the regular consent of the data subject.

But the legitimacy of the processing of sensitive data is definitely and very usefully strengthened by the additional consent of the data subject. That is the reason why we must firmly approve and recommend the ethical practice aiming to obtain the consent of the data subject when processing medical data. This practice is frequent in the conduct of clinical trials and in telematic networks in healthcare.

Finally, it has to be stressed that the data controller may not legitimate the processing of sensitive data on other bases. That excludes necessarily the use of the hypotheses of formal legitimacy enumerated in article 7 of the Directive for non-sensitive personal data. By example the data controller may not legitimate the processing of sensitive data by the balance of the interests in presence without respecting the hypotheses enumerated in article 8.

In conclusion, we can confirm that the protection of sensitive data implies to fix the rules applicable to the processing of sensitive data and hence to determine their conditions.

With regard to their highly sensitive nature, medical data require a special protection taking into account their content and the purpose of their processing. Therefore Directive 95/46/EC has decided to prohibit the processing of medical data. However the Directive provides that this ban does not apply in several cases. In these cases the legitimacy of the processing of medical data is formally assumed without prejudice for the other conditions ensuring the lawfulness of the data processing. These exceptions to the ban on processing medical data have to be restrictively interpreted.

Furthermore the Data Protection Directive would still be applicable, if such an exemption would be used to legitimate the processing of genetic data. It would be much more practicable for a scientific researcher involved in a trans-European project like ACGT, if the data he or she uses would not fall under the scope of the Directive at all. As mentioned above, only “personal data” fall under the scope of the Data Protection Directive. From just the legal point of view it would be the best for scientific researcher, if he or she could use non-personal data for his or her research. On the other hand, the identification of the data subject is needed from the medical point of view, as he or she may benefit from the scientific research with his or her data.

In the following it will therefore be examined, whether genetic data can be anonymized in a legal sense at all and if yes under what conditions. Besides it must always be taken into account that the data subject shall benefit from the research for example carried out in trans-European research projects like ACGT and must therefore be identifiable.

3.3.2.1.2 Anonymous genetic data

As described above, the data flow model for ACGT has to take into account both: the legal situation and the medical requirements. That means the model must ensure the legitimate processing while the medical requirements, i.e. the re-identification of the data subject to provide him or her new developed treatments, must not be forgotten. It is the challenge to develop such a model that combines these two approaches in a practicable and lawful way.

The solution used most often in scientific research projects not using unique data like biometric or genetic data is to pseudonymize the data used for the research. Most of the times, for researchers it is of no importance to know the exact person to which the data, he or she examines, refer. So, the data subject’s name and other identifying characteristics are replaced with a label, in order to preclude identification of the data subject or to render such identification substantially difficult. The person can only be re-identified by using the appropriate key. This pseudonymous data may be regarded as anonymous data for the researcher who doesn’t have the link to the data subject. Hence the Data Protection Directive would not be applicable to this data processing anymore.

Besides Art. 6 para. 1 lit. e) Dir. 95/46/EC states that, in principle, i.e., as soon as the research purpose allows it, genetic data has to be rendered anonymous in such a way that the data subject is no longer identifiable (see recital (26)). As soon as his or her data is rendered anonymous, the data subject requires no further protection, because re-identification is impossible due to the lack of reference to the said person. As the processing of anonymous data offers the best protection for the said person, anonymization of personal data has to be given priority over possibly relevant exemptions from the general prohibition on processing sensitive data (Art. 8

Dir. 95/46/EC). Consequently, when genetic data has to be processed, it must be considered carefully, whether it is possible to process it in anonymized form. If this is the case, it is not necessary to obtain the said person's consent, because the processing of anonymous data does not fall into the scope of the Data Protection Directive. As a result, anonymous data can be processed without restrictions. At least from a data protection point of view, due to the lack of reference to a person, anonymous data can be collected, stored and published without restrictions.

The important question at this stage is, whether also pseudonymous genetic data can be regarded as anonymous data for the data controller. Or does genetic data always have to be qualified as personal data because of the uniqueness of such data?

Take the example of a study on HIV. In the course of the study, a gene sequence, which is sufficiently large for identifying a person, is published on the internet without personal details. If there is already genetic information about the concerned person stored for a different purpose, e.g. because of a saliva-test, which covers a whole area, or as a compulsory requirement for the signing of a life insurance contract with a high amount insured, an identification of the person concerned and his or her HIV disease would be possible for all persons, who have access to these data bases, by a matching-procedure.

Although this scenario is not immediately approaching, it shows that the unique quality of genetic data causes the problem, that despite comprehensive anonymization, a re-identification of the said person is possible, if relevant additional knowledge exists.

If this is the case, the question arises, whether it is possible at all to render genetic data anonymous in order to comply with data protection legislation, or if genetic data generally has to be classified as personal data. This is the big difference between "normal" data and unique data like biometric and genetic data. Whenever there is a personalized reference data set available, the concerned data subject can always be identified by a matching procedure. This is generally not the case if "normal" data is processed.

The crucial point is, how to define the term "anonymous". The Directive itself doesn't contain an explicit definition of this term, as the definition of this term was deleted from the original draft of the Directive during the consultations.

Only Recital (26) of the Directive contains a definition of this term:

(26) Whereas the principles of protection must apply to any information concerning an identified or identifiable person; whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person; whereas the principles of protection shall not apply to data rendered anonymous in such a way that the data subject is no longer identifiable; whereas codes of conduct within the meaning of Article 27 may be a useful instrument for providing guidance as to the ways in which data may be rendered anonymous and retained in a form in which identification of the data subject is no longer possible;

According to the wording of Recital (26), data can only be classified as anonymous, if the anonymization is irreversible and thus re-identification of the data subject is impossible for everybody. As stated above, the re-identification of a data subject is always possible (at least with a certain effort) if a reference data set of the data subject's genetic data is available. Therefore genetic data can never be classified as anonymous data according to Recital (26), as genetic data can never be

anonymized in a way, that a re-identification of the concerned data subject will never and under no circumstanced is impossible for everybody.

Nevertheless as mentioned above under 3.2.1.2.1.1, on the basis of European legislation, too, the anonymization of genetic data seems to be possible, accepted and not objected. For example, the Article 29 Data Protection Working Party accepts the anonymization of genetic data - which, according to the wording of the data Protection Directive cannot be rendered anonymous - as a means to limit the dangers of genetic research.[388]

On the contrary: In the first place, the European Economic and Social Committee (EESC) supported the deletion of the term "disproportionate effort" from the draft. They argued that the current definition of anonymous data in the Data Protection Directive restricts the scope of the definition. Furthermore, they said, that the term "disproportionate effort" is misleading, facing the rapid development of electronic data processing (EDP).[389]

But there is a new view in coming: In the First Report on the implementation of the Data Protection Directive 95/46/EC,[390] the Commission states, that the interpretation of the Directive must be sensible and flexible, and draws attention to an article of the European Privacy Officers Forum (EPOF),[391] which emphasizes the practical orientation and exemplary function of the German definition of "anonymization".

The German transposition of the Data Protection Directive contains a broader definition, which is similar to the definition of the first suggestion of the Commission with regard to the Data Protection Directive.[392] Section 3 para. 6 BDSG (Federal Data Protection Act) defines anonymization as the modification of personal data, so that the information concerning personal or material circumstances can no longer or only with a disproportionate amount of time, expense and labour be attributed to an identified or identifiable individual. In conclusion, the BDSG accepts two groups of anonymous data: First, data which can no longer be turned into personal data, and secondly, data which is *de facto anonymous*, because it can only be turned into personal data with a disproportionate amount of time, expense and labour.[393]

Therefore, according to that definition, also genetic data can be regarded as anonymous data under certain conditions. Under which conditions genetic data can be qualified as anonymous data for a data controller, for example a researcher within ACGT, shall be examined in the following.

Although the wording of Recital 26 of the Data Protection Directive 95/46/EC does not immediately suggest this, it is generally assumed - in compliance with the

[388] See Working Document of the Art. 29 Data Protection Working Party: Working Document on Genetic Data, p. 11 (available at: http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf)
[389] Official Journal C 159, 17/06/1991, p. 38 (40)
[390] First report on the implementation of the Data Protection Directive (95/46/EC) of 2003; available at: http://eur-lex.europa.eu/LexUriServ/site/en/com/2003/com2003_0265en01.pdf
[391] EPOF, Comments on Review of the EU Data Protection Directive (Directive 95/46/EC) of 2002, available at: http://www.html.dk/log/D25.pdf.
[392] Art. 2 lit. b of the Proposal for a Directive of the European Parliament and of the Council on the protection of individuals with regard to the processing of personal data and on the free movement of such data of 18/7/1990.
[393] See: Metschke / Wellbrock, Datenschutz in Wissenschaft und Forschung, Berlin 2002, pp. 20 ff., available at: http://www.datenschutzberlin.de/infomat/dateien/mat_28.pdf.

Directive - that data, which can be de-anonymized only with a disproportionate amount of time, expense and labour, can be classified as anonymous.[394]

The question at this stage is how to define the term disproportionate and especially for which person the amount of time, expense and labour has to be disproportionate to de-anonymize the concerned data subject. In other words: is it possible, that a piece of genetic data is anonymous for one researcher, while it is personal for another; does the classification of disproportionate effort depend exclusively on the data controller or also on a third person?

Recital 26 of the European Data Protection Directive states: "Whereas, to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person." However, it is pointed out[395] that, following this view, data might be regarded as anonymous data although a risk of de-anonymization still exists.

Despite Recital (26), for this opinion, the central question is, of whether de-anonymization is possible for the data controller or not. Following this view, the initial point is the distinction[396] between a data controller, who actually has access to additional knowledge, which enables him to identify the said person, and a data controller, who does not have access to this knowledge, which means that the person is not identifiable for him. Therefore, it is assumed that the term „personal data" is relative.[397]

Given that the term „personal data" is relative, i.e. depending on the additional knowledge of each particular data controller, the question arises, of how pseudonymous data - i.e. data, whose identifying characteristics were replaced by a reference code in order to eliminate the possibility of identification of the concerned person, or at least, to make it significantly more difficult - has to be treated by a data controller, who does not have access to the additional knowledge.

As stated above, pseudonymized data is significantly more useful in the framework of a medical research project. Only if the identification of the said person remains principally possible, the patient can benefit from the research results. If the data controller does not have access to the key, which enables him or her to identify the particular patient, the data in question is anonymous for the data controller. The risk of identification for the said person remains the same. On closer examination, the key, which is used for decrypting the pseudonym, is merely accessible through additional knowledge, which turns anonymized or pseudonymized data into personal data, provided that the data controller has access to the additional knowledge. Therefore, safely encrypted pseudonymized data has to be classified as anonymous data, if the data controller does not have access to the key. In consequence, data protection legislation is not applicable to this particular data processing of this particular data controller[398].

Therefore it depends on the additional knowledge of the data controller, whether certain data can be qualified as anonymous data or not.

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[394] Redeker, Konrad/ Karpenstein, Ulrich: Über Nutzen und Notwendigkeit, Gesetze zu begründen, in: NJW 2001, p. 2825 (2830).
[395] Metschke/Wellbrock: Datenschutz in Wissenschaft und Forschung, Berlin 2002, S. 21, available at: http://www.datenschutz-berlin.de/infomat/dateien/mat_28.pdf.
[396] See also figure 2.
[397] Ibid.
[398] See for example: Gola, Peter/ Schomerus, Rudolf: BDSG, Munich 2005, § 3 marginal number 46.

But the crucial question is, which additional knowledge can be attributed to the data controller.

It mainly depends on the accessibility of additional knowledge, which allows the re-identification of the particular person.[399] Beyond dispute is that additional knowledge, which the data controller actually has, is attributable to him or her. If the data controller actually has access to additional knowledge, e. g. a data bank, which includes both, the genetic information of the said person and his name or other identifiers, the genetic data of the concerned data subject has to be treated as personal data, with all the consequences and all restrictions of processing.[400] This applies even if the genetic data of the data subject is processed anonymously and a matching procedure is not planned. The possibility to link the data to a certain data subject is sufficient to qualify primarily anonymized data as personal data. The intention of the data controller, whether he or she wants to establish the link and de-anonymize the particular data, remains unnoticed.[401]

As a second step the question arises, if and to what extent additional knowledge is attributable to the data controller, he or she does not have, but which could be obtained by him or her or any other person. Two different aspects have to be considered by answering this question: First, it has to be determined, if only legally accessible additional knowledge is attributable to the data controller; and secondly, the question of whether additional knowledge, that is only available to a third person, is also attributable to the data controller, who him- or herself doesn't have access to that knowledge.

[399] Dammann, Ulrich, in: Simitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006 § 3 marginal number 29.
[400] See also figure 2.
[401] Gola, Peter/ Schomerus, Rudolf: BDSG, Munich 2005, § 3 marginal number 44.

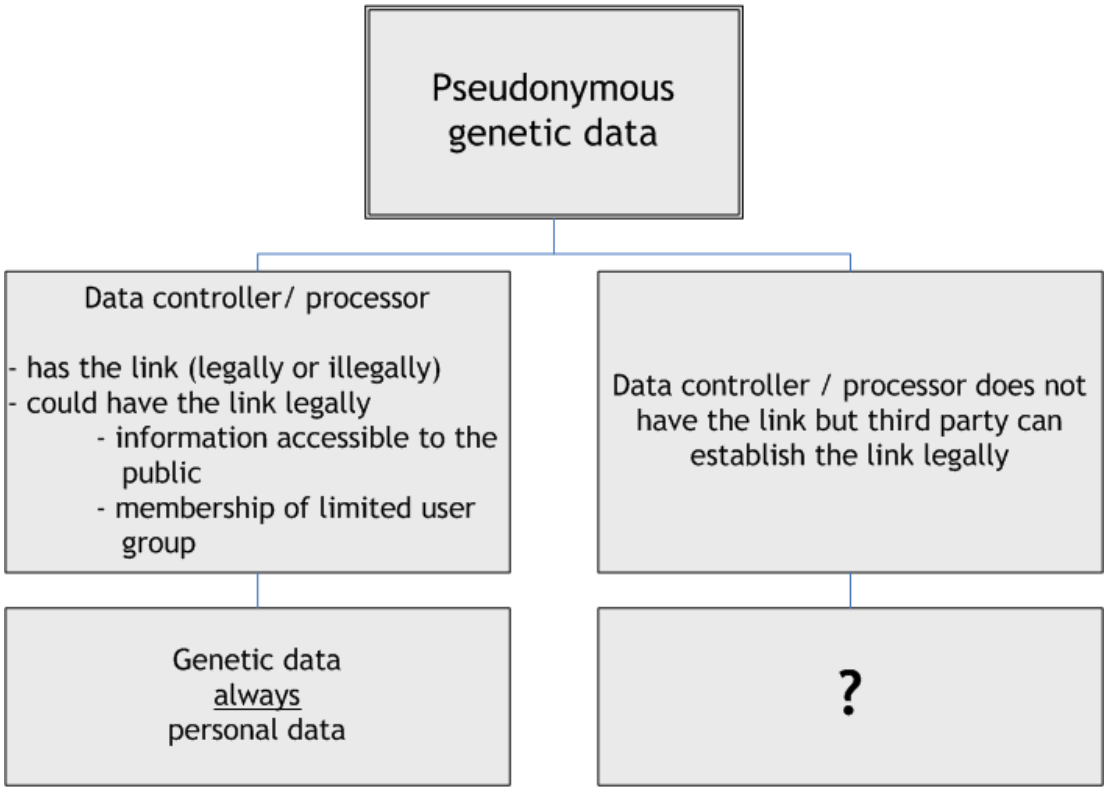

Figure 2: Quality of pseudonymous genetic data

3.3.2.2 Relevance of the character of data processing for the distinction between personal data and anonymous data

Austria already introduced a solution for that problem in its Data Protection Act. Therefore a new category of data in addition to personal data and non personal data was introduced in the course of the transposition of the Data Protection Directive in Austria: indirectly personal data (sec. 4 no. 1 of the Austrian Federal Act Concerning the Protection of Personal Data (DSG 2000). [402]

Data is indirectly personal for "a controller (sub-para. 4), a processor (sub-para. 5) or recipient of a transmission (sub-para. 12) when the data relate to the subject in such a manner that the controller, processor or recipient of a transmission cannot establish the identity of the data subject by legal means".[403] The use of indirectly personal data is not considered an infringement of confidentiality interests requiring protection, neither if

[402] Compare: Government bill for the Data Protection Act 2003, 1613 of the annexes to the Stenographic Records of the National Council XX. GP, 37: *„Um hier im Hinblick auf das Schutzinteresse eine sinnvolle Abstufung vornehmen zu können, wurde die in der Richtlinie enthaltene Unterscheidung zwischen direkter und (nur) indirekter Identifizierbarkeit nutzbar gemacht; wenn es für den konkreten Verwender der Daten nicht möglich ist, den – z.B. in Form einer laufenden oder sprechenden Nummer – vorhandenen Personenbezug auf eine in ihrer Identität bestimmte Person zurückzuführen, dann ist der Gebrauch solcher "nur indirekt personenbezogener" Daten durch diesen Verwender unter erleichterten datenschutzrechtlichen Bedingungen erlaubt."*

[403] § 4 No. 1, 2. clause DSG 2000.

non-sensitive data is processed (section 8 par. 2 DSG 2000) nor if sensitive data is processed (section 9 no. 2 DSG 2000).

If data is only indirectly personal for a recipient (e.g. pseudonymized data), transborder transmission and committing of data do not require authorisation (section 12 sub-para. 3 no. 2 DSG 2000). Data applications that merely include indirectly personal data are not subject to notification (section 17 sub-para. 2 no. 3 DSG 2000). The data subject cannot exercise the right to information (section 26 DSG 2000), to rectification and erasure (section 27 DSG 2000) and to objection (section 28 DSG 2000), if only indirectly personal data is used.

If data is only indirectly personal for the controller (section. 4 no. 4 DSG 2000) and it will be used for scientific or statistical research purposes, whose goal is not to obtain results in a form referring to specific data subjects, the controller has the right to use indirectly personal data without having to comply with further requirements (section 46 sub-para. 1 no. 3 DSG 2000). In this case he does not need an informed consent of the concerned data subject to process its data lawfully.

Whenever it is possible, data used for scientific purposes should be rendered pseudonymous or anonymous (section 46 para. 5 DSG 2000). This applies especially for the medical field, where the Austrian Medical Drugs Act imposes the duty to pseudonymize the data concerned.[404] Further safety requirements for indirectly personal data can be found in the "Medizintelematikgesetz".[405]

In conclusion, according to the Austrian data protection legislation, additional knowledge is only attributable to the data processor, if it is accessible to him by legal means, e.g. by using Internet, which is open to the public. The ability of third parties to re-establish the reference to the individual concerned remains unconsidered.[406]

[404] Compare: §§ 46 Abs. 3, 36 No. 8 AMG, 55 Abs. 1 MPG; Compare: Knyrim, Rainer/ Momeni, Daria: Datenschutz bei klinischen Prüfungen und medizinischen Studien, in: RdM 2003 p.68.
[405] Art. 10 of the Health reform act 2005, BGBl I 2005 Nr. 179.
[406] See figure 3.

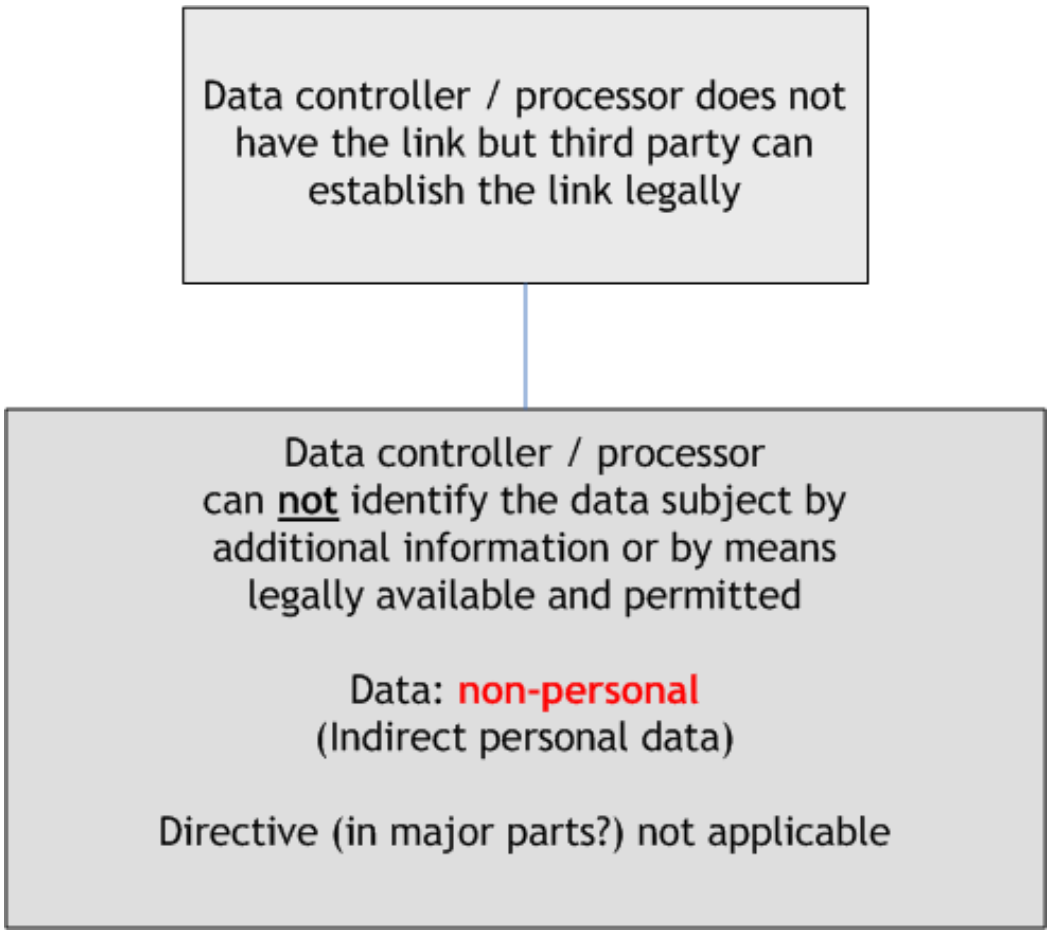

Figure 3: Indirect personal data (Austrian approach)

However, the Austrian regulation regarding research in genetic data in accordance with data protection requirements cannot simply be applied to other Member States of the European Union. Although the European Directive on the Protection of Personal Data (95/46/EC) has harmonized data protection legislation throughout Europe, a certain amount of freedom was given to the Member States to implement the Directive into national law.[407] Moreover, the Directive does not contain any regulation in certain areas, so that, in consequence, data protection legislation in the EU Member States still differs significantly.[408]

[407] See for example: Brühann, Ulf: Die Veröffentlichung personenbezogener Daten im Internet als Datenschutzproblem, in: DuD 2004, p. 201 (201).

[408] But national transposition of the Directive 95/46/EC must not violate fundamental rights or principles like the principle of proportionality protected by Community Law, see: ECJ "Lindqvist" judgement of 06.11.2003, C-101/01: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CELEX:62001J0101:EN:HTML, see summary 5 f. and holdings 87, 91 ff. The Member States may only take measures to ensure the protection of personal data that are consistent both with the provisions of Directive 95/46 and with its objective of maintaining a balance between freedom of movement of personal data and the protection of private life. However, nothing prevents a Member State from extending the scope of the national legislation implementing the provisions of Directive 95/46 to areas not included in the scope thereof provided that no other provision of Community law precludes it.

The question to what extend and whose additional knowledge can be attributed to a data controller is discussed controversially.

First it is discussed, whether knowledge the data controller does not have him- or herself and he or her could only get by using illegal means (for example by hacking into a database, like a biobank) is attributable to him or her.

There is one opinion, which states, that it can remain unnoticed, whether additional knowledge was or could be obtained lawfully or unlawfully. Following this view, it only depends on the actual availability of knowledge, which can be used to identify the concerned data subject.[409] This would mean that although the data controller doesn't have legal access to the knowledge, this knowledge would have to be regarded as his or her knowledge. So, whenever there is a reference data set available for a particular data subject the processed data has to be regarded as personal data for the data controller, although he doesn't have legal access to this additional knowledge. In practice this means, that a data controller has to regard all the data to be processed as personal data, as he cannot know, whether a reference data set is available somewhere in the world or not.

As genetic data contains very sensitive information about the concerned person, this opinion provides a comprehensive safeguard for this person. Nevertheless, from our point of view, this opinion is not in accordance with Recital (26) of Directive 95/46/EC, which states that "account should be taken of all the means likely reasonably to be used […] to identify" the said person. The opinion presented above states, that every kind of additional knowledge is attributable and not only such additional knowledge, which can be reasonably used. Consequently, this is not in accordance with the Data Protection Directive. Moreover, in practice, a distinction between personal and non-personal data would no longer be possible for the data controller, so that the scope of application for regulations on data protection would be extended too far. For these reasons, under the rule of law, additional knowledge, which is attributable to the data controller, should be reasonably at his disposal, which normally means, that it could be legally obtained.[410]

Secondly, the question arises, whose knowledge can be attributed to a data controller. In other words: Can only this kind of knowledge be attributed to a data controller, he him- or herself actually has or could legally have access to? Or can also this kind of knowledge be attributed to a data controller, only a third person has access to?

With regard to this question, scientists in German legal literature, as presented above, predominantly hold the view, that only knowledge, which the data controller actually

[409] Weichert, Thilo: Rechtsquellen und Grundbegriffe des allgemeinen Datenschutzes, in:Kilian, Wolfgang/ Heussen, Benno (Eds.): Computerrechts-Handbuch, Munich 2006, No. 131 p. 14 marginal number 58.

[410] See for example: Saeltzer, Gerhard: Sind die Daten personenbezogen oder nicht?, in: DuD 2004, p. 218 (220); Dammann, Ulrich, inSimitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006, § 3 marginal number 37; Sieber, Ulrich: Strafrecht und Strafprozeßrecht, in: Hoeren, Thomas/ Sieber, Ulrich (Eds.): Handbuch Multimedia Recht, Munich 2006, No. 19 p. 206 marginal number 552. Bygrave emphasizes the criterion of probability. All probably used means should be taken into account. It has to be decided in each single case, whether the use of illegal means is probable in that case, but the criterion of probability should be construed more stringently if the means are illegal: see Bygrave 2003, p. 45.[411] Compare for example: Dammann, Ulrich, in:Simitis, Spiros (Ed.): Bundesdatenschutzgesetz, Baden-Baden 2006, § 3 marginal numbers 37 ff.Saeltzer, Gerhard: Sind die Daten personenbezogen oder nicht?, in: DuD 2004, p. 218 (222); Roßnagel, Alexander/ Scholz, Philip: Datenschutz durch Anonymität und Pseudonymität - Rechtsfolgen der Verwendung anonymer und pseudonymer Daten, in: MMR 2000, p. 721 (723).[412] See also: Bygrave 2003, p.45.

has or which is legally accessible for him- or herself, can be attributed to this data controller.[411] In this respect, the German position is similar to the Austrian concept. Consequently, only such knowledge, which is accessible for him or her, e.g. on the Internet, can be attributed to the data controller, whereas knowledge stored in data bases, e.g. of law enforcement agencies, which are not legally accessible to the data controller, is not attributable to him or her.

The data controller would thus be free to deal with the data as he chooses, e.g. publish it on the Internet, as this kind of genetic data would have to be regarded as anonymous data according to that opinion. The Data Protection Directive would not be applicable in that case.

But this would enable for example law enforcement agencies or any other third party having a reference data set or another link to re-establish the reference to an individual by matching the data published on the Internet with data from their own data bank. The privacy of the data subjects, for example of the patients taking part in ACGT, would be affected.

With regard to the Data Protection Directive 95/46/EC, this opinion cannot convince. The question of whether certain additional knowledge is attributable to the data controller, and if, in consequence, a person is identifiable for the data controller, must, in the first place, be answered by statutory interpretation of the European Data Protection Directive (95/46/EC), corresponding with European law. Recital (26) states, that in order to determine, whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the data controller or by any other person to identify the said person. The interpretation of the wording of the Recital suggests that not only those means, which can be legally used by the data controller him- or herself, can be attributed to the data controller. Furthermore, the Recital states, that means, which can be reasonably used by a third person to identify the said person, must be attributed to the data controller. Without doubt, one of the means, which can be reasonably used by a third person, is the use of knowledge, which is legally accessible to the third person und which the third person can use with reasonable effort. The conclusion drawn from this directive-corresponding interpretation is that not only knowledge, which is accessible to the data controller him or herself, is attributable to the data controller, but also knowledge, which is accessible only to a third person.[412]

A teleological interpretation of Art. 2 lit a) and Recital (26) of the Directive and suggests, that the interpretation presented above is convincing. According to Art. 1 No. 1 of the Directive, the Data Protection Directive 95/46/EC aims to protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data. This Directive comprises the protection of the individual against unlimited collection, storage, use and transmission of his or her personal data.

In the framework of a genome research project, the data processor usually doesn't have access to the reference data set to link his data to a particular person. If the opinion, that only this kind of knowledge could be attributed to the data controller, he has actually or could legally have access to, the data dealt with would be de facto anonymous data, which wouldn't fall into the scope of data protection legislation. The data processor could do with this genetic data whatever he wants, for example publish it on the internet or transmit it abroad. As a result, third parties could access the data and re-establish the link to the said person, if they had a reference link to the person and an interest in the connected information. Criminal prosecutors or insurance companies, which sometimes own gene banks, could, for example, have a great interest in knowing, if a person, whose reference link they have got, has a certain

disease. But this would be an infringement of the citizen's right and freedom to decide for him- or herself, who is at which point of time allowed to access which particular part of his or her personal data. The aim of data protection law and the Data Protection Directive 95/46/EC would be undermined.

For this reason it is necessary, in accordance with the wording of the European Data Protection Directive and the sense and aim of data protection law and the Directive, to attribute also that kind additional knowledge to a data controller, to which only a third person has legal access. If a third party can legally access knowledge, which can be used to identify the said person, the genetic data concerned is personal data for the data processor as well, although the data processor himself cannot identify the person.

As consequence the data processor would have to treat all genetic data as personal data in order to avoid responsibility, as he cannot know, whether there is a reference link to a person for a certain set of genetic data he uses available to a third party. Every data processing operation of personal data requires permission, either by law or by consent of the concerned person. Therefore the data controller in ACGT would need an informed consent for each data processing operation as a consequence of that opinion, since a legal basis is generally not available for this kind of data processing taking place within ACGT.

On the one hand, the said person's privacy would be effectively protected. But on the other hand, this interpretation would have the effect of a strong restriction on medical research, as an informed consent would be needed for each single data processing operation. The legal validity of an extensive consent of the said person, which also comprises future data processing, including operations which are not known at the point of time when the consent is given, is debatable. The processing of genetic data would be hindered, if not impossible at all, so that as a consequence (future) medical genetic research would be affected adversely.

For these reasons, the interpretation supported above must be applied restrictively. The privacy of the concerned data subject is not in danger, if, first, the data processor him- or herself cannot legally access the additional knowledge of a third party and, secondly, also the third party cannot access the data processor's data. In these cases, when neither the data controller nor the third party can establish the link alone, the identification of the said person is not possible, at least in consideration of the present state of the art, or the identification would require an unreasonable effort. Attributing additional knowledge of third parties to a data controller also in these cases would extend the scope of data protection legislation too far and would oppose the aim of data protection in general.

In conclusion, the attribution of additional knowledge of third parties depends on the situation of the data processing operation in question.[413] If there is a danger, that a third party can access the data processor's data (e.g. following publication or data transmission) and identify the said person, data protection legislation must provide effective protection of the individual's privacy. For this reason, additional knowledge of a third party must be attributed to the data controller, if data processing causes any danger for the person's privacy, e.g. in case of data transmission or publication. In consequence this would mean that for every transmission or publication of de facto anonymous data a permission (either by law or consent of the said person) is required, because the data processor cannot know, for which of the genetic data sets to be processed additional knowledge (e.g. a personalized reference data set) exists.

[413] See figure 4 below.

In this context it is important to remember that in the legal sense a transmission only takes place, if the data is transmitted to a third party, that means to a body other than the data subject, the controller, the processor and the persons who, under the direct authority of the controller or the processor, are authorized to process the data.

That means that in the legal sense no transmission takes place, if data is transferred within ACGT, so that no permission (by law or the data subject) is needed for this operation. Only if data is transmitted from ACGT to a body outside of ACGT permission either by law or by the concerned data subject is needed for this processing operation.

Data processing operations, which do not cause any danger for the individual's personal rights and privacy, e.g. adequately secured storage or use of the de facto anonymous data, do not require any consent of the patient or any permission by law:

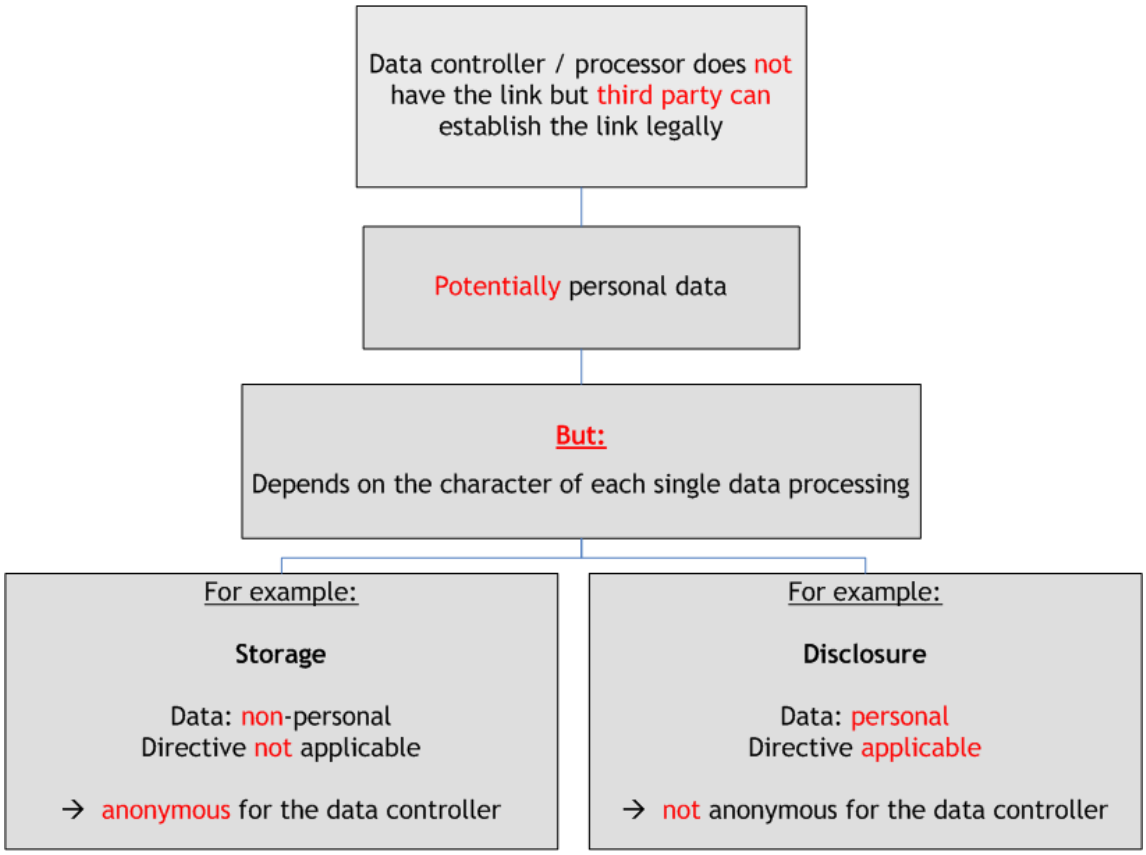

Figure 4: Character of each single data processing (ACGT approach)

This solution offers sufficient protection of the concerned individual's right of privacy without restricting medical research too much. The opinion supported above is also in accordance with recital (26) of the Data Protection Directive, which states explicitly, that in order to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or any other person to identify the said person. Reasonably, a third person only uses means to identify the said person, if she can also access the data to be processed. If she cannot access the data, the third person does not reasonably use any means for identification, so that, following the directive-corresponding interpretation of Art. 1 No. 1 and recital (26) of the Data Protection Directive 95/46/EC, these means and also the third person's

knowledge cannot be attributed to the data controller with the result, that this data for him is de facto anonymous data.

Therefore Data Protection legislation **is applicable**, whenever de facto anonymous data is transmitted and published. Data protection legislation **is not applicable**, when de facto anonymous genetic data is stored and used if,

- first, the data processor cannot legally access additional knowledge of third parties and
- secondly, third parties cannot access the data processor's data.

3.3.2.3 Data controller within ACGT

The data controller is the person or organization who/which determines the purposes and means of data processing.[414] Therefore the question arises of whom or which entity will be the data controller within ACGT.

This issue is very important for the compliance of ACGT with current data protection legislation, as the data controller is the person or entity who/which has to ensure this compliance. As the compliance with current data protection legislation is crucial for the success of ACGT this decision has to be made very carefully. A solution could be to establish several data controllers within ACGT. That means that, for example, every physician, hospital or user of the ACGT database could be regarded as a data controller within ACGT. In consequence, each of these data controllers would have to ensure compliance with current data protection legislation, i.e. would need an informed consent of each patient.

But that solution would not be practicable. Firstly not all of these possible data controllers would be able to comply with data protection legislation just due to a lack of knowledge. Persons or entities not familiar with data protection legislation are simply not able to get familiar with all the relevant legislation in an economically justifiable amount of time. But as they would be responsible for each data processing they carry out they would have to get that knowledge in order not to risk any liability. This solution would therefore be a great obstacle for ACGT as a lot of potential participants of ACGT would just not take part in the project as they neither have the ability nor the resources needed to ensure compliance of the data processing with current data protection legislation and would therefore face the risk of being held liable for an unlawful processing of data. Secondly, from the patient's point of view, this solution can not be recommended, as in case of violation of his rights, the patient would not know against which data controller he would have to assert his claim. Thirdly, from a practical point of view, this solution can also not be recommended, as the transmission of personal data between different data controllers always is a data processing within the scope of the Data Protection Directive, as in case of transmission to third parties even de-facto anonymous data has to be qualified as personal data. Therefore each data controller would require a legal basis (which does not exist for all data processing within ACGT) or an informed consent of the patient.

Another solution could be to establish only one data controller within ACGT and the particular independent Trusted Third Party (TTP), who/which would be responsible for the compliance of the whole project with current data protection legislation. All the other

[414] See Bygrave 2003, p. 21; see also Art 2(d) of the EC Directive.

project participants would have to be regarded as data processors, who/which actually carry out the processing of the data. The central data controller would be responsible for the data processing.

The advantage of this solution would be that a person or entity could be determined as data controller, who/which is an expert in the field of data protection within scientific research projects dealing with genomic data and who/which therefore would be able to ensure compliance of the data processing within ACGT with current data protection legislation. This central data controller and the TTP would have to be informed of all data processing taking part in their area of responsibility within the project and it would be the duty of them to take appropriate measures to ensure compliance of each data processing operation with data protection legislation. The TTP would be responsible for the (second) pseudonymization and the protection of the links. The central data controller of ACGT would be responsible for the processing of the data relating to the ACGT data base(s) and the GRID infrastructure. Another advantage of this solution would be that the informed consents regarding the processing of data within ACGT could be concluded by this central data controller, who/which would refer to the TTP also, the patient therefore has to consent only once.

In order to implement this central data controller solution in ACGT the design of the data flow within ACGT is very important. Only if this model is designed in a way that it complies with data protection legislation and the data flows are transparent, the data controller of ACGT will be able to ensure compliance. This was also taken into account, when the new data flow model for ACGT was developed. As this compliance is a crucial factor for the success of the whole project, the selection of an adequate and competent data controller is of highest importance for ACGT. Such a competent and trustful data controller could also be a great dissemination tool and a good reason for patients to take part in the project.

It is very important to state that this central data controller and the TTP will only be responsible for the data processing within ACGT. The responsibility for the data processing within the participating hospitals will stay with the local data controllers in the participating hospitals. The reasons for this are that a central ACGT data controller and the TTP simply are not able to ensure compliance of the data processing in each participating hospital with data protection legislation and that no hospital would allow a central ACGT data controller to survey its data flows. The advantage of that solution would be that each data controller of the particular hospital could ensure compliance of the data processing with the applicable national data protection legislation. Therefore this central data controller solution is also in line with the principle of subsidiarity.

3.3.2.4 Trusted Third Party

Generally a Trusted Third Party (TTP) is a party, which at least two other parties trust. In the context of data protection a Trusted Third Party is regarded as a trustful custodian for personal data or the links to identify the concerned data subject, which shall ensure the privacy of the concerned data subject.

3.3.2.4.1 Demands on the Trusted Third Party

The Trusted Third Party in ACGT shall ensure that only persons needing to know the identity of a patient get personal data about a patient participating in ACGT. The TTP has to assure that as few persons and entities as possible get access to data

revealing the identity of a patient. For most researchers participating in ACGT this information is not needed as their research can also be carried out with anonymous data. But especially if a new treatment is developed the concerned patient shall benefit from this research results. Therefore the patient having a particular gene structure must be identified.

In practice personal data is collected from the participating patients in the local hospitals, which is only needed in anonymous form by the ACGT researchers and later on during the project, anonymous data is examined by the researchers, that may have to be de-anonymized to identify the concerned patient so that he can benefit from the research. It is the duty of the TTP to de-facto anonymize the patient's data by pseudonymizing the data and to enable the de-anonymization of the pseudonymized data at the same time.

Therefore the TTP has to replace all the identifying characteristics of the genetic data of a certain patient and replace them with a pseudonym. The TTP must be the only party able to link this pseudonym with the patient, or, if the TTP gets the genetic already in a pseudonymized form from the hospital (as we suggest) it must be the only party to link this second pseudonym with the first pseudonym given from the hospital and the name of the hospital. The hospital can link the genetic data, which is then only tagged with the pseudonym of the hospital, to the concerned patient again.

There are two ways of how a TTP could provide this service. One solution could be that all the (pseudonymized) genetic data could be sent from the hospitals to the TTP so that the TTP can pseudonymize the data for a second time. But this solution would be quite impracticable. Therefore, another solution is that the TTP could provide a software tool, which could perform the second pseudonymization. The (pseudonymized) genetic data would have to be sent from the hospital "through" this software tool to the ACGT database. The TTP would then have to ensure the software tool provides an adequate level of anonymization and safety. The data flow within ACGT will be described in more detail at 3.3.2.5.

3.3.2.4.2 Technical and organizational measures

The TTP must be bound to professional discretion to protect the links of the participating patients sufficiently. The links have to be protected by the TTP against (unlawful) access and also against seizure. It is the duty of the TTP as an independent data controller to provide adequate technical and organizational measures. These technical and organizational measures are described in detail at 3.2.1.3.1.2. If the TTP already gets pseudonymized data, and therefore de-facto anonymous data, from the hospitals, the Data Protection Directive would not be applicable. But as it can not be guaranteed that all participating hospitals pseudonymize their patients' genetic data sufficiently (or even at all) although contracts between ACGT and these hospitals may stipulate this, we strongly recommend that these regulations should be obeyed by the ACGT data controller and the TTP in any case to avoid liability and a lack of trust on the patients, physicians and researchers side.

3.3.2.4.3 Contracts

As the Trusted Third Party shall act as a trustee, it is of high importance that it acts independent from every other participant of the project. It has to be a data controller next to the central data controller of ACGT, therefore not having to justify its decisions to the central data controller or anybody else[415]. Only if the TTP is a data controller it can be seen as a Trusted THIRD Party guaranteeing the safety of the links to the data subjects as a security authority.

For the purposes of keeping proof, the parts of the contract or the legal act relating to data protection and the requirements relating to the technical and organizational measures shall be in writing or in another equivalent form

The contracts between the ACGT data controller and the TTP should include the conditions and the procedure for the de-anonymization process as well as rules regarding the storage of the links, the access control to the data base and other data security issues.

3.3.2.5 Data Protection Architecture for the dataflow within ACGT

Designing a Data Protection architecture for data flows within ACGT and taking into account all considerations mentioned above, the first aim to achieve is to work with anonymous data wherever this is possible. Therefore it is of high importance to use anonymization as a means to get as much data processing as possible outside of the scope of the Data Protection Directive.

Hence it is essential to render the processed genetic data de facto anonymous (see 3.3.2.1.2). For, as analyzed above (see 3.3.2.2), the Data Protection Directive is not applicable for the storage and use of de facto anonymous genetic data.

To assure Data Protection for transmitted and published de facto anonymous genetic data as well, it is secondly essential to define and create the necessary consent forms and legal agreements/contracts. The consent of the concerned data subject is needed for various reasons. Firstly, whenever genetic data is transmitted to bodies outside of ACGT or the data is disclosed, the de-facto anonymized data used in ACGT has to be qualified as personal data (3.3.2.2). Therefore permission for this processing operation is needed. As a statutory legal basis is not available, the consent of the data subject (e.g. the concerned patient) is needed for that. Furthermore consent might also be needed, if genetic data shall be transferred to third countries. Such a transmission may take place, if a researcher not participating in the ACGT project wants to use the data for his research or if the research unit is not located within the EU. A disclosure may occur for example, if a researcher wants to publish an article in a medical magazine and the disclosure of genetic data is needed to demonstrate and verify his or her results.

Secondly, the consent is needed as a “fallback option”. Although the ACGT Data Protection Framework (3.3.2.5) was developed to guarantee that only de-facto anonymous genetic data is used within ACGT and that ACGT complies with current data protection legislation, it still might happen, that personal genetic data is processed, for example because an error occurred during the anonymization process or due to human failure. For these unpredictable cases, in which personal data is

[415] Wellbrock, Rita: Generische Datenschutzmodelle für Biomaterialbanken, in: DuD 2007, S. 17 (21).

processed, permission is needed as well. And as, again, no statutory legal basis is available, the consent of the data subject is required to process this data and to ensure compliance with current data protection legislation.

Furthermore the consent of the patient is needed from an ethical point of view. The patient should be able to determine which data referring to him shall be processed by which processor and for which purposes.

Therefore an informed consent of the patient concerned is required for ACGT, although the ACGT Data Protection Framework shall guarantee the use of de-facto anonymized data within ACGT and ACGT's compliance with current data protection legislation.

Apart from these, from a legal point of view, most important issues, it has to be taken into account that the proposed ACGT platform has to be compatible with the ICT infrastructure and policies of all participating healthcare organizations. Therefore a data protection architecture within ACGT will be characterized by a multiplicity of security and network infrastructures. Thus it will be of high importance to have minimal impact on the local IT infrastructure of every healthcare organization for two major reasons: firstly, it is most likely that access from the outside to the hospitals' IT-infrastructure is heavily restricted if not forbidden, secondly, and from a legal point of view even more important, ACGT should not be responsible for data protection compliance of the participating healthcare organizations in any case. The proposed Data Protection Architecture therefore has to run independently from the local IT-infrastructures being a self-contained data protection framework in compliance with the applicable data protection legislation.

3.3.2.5.1 Anonymization of genetic data within ACGT

The following figure 5 illustrates the recommended solution for the de facto anonymization of genetic data within ACGT.

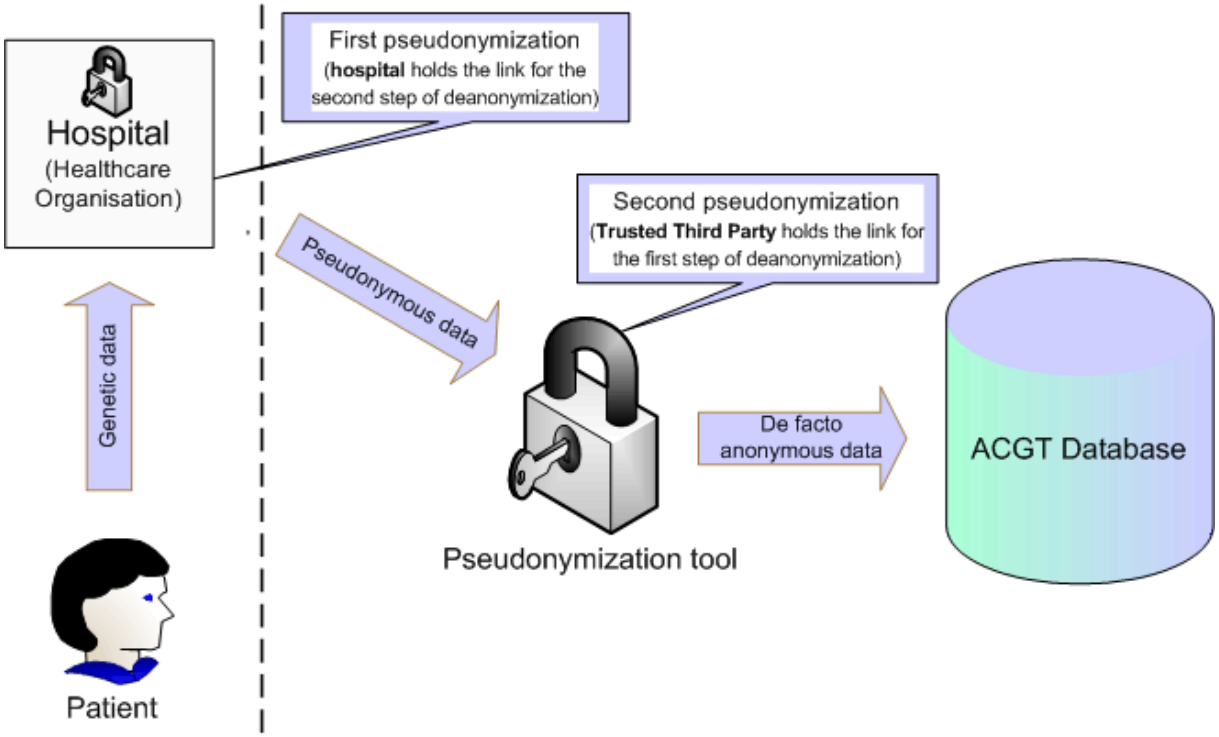

Figure 5: De facto anonymous genetic data

Genetic data of the patient, that is taken by the treating physician in the hospital, is analysed and stored within the hospital. The hospital and its different departments are obligated to work with pseudonymized patient's data, where the physical examinations do not need the identification of the patient.

If a patient agrees to participate in an ACGT trial the physician transmits his or her data in a pseudonymized form to ACGT (first pseudonymization). Beside the legal obligation to pseudonymize the patient's data it is a contractual obligation of the hospital against ACGT (see below 3.3.2.5.3) as well. The link that establishes the connection between the pseudonym and the specific patient, which in other words allows the re-identification of the patient is held only by the hospital, concretely in most of the cases by the physician, as he inherently has access to the nominative patient-data (in the care context), he is the ideal person to guard the link.

Taking into account that pseudonymous data in principle for everybody not having the link is de facto anonymous data when it is stored or used (see 3.3.2.2) the data transmitted by the hospital to ACGT can be seen as de facto anonymous for ACGT-users already, provided that they have no access to the link in the hospital. It would be possible to make available a pseudonymization tool designed by the Trusted Third Party to hospitals that ask for it. But as the hospitals are responsible for data security and data protection issues in their own hospital (see 3.3.2.5.3), ACGT can not commit them to use such tool, it only can commit the hospitals by binding contracts to guarantee a state-of-the-art pseudonymization. Considering the different structures, customs and security-levels in hospitals all over Europe it is inadvisable to trust in pseudonymization tools that are not designed by ACGT, i.e. by the TTP. Therefore for hospitals not using a pseudonymization tool provided by ACGT it is recommended to have a second pseudonymization done within in the ACGT Data Protection Architecture to guarantee at least one state-of-the-art

pseudonymization and therefore assure ACGT´s compliance with data protection legislation.

During the transmission to the ACGT-database this pseudonymized data, provided that the hospital didn't use the ACGT pseudonymization tool, would therefore be pseudonymized a second time by a pseudonymization tool of ACGT. This second (for hospitals using the ACGT pseudonymization tool "first")pseudonymization has to guarantee an equivalent high standard for all genetic data transmitted from the participating hospitals to ACGT with the effect that all genetic data processed within ACGT is pseudonymized on a level that is state-of-the-art. The link of this second pseudonymization is held by a security authority named "Trusted Third Party" (see 3.3.2.4). After this second pseudonymization the data is stored in the ACGT-database, possibly located at the Trusted Third Party. De facto the data is anonymous now. The de facto anonymous data and the links from the second pseudonymization will be stored in different data bases. ACGT-users will only work with de facto anonymous genetic data.

However, if a patient needs to be reidentified, in case a user (researcher) of the data detected an anomaly in his or her data or a high risk health condition, the cooperation of the Trusted Third Party is necessary - as only this security authority has the link for deanonymization and the knowledge which of the participating hospitals is the treating hospital. Secondly, in those cases where the hospitals do not use the pseudonymization tool of ACGT, the treating hospital is needed to identify the specific patient and finally give feedback, as only the hospital is able to re-identify the concerned patient by his/her clear name, since it holds a second key for re-identification.

This is the highly recommended Data Protection Architecture. Nevertheless there might arise the problem, that participating hospitals do not agree to have their data stored in an ACGT-database outside of the hospital. Only in that case we suggest to install an ACGT database within the specific hospital, that is physically as well as organizational disconnected to the hospitals database and is administrated only by a Trusted Third Party chosen by ACGT. The hospital therefore would send its data through the TTP´s pseudonymization tool to the ACGT database that is located in the same hospital. The ulterior motive of this construction is that ACGT would still be the data controller regarding the processing of the data stored in the ACGT database in the hospital.

And finally only for the case that for organizational reasons it would not be realizable to have the TTP administrate the ACGT database within the hospital, it is proposed to have it administrated by an assistant of the hospital. This assistant should by no means be responsible or even involved in the administration of the database of hospital containing the treating data. There would have to be a specific subsection in the contract between ACGT and the hospital that ensures this division. The assistant would – as the TTP in the scenario before – process the data on behave of ACGT that would be the data controller.

3.3.2.5.2 Participating actors

3.3.2.5.2.1 Patient

The most important actor of course will be the patient participating in the ACGT-trials, although he or she will not get in contact directly with the ACGT-project but through his or her treating healthcare organization or through his or her treating physician.

3.3.2.5.2.2 ACGT Data Protection Board

Furthermore ACGT is an actor in this proposed data protection framework of course. But as ACGT is not a legal body, it will be necessary to establish a body within ACGT. Therefore we suggest to establish an "*ACGT Data Protection Board*". This ACGT Data Protection Board will be the central data controller of ACGT and will therefore be responsible for the compliance of ACGT with current data protection legislation.[416] Furthermore this Board can act legally and sign legally binding agreements regarding data protection issues. The ACGT Data Protection Board as a legal body will therefore be able to sign all contracts needed to ensure the compliance of all parties with the data protection framework, particularly with regard to ACGT´s policies and procedures.

Further the ACGT Data Protection Board is supposed to closely cooperate with and audit the participating parties (Trusted Third Party, healthcare organization and end-users). These audits will ensure that ACGT´s policies and procedures are implemented and followed among the parties.

3.3.2.5.2.3 Healthcare organizations (hospitals)

The healthcare organizations provide the source for all patient data processed within ACGT. They are the connection between patients willing to participate in an ACGT-trial and ACGT itself. Any contact between ACGT and the patients is supposed to be mediated through the healthcare organizations. They are responsible for safeguarding patients´ rights and data security issues in their own organization.

3.3.2.5.2.4 Trusted Third Party

As shown before (see 3.3.2.4) the involvement of a Trusted Third Party in the Data Protection Framework increases the data-security-level tremendously, as it is an independent security authority, which has no interest in the content of the processed data and therefore can be trusted by all participants of the ACGT-project. There could be only one but also several Trusted Third Parties in the project. Since a Trusted Third Party is specialized in data security issues it should be represented in the ACGT Data Protection Board. On the other hand this might lead to legal problems, as representatives of the supposed TTP may have to

[416] The role and the duties of the central data controller of ACGT are described in detail at 3.3.2.3.

choose their own company as TTP, audit and supervise themselves and conclude contracts with their own company. This could put at risk the independence of the Data Protection Board and the TTP. So, as a solution, the participation of the TTP's representatives should be excluded from any decision of the Data Protection Board regarding the TTP, while the expertise of the representatives could be used for all other decisions.

It will host a repository of access rights to the anonymous databases, granted by the ACGT Data Protection Board. An ACGT end user requesting to access a data source protected by the Data Protection Framework will receive credentials according to the decisions made by the board. A detailed audit trail of all access requests will be kept by the TTP to ensure accountability and to be able to detect abuse.

3.3.2.5.2.5 ACGT end user

Finally the ACGT end users are part of the ACGT Data Protection Framework. End user is anyone who is allowed to have access to the ACGT databases, namely researchers working in one of the participating healthcare organizations. The ACGT Data Protection Board will grant access to end users if required. It is planed not to run the procedure for every single request but to give access for the duration of the complete project in a single request and revoking the access to the data bases in any case of abuse.

3.3.2.5.3 Necessary legal agreements, contracts and informed consents

A patient, who is willing to participate in an ACGT-trial, has to sign after having received all information wanted from his or her treating healthcare organization an informed consent regarding the processing of his or her data within ACGT. This consent form will explain and define the context and limitations in which the data can be examined, analyzed and used. This will be done by referring to a **general terms document**[417] that is included in all legal documents used in the ACGT Data Protection Framework.

Each healthcare organization will have a contractual agreement with ACGT concerning data protection and security issues. The agreement between the healthcare organizations and ACGT will rule in particular that regarding the processing and storage of the patient's data within their own organization the hospitals will be responsible for the compliance with both, data protection regulations and the procedures and policies provided by ACGT. Additionally, ACGT has to commit the healthcare organizations to guarantee for the fact that its employees (physicians, IT-staff etc) adhere to the procedures and policies provided with the framework. They have to make sure that the access to the anonymous data is protected by the security mechanisms defined in the ACGT framework. Taking into account the multitude of IT-infrastructures and different national legislation to draw up those contracts will be both, of high importance and substantial.

To ensure that the physicians represent the hospital towards the patient and agree with the general terms of ACGT a further agreement between the physicians and the ACGT Data Protection Board will be necessary.

[417] Part of D 10.1

The Trusted Third Party has to enter into a contractual agreement with the ACGT Data Protection Board as well. This contract will have to contain rules regarding the storage of the links, the access control to the data base and data security issues. More details regarding the contracts between ACGT and the TTP can be found at 3.3.2.4.3.

Finally agreements with ACGT-end-users are needed, which grant them access and make sure, that they agree with the general terms of the ACGT framework. These could be either concluded by the ACGT Data Protection Board or by participating healthcare organizations, provided they are binding them to the general terms.

Figure 6 illustrates the proposed architecture:

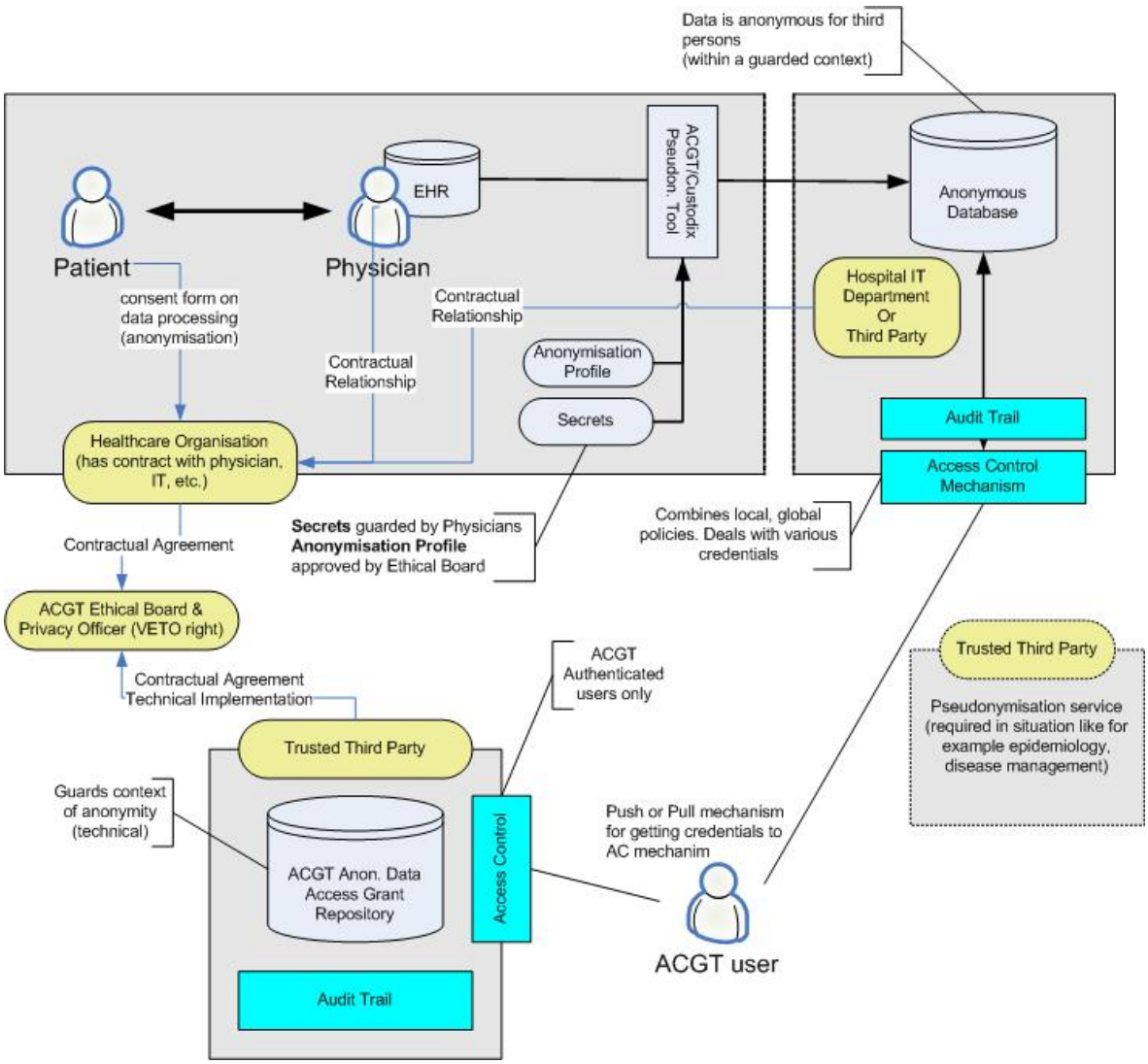

Figure 6: Data Protection Framework of ACGT

3.3.2.6 Transfer of genetic data to third countries

The general principles and conditions for the transfer of genetic data to third countries are described in detail already in 3.2.1.6. Furthermore, as described in 3.3.2.2, an informed consent of the concerned patient compulsory for each transfer of his genetic data to third countries even if it is processed pseudonymously.

Nevertheless ACGT can conclude a contract with a person or an entity situated in a third country not providing an adequate level of protection according to Art 26 Para 1 (c) of the Data Protection Directive to transfer the data to this person/entity. But the transfer of the data is even in this case only allowed, if it is necessary for the conclusion or performance of this contract, which must be, in addition, concluded in the interest of the data subject between the controller and the third party.

Furthermore, according to Art 26 Para 2 of the Directive, a Member State may authorize a transfer or a set of transfers of personal data to a third country which does not ensure an adequate level of protection, where the controller adduces adequate safeguards, which may in particular result from appropriate contractual clauses.

Such contracts with third parties situated in a country not providing an adequate level of protection regarding the transfer of personal have to comply with very strict conditions and it can be recommended to ACGT to conclude such contracts only if the transfer to a third country with no adequate protection is absolutely needed, not only because of the legal complexity of such a contract, but also for public relations reasons, especially as ACGT deals with genetic data, which is very sensitive and vulnerable. Therefore it is highly recommended to transfer genetic data to third parties situated in countries with no adequate level of protection only if the data subject has given his or her consent and if it is of overwhelming importance for the research.

3.3.2.7 Information and consent

Directive 95/46/EC[418] bans the processing of personal data concerning health (medical data)[419]. This *petitio principii* could have led to serious problems, if the Directive had not provided that this ban does not apply in several cases[420], especially in case of an informed consent of the data subject.

[418] On the Directive : Y. Poullet, M.-H. Boulanger, C. de Terwangne, Th. Leonard, S. Louveaux et D. Moreau, La protection des données à caractère personnel en droit communautaire, Journal des Tribunaux de droit européen, Bruxelles, Ed. Larcier, 1997, p. 121 (in three parts).

[419] *Directive 95/46/EC*, art. 8.1. The notion of medical data includes all information relative to any aspect, physical or psychological, of the present, past or future health condition, good or bad, of a living or dead natural person. On the definition of medical data : *Explanatory report of Convention n° 108*, recital 45 ; *Rec. (97) 5 of the Council of Europe relative to the protection of medical data*, art. I of the annex ; *C.J.C.E.*, 6 Nov. 2003, Bodil Lindqvist, case C-101/01, obs. C. de TERWANGNE, « Affaire Lindqvist ou quand la Cour de justice des Communautés européennes prend position en matière de protection des données personnelles », *R.D.T.I.,* 2004, pp. 67-99 ; *Groupe européen d'éthique des sciences et des nouvelles technologies*, avis n° 13 du 30 juillet 1999 sur les aspects éthiques de l'utilisation des données personnelles de santé dans la société de l'information.

[420] Directive 95/46/EC, art. 8.2.

According to the Directive the ban on processing medical data does not apply where the data subject has given his or her explicit consent to the processing of his or her medical data[421].

In this case the Directive entrusts the data subject with the power to authorize the processing of his or her medical data[422]. This empowerment of the data subject represents without any doubt a very strong expression of his or her informational self determination – the power of the data subject upon his or her personal data –[423].

But this empowerment could also surprise. Is the data subject always capable to decide in a reasonable way about the processing of his or her medical data? Isn't it too dangerous to give the data subject such power when most of the time he or she represents the "weakest" party or at least the "demanding" person in the processing his or her medical data? By example, how could a patient oppose the processing of his or her medical data for scientific purpose (ex. for a clinical trial) before a surgery or any other investigation? How to ensure the validity of the data subject's consent and avoid a complete masquerade?

This empowerment of the data subject should not be seen as unlimited or under no control. In fact when given this power the data subject has to evaluate the interest(s) that could justify the processing of his or her medical data. With this end in view the data subject has to put correctly into balance the interests in presence and to act accordingly. Otherwise the consent will not be able to legitimate the processing of his or her medical data (see *infra* about the real control of the legitimacy of the processing of medical data and the determination of the interests in presence).

The Directive confirms this analysis.

Regarding the Directive the data subject's consent means "any freely given specific and informed indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed"[424].

First the consent has to be indubitable, indisputable, without any doubt.

Then the consent of the data subject must have been freely given. In this regard the consent has to be free of any vice, constraint or pressure. With respect to this any direct profit (such as the benefit for his or her health) or indirect profit (such as the participation to the progress of medical science) for the patient should not affect automatically the validity of the data subject's consent. Would the financial retribution of the data subject (beyond the cover of his or her eventual expenses) invalidate his or her consent? Again, the answer to this question should not be absolute. It should depend upon the circumstances of each considered case and on how the applicable law deals with the protection of the data subject.

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[421] *Directive 95/46/EC*, art. 8.2. a. The national law may provide that the data subject's consent may not lift the prohibition.

[422] Directive 95/46/EC, recital 33.

[423] On the notion of informational self-determination : Fr. RIGAUX, *La protection de la vie privée et des autres biens de la personnalité*, Bruxelles, Paris, Bruylant, L.G.D.J., 1990, p. 588-589, n° 532 : « (…) *La juridiction constitutionnelle a déduit du droit de la personnalité l'un de ses attributs, à savoir : « le pouvoir reconnu à l'individu et résultant de la notion d'auto-détermination, de décider en premier lieu lui-même quand et dans quelle mesure des faits relatifs à sa propre existence sont divulgués (…) Cet attribut du droit de la personnalité est appelé « droit à la maîtrise des données personnelles* » (…) Il n'est toutefois pas sans limite. (…) » ; Council of Europe, *Resolution 1165* (1998), 26 June 1998, Droit au respect de la vie privée (24th Session), point 5.

[424] Directive 95/46/EC, art. 2, h.

Moreover the consent of the data subject has to be specific and informed. To be specific reminds insistently that the data subject must know exactly what he or she consents to. The latter implies necessarily the prior and adequate information of the data subject concerning the processing of his or her medical data. In the context of ACGT, information concerns – among others - the processing of the anonymization of the data by the implication of a trusted third party, the use of the anonymized data and the rights of the data subject as seen in the deliverable 10.1. Without this prior and adequate information the consent of the data subject shall not be specific. Therefore and in any case the consent of the data subject could not ground the processing of his or her medical data.

In this view the next question is logically the determination of the detail level of the provided information to the data subject. Articles 10 and 11 of the Directive determine the minimum content of this information. The latter must permit the complete enforcement of all the aspects of the data processing – such as the data quality, the data subject's rights, the security and confidentiality measures, the notification to the supervisory authority, etc. –. However there is no doubt that the information has to be more accurate and complete particularly since very sensitive data as medical data are processed.

In any case the data subject may not give an unspecified or uninformed consent to the processing of his or her medical data.

Further processing of medical data is prohibited when incompatible with the initial purpose for which data have been collected.

The consent must be given prior the time of the data collection. It must not be given necessarily at the same time; it only has to be obtained prior the processing.

The consent of the data subject must be explicit to allow the processing of his or her medical data[425]. That means that the data subject must be fully informed on the processing which will be made on his/her data and its purpose. The data subject has also to be informed about his rights and duties. The Deliverable 10.1 gives examples of consent forms which include information.

A contrario, the requirement of an explicit consent should exclude any implicit consent – whatever could mean this last notion –. With respect to this, beyond the indisputable character of the data subject's consent, its explicit characteristic presumes that it has been expressed. Several Member States have decided to transpose this requirement by asking for a written consent from the data subject.

However the explicit consent could be deduced from some other behaviour of the data subject especially regarding the circumstances of the case. Indeed some positive actions could express the explicit consent of the data subject to the processing of his or her medical data, such as the participation to a foundation fighting against the disease affecting the data subject or as the demand to be treated in a special medical unit notoriously known as being a research unit.

In all these circumstances the consent of the data subject induces a presumption of legitimacy of the processing of his or her medical data. It is assumed that the data subject has correctly assessed the interests in presence and acted accordingly. If the data subject has not correctly assessed the interests in presence and if the interests in presence are not respected, his or her consent will not legitimate the processing of his or her medical data. The latter will not be legitimate on this ground.

[425] *Directive 95/46/EC*, art. 8.2, a) and recital 33.

In other words the consent of the data subject does not exonerate the data controller from pursuing a legitimate purpose (inducing the balance between the interests in presence) and the consent of the data subject may not cover the illegitimate interest or the lack of interest of the data processing.

The Directive provides that Member States may oppose the possibility for the sole consent of the data subject to lift the prohibition from processing medical data[426].

In any case the data subject may always revoke his or her consent to the processing of his or her medical data. What are the consequences of this revocation? Does it mean that, in the future, new operations upon the data subject's medical data will not be any more possible (without any effect on the existing data processing) or do we have to considered that the operations realised upon the medical data on the ground of the initial consent of the data subject may not be pursued ?

Since the data subject has revoked his or her initial consent there is no more legitimate base for the processing of the medical data. The operations may not be pursued. That does not mean that the past operations realized upon the medical data of the data subject are now unlawful. It simply means that they can not be pursued except on the ground of another base of legitimacy.

Finally the Directive gives no formal indication on the nature of the consent given by the data subject or on the possible contractual relationship between the data controller and the data subject.

In our views the solution to these questions depends on how the applicable law deals with the relationship between the data controller and the data subject and with the relationship between the data subject and his or her personal data. In any case the possible contract should obey the special rules imposed through the transposition of the Directive in the applicable law such as the characteristics of the data subject's consent, the data quality, the data subject's rights, the security and confidentiality measures, the notification to the supervisory authority, etc.

The applicable law determines also the capacity to consent for underage or disable persons.

Regarding the previous developments, it is not sure that the consent of the data subject represents the best solution to ground the legitimacy of the processing of medical data in ACGT. Fortunately the Directive provides alternative solutions to legitimate the processing of medical data which this deliverable has done a quick review of (*cfr.*: 3.3.2.1.1).

The explicit and valid consent of the data subject constitutes the very first source of legitimacy for the processing of his or her medical data even if, at the same time, it is the weakest base to legitimate the processing of medical data due to the strict conditions for its validity and to the possibility for the data subject to revoke his or her consent at any time and without justification (but with reasonable notice in some case?).

Nevertheless even if the data controller may legitimate the processing of medical and even with the consent of the data subject, the legitimacy of the data processing must be really assessed in each case by the balance of the interests in presence. These include the interests of the data subject, of the data controller, of third concerned parties and of the society.

[426] Directive 95/46/EC, art. 8.2, a).

In any case the consent of the data subject does not cover the lack of legitimacy or the illegitimacy of the processing of his or her medical data. The consent of the data subject only creates the presumption of legitimacy of the processing of medical data until proof of the contrary.

Finally we must approve and recommend very strongly and warmly the ethical practice requiring the consent of the data subject when processing medical data, even the latter might rely on another base of legitimacy.

3.3.2.7.1 The informed consent of minors

Many patients involved in the research into cancer – and more specially nephroblastomia -, are minors. Considering this fact, we need to analyze the consent of the data subject who is a minor and, therefore, is represented by his/her legal representative in the exercise of his rights.

In a lot of countries in Europe, the age of majority is fixed at 18 years old. Before that age and in many countries, and more specially in Napoleonic law, the legal representative is empowered to represent the minor.

That means that the minor holds rights but is not allowed to exercise them directly (except with special and legal authorization). He always needs to be represented by his/her legal representative. The legal representation covers the administration of the person and the goods of the minor. Then, it's a general prohibition of exercise for the minor.[427]

However, the minor is – more and more often – associated in the decision concerning his/her health. Even, in some matters like medical law (therapeutic or sexual life), he can take decisions by himself/herself without being represented by his legal representative[428]. Those matters must be interpreted on a very restrictive way and, sometimes (medical treatment), the appreciation of the minor's capacity to act by himself/herself is in the hands of the medical doctor.

This matter is regulated by the different national laws which set the principles and exceptions about the exercise of his/her rights by the minor.

This concept of national regulation imposes on the physicians to check in their own national regulation the rules concerning the capacity of the minor.

However, we should have a look on the position of the minor in the ACGT project. As saying before, the minor can enjoy the use of his right but will exercise them through his legal representative who will take decisions which will have effects even after the minor gets the majority.

Then and in the context of data protection and more specially relating to the Directive 95/46/EC which doesn't deal with that issue, the minor is certainly the data subject from the beginning but his/her rights (acceptance, withdraw, etc…) will be exercised by his legal representative until he reaches the majority. After reaching this majority, he will be empowered to exercise his rights by himself amongst which there is the right of withdraw. Asking a new consent from the minor would be a real

[427] P. – Y. Leleu, Droit des personnes et des familles, Bruxelles, Larcier, 2005, pp. 217 and following.

[428] In the Belgian law concerning the patient rights (22.08.2002), the minor – under some conditions – can exercise all the rights set by the law including the right to privacy.

non sense relating to the concept of the legal representation and hardly feasible for the practitioner.

However, the association of the minor to the decision should be promoted through ACGT project to give him a sense of responsibility. From a legal point of view, it's feasible and won't infringe any regulation.

That position joins the World Medical Association which has set that:

"When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorised representative."[429]

3.3.2.7.2 Informed consents by relatives?

We have already had the occasion to deal with the question concerning the genetic research (*Cfr.* 3.3.2.1). Another important issue is the problem of the consent. Who has to consent in case of genetic research? As explained in detail above (Cfr. 3.3.2.1), *"the genetic information is unique and distinguishes an individual from other individuals, it may also at the same time reveal information about and have implications for that individual's blood relatives (biological family) including those in succeeding and preceding generations, Furthermore, genetic data can characterise a group of persons (e.g. ethnic communities); genetic data can reveal parentage and family links."*[430]

That means, the genetic data contains information about the patient but also of blood relatives. That is why not only the privacy of the patient him- or herself is affected, but also the privacy of his/her relatives. This might mean that the relatives of the patient concerned might also have to consent to the genetic research. In the context of data protection, we have to be aware about this particularity of the genetic data. In other words: Who is the data subject of the genetic data?

On the other hand this would make genetic research almost unfeasible, if the consent from each relative is requested to examine only one set of genetic data. So, a conflict between the interests of research and the privacy of the concerned relatives occurs, that has to be solved. We need to make a balance between those two concepts. It's also a question of proportionality.

Let's return to the Art. 2 lit (a) of the Data Protection Directive which defines the data subject as an identified or identifiable natural person to whom information relates to. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

Whenever additional information of these relatives (such as their name etc) is collected together with the genetic data of the patient, the consent of these relatives is also needed, as their genetic data is very similar to the data of the patient, so that conclusions about these relatives could also be drawn from the patient's data. The privacy of these relatives would be affected, so that an informed consent of the concerned relatives is needed.[431] But this provision must be interpreted restrictively. The consent should be only needed of first-grade relatives (such as the parents or

[429] WMA 2004, paragraph 25; see also D10.2, 2.2.2.2.3

[430] Group 29, *"Working document on genetic data"*, 17.03.2004, http://ec.europa.eu/justice_home/fsj/privacy/docs/wpdocs/2004/wp91_en.pdf.

[431] See Weichert, DuD 2002, p. 133 (138)

children), as only their data sets contain enough similarities to the data set of the patient that their privacy is affected.[432] In all other cases, consent of the relatives is not needed because of the marginal similarities and the missing threat for their privacy. The interests of genetic research must prevail in these cases, as otherwise the improvement of genetic research would be put at risk, if not prevented.

Regarding first-grade relatives Recital 26 states, that in order to determine whether a person is identifiable, account should be taken of all the means likely reasonably to be used either by the controller or by any other person to identify the said person. Nobody would likely reasonably use any means to determine the relative of a patient, if there are not enough similarities in the data sets to determine the relative and/or to draw any conclusions about them out of the available genetic data.

Therefore only the patient concerned has to be regarded as data subject of his or her genetic data, so that in general only the patient has to give his or her informed consent. If additional information about first-grade relatives, that allows the identification of this relative, is collected together with the genetic data of the patient, also the informed consent of the relative concerned is needed. Asking that consent, will necessarily oblige the physician to disclose the legal medical secrecy because he'll have to inform that concerned relative to get an informed consent.

To answer to the question to know if the physician is allowed or not, an analyze of the national regulations is needed. Actually, we have to know if the disclosure of the secrecy is possible by the only patient consent.

When a minor is concerned, the parents know the "secret" because they have to give their consent to the data processing. The question is more sensible when the data processing concerns a major age patient.

[432] See Weichert, DuD 2002, p. 133 (138)

4 ETHICAL AND LEGAL CONCLUSION

As shown above it is possible to create a framework that takes into consideration both the needs of modern scientific genetic research projects such as ACGT and the needs of the patients participating in those research projects regarding data protection and privacy. Only if these two conditions are met, such research projects can succeed.

In order to protect the individual rights of patients who donate blood and tumour samples or the data generated from these samples, ACGT has to take several ethical requirements into account.

First at all, donors have to be provided with adequate information to consent voluntarily and explicitly to data sampling, storage and usage (informed consent). The given information has to be comprehensive and understandable and should at least include the main intentions of ACGT and the range of possible uses of data, measures token to protect donors' personal rights, the possible risks and benefits, and further implications of participation.

Since clinico-genomic data are collected and used not only for specific research questions, but also for future research projects which cannot be defined at the time consent is requested, a model of consent referring to a purpose of intermediate scope (clinico-genomic research on cancer) in the context of a specific structure or project (ACGT) is proposed (tiered consent).

Not only the donors, but also the authorized users of the ACGT Grid structure have to be informed and give consent explicitly before getting access. They should declare that they will meet the requested standards of ACGT regarding the protection of data and privacy.

Regarding the disclosure of research results, ACGT has to make sure that general study findings are accessible for donors. Furthermore, donors have the legal right to access data stored about her or him on request. Therefore, the implementation of this right requires an organisational structure that is suitable to reply on donors' request.

It is furthermore recommended that ACGT provides the technical and organizational means for individual feedback processes of individually relevant results initiated by the investigator. The only way to enable investigator driven individual feedback processes – and to allow individual donors to withdraw consent – is the pseudonymization of data. However, the relevance of personal research results is – especially in new research areas such as gene expression studies – not easily to approach. Operators of ACGT should, therefore, carefully assess the relevance of the results they expect and inform donors' physician about their conclusions in regard to the quality of the findings. Donors who have initially consented to participate in feedback processes should than be contacted by the doctor and asked whether he/she wants to receive results which could be important for him/her.

To avoid that unauthorized persons access stored personal data, it is proposed that the donor and his/her physician of choice get access to individual genetic data only together before the donor's physician has proved to be entitled to trigger the individual feedback process. Furthermore, individual feedback processes should also be accompanied by counselling. Given the complexity of the ethical aspects regarding the disclosure and feedback, it is suggested establishing within the ACGT structure a multilingual, internet-

based information service for donors. The information service could be designed as an initial contact point for donors who look for more or specialized information. Especially when more clinics and trials become involved in ACGT, it is advisable to integrate such a service into the architecture of ACGT.

The needs for information will be high, because genetic data are very sensitive and vulnerable, as it contains very sensitive information about the data subject. One of the main ethical and legal challenges in ACGT is therefore the sensitivity and vulnerability of genetic data. Besides genetic data have some special characteristics: it is not possible to render genetic data completely anonymous. As it is unique it can only be rendered de-facto anonymous. This is the big difference to normal, conventional data. This is also the big challenge for the application of data protection regulation.

As described above it is possible to keep the data flow in major parts outside of the scope of the Data Protection Directive 95/46/EC, if certain conditions are fulfilled. Therefore it is important, that de-facto anonymous data has to be regarded as anonymous data within the meaning of the Data Protection Directive. Following that, the Data Protection Directive is applicable, whenever the particular Data Controller has the link from the genetic data to the concerned data subject or whenever he can get this link with legal means.

Furthermore the Directive is applicable, if a third party could establish this link. Therefore the genetic data has to be regarded as personal data in the case of transfer and disclosure, too, as the privacy of the concerned data subject is affected in this case as well. In case of all other data processing, for example use and storage, the Data Protection Directive is not applicable, provided that the data controller has no legal access to the link.

Following these legal considerations a Data Protection Architecture could be created, as described in part,3.3.2.5 to ensure the compliance of ACGT with data protection regulation. The main parts are a double pseudonymization procedure, encryption and the introduction of a central data controller within ACGT as well as the introduction of a Trusted Third Party and finally an informed consent of each patient for ethical reasons on the one hand and the unlikely case, that we will have personal data in some situations on the other hand. If this architecture is implemented in ACGT, participating researchers could do their research without having too big obstacles because of data protection reasons. They could concentrate on their scientific research, so that this architecture would ensure and improve the efficiency of ACGT.

As indicated, the implementation of the ACGT Data Protection Framework requires the set up of a central data controller within ACGT, the introduction of a Trusted Third Party and contracts between the participating hospitals and research-entities with ACGT Data Protection Board.[433] All these conditions still have to be examined very carefully to ensure compliance of ACGT with data protection regulation and avoid any liability. Especially for ethical and dissemination reasons compliance of ACGT with current data protection regulation is of vital importance. Therefore these conditions have to be examined very carefully in a second step.

A central data controller within ACGT has to be set up. Such data controller could for example be the ACGT Data Protection Board, in which experts from all relevant professions within ACGT are represented. That would guarantee the needed expertise to ensure the success of ACGT. This board could consist for example of legal, technical and medical

[433] Contracts between the participating patients and ACGT can be left out of sight at this point.

experts. In order to introduce such a Board, the Consortial Agreement of ACGT could be modified.

Furthermore one or several Trusted Third Parties would need to be chosen by ACGT to carry out the second step of pseudonymization and contracts would have to be signed with this TTP or these TTPs. This would then also be done by the ACGT Data Protection Board.

Besides contracts between the ACGT Data Protection Board and the hospitals and the participating research entities must be drafted and concluded to ensure compliance of these parties with data protection regulations.

The fulfilment of these conditions is a crucial factor for the compliance of ACGT with current data protection regulation, which is itself of vital importance for the success and acceptance of ACGT. These conditions will have to be examined very carefully in the future in a second step, so that the elaborated Data Protection Framework can be implemented in ACGT to ensure compliance with data protection law.

This deliverable contains therefore the basis to ensure this compliance and if the just described steps are taken in a second step, that means if these conditions are examined and then implemented in a second step, this architecture could be a major factor to guarantee ACGT's compliance with data protection regulation.

As shown above it is possible with this Data Protection Framework to ensure compliance of ACGT with current data protection regulation while efficient scientific research is guaranteed at the same time. Therefore the implementation of the elaborated Framework and the examination of the newly arisen conditions should be followed with high priority. By implementing this Framework the needs of the researchers, hospitals and patients can be satisfied at the same time, so that the ACGT Data Protection Framework can be one part to lead ACGT to success.

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Appendix 1– Legal Terminology

Admissibility of data processing

The collection, processing and use of personal data shall be admissible only

1. if permitted or prescribed by law or

2. if the data subject has consented.

This is the basic message of data protection law.

If ACGT processes personal data one of these two exceptions must be corresponding. Therefore it should be an aim for ACGT to process as little personal data as possible.

Anonymous data / Rendering anonymous

Rendering anonymous means the modification of personal data so that the information concerning personal or material circumstances can no longer or only with a disproportionate amount of time, expense and labour be attributed to an identified or identifiable individual. Personal data that was anonymized is no longer “personal data” in the legal sense. It will have to be an aim to have as much anonymized data within ACGT as possible and reasonable.

Automated decision

Every person has the right according to Art. 15 (1) Directive 95/46/EC not to be subject to a decision which produces legal effects concerning him or significantly affects him and which is based solely on automated processing of data intended to evaluate certain personal aspects relating to him, such as his performance at work, creditworthiness, reliability, conduct, etc (automated decision). Automated decisions are allowed, if that decision is taken in the course of the entering into or performance of a contract, provided the request for the entering into or the performance of the contract, lodged by the data subject, has been satisfied or that there are suitable measures to safeguard his legitimate interests, such as arrangements allowing him to put his point of view. Such automated decisions are also permitted, if they are authorized by a law which also lays down measures to safeguard the data subject's legitimate interests. Every data subject has then the right to know the logic involved in the automatic processing of data concerning him (Art. 12 (a) Directive 95/46/EC). For ACGT this means that all decisions that produce legal effects on a person should generally be made by an individual person and not by a computer or any other data processing system.

Coded (encrypted) data

Coded data is encrypted data. If it is personal data it can only be linked directly or indirectly to a natural person through a code. In ACGT the data will be coded. The data concerning a data subject shall be either encrypted by a code and/or via an alias.

Confidentiality

Persons employed in data processing shall not collect, process or use personal data without authorization (confidentiality). On taking up their duties such persons shall be required to

give an undertaking to maintain such confidentiality. This undertaking shall continue to be valid after termination of their activity. Any person acting under the authority of the controller or of the processor, including the processor himself, who has access to personal data must not process them except on instructions from the controller, unless he is required to do so by law.

Researcher in the context of ACGT are therefore only allowed to collect, process and use personal data of a patient in compliance with the patient's informed consent. They are not allowed to disclose any data, unless they are authorized by the particular patient.

Consent

The data subject's consent means any express indication of his wishes by which the data subject signifies his agreement to personal data relating to him being processed, on condition he has available information about the purposes of the processing, the data or categories of data concerned, the recipient of the personal data, and the name and address of the controller and of his representative if any.

The data subject's consent must be freely given and specific, and may be withdrawn by the data subject at any time. If the data subject is incapable of a free decision or domestic laws don't permit the data subject to act on his/her own behalf, consent is required of the person recognized as legally entitled to act in the interest of the data subject or of an authority or any person or body provided for by law. An informed consent of the particular patient is a vital requirement in order to collect and use the data needed for ACGT lawfully, though it is not the only possibility. The processing of personal data can be permitted expressively by law also. If the data subject is a minor, the informed consent of the legally entitled persons (cfr. Legal representative), normally the minor's parents, is needed.

Data controller

The controller is, according to the Data Protection Directive 95/46 EC, the natural or legal person who alone, or jointly with others, determines the purposes and means of the processing of personal data. The controller is the one liable for the legality of the processing and the fulfillment of the obligations towards the national data protection authority and the data subjects.

Data processor

Data processor shall mean a natural or legal person, public authority, agency or any other body which processes personal data on behalf of the controller who is liable for the legality of the processing and the fulfillment of the obligations towards the national data protection authority and the data subjects.

Data reduction / Data economy (Minimality)

Personal data must not be excessive in relation to the purposes for which they are collected and/or further processed. It is therefore not allowed to process any data unless the data is necessary to achieve the purpose mentioned for which the data are collected and further processed. In case the processing of data is needed, only as little personal data as possible should be processed. The processed personal data has to be erased or anonymized once they are no longer required for the purposes for which they have been kept.

For ACGT this means that it is only allowed to process (collect, use etc.) this kind of personal data of a patient that is needed for this project.

Data Subject

The data subject is the subject of personal data, i.e. an identified or identifiable person whom the personal data refers to. An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity.

Regularly the patient, whose genomic data is collected and used for the ACGT-studies, will be the data subject.

Disclosing

The disclosure of personal data to third parties or recipients is a processing operation and, as such, is subject to the legal requirements of processing. The rule for the technical and organizational requirements is the confidentiality of the personal data. Therefore, the controller must ensure the confidentiality of personal data, meaning that unauthorized access to, or disclosure of, the personal data, must be prevented.

If there is a disclosure to a third party or a recipient, the controller should check whether or not this transfer or disclosure falls within the scope of the initial purpose or is still compatible with this purpose, in order to determine whether or not they can transfer or disclose the data. Anonymous data can be transferred without being subject to specific requirements.

It's, also, used to fix some delay for the execution of obligation. For example, the controller (or his representative) must provide the required information to the data subject, if disclosure to a third party is anticipated, no later than the time when the data are first disclosed, except when the data subject has already been provided with the information.

A disclosure can also take place by transmission to third parties (see Art. 2 lit. b of the Data Protection Directive).

Hospital

Hospitals are health institutions where patients are treated and their personal data are collected for the purpose of the ACGT project.

Legal representative

The legal representative(s) is/are the person(s) who has/have the power by law or legal decision to decide for a minor patient (or equivalent status).

Modification

The modification of personal data is considered by the Data Protection Directive 95/46 EC as part of the processing and concerns different things as the rectification, erasure and blocking.

The data subject has the right to obtain from the controller the rectification, erasure or blocking the data processing because of the incomplete, inaccurate nature or illegal processing of the data.

Necessary processing

When deciding which data will be collected and further processed, the controller must limit these data to the extent strictly necessary to achieve the purpose of processing. This means that personal data will only be processed when it is necessary for the project.

Obtaining/Collecting

Collecting or obtaining the data is considered by the Data Protection Directive 95/46 EC as part of the processing.

We use the term of:

• primary collection when the collection of personal data is directly obtained from the data subject, i.e. either directly provided by the data subject or obtained through observation of the data subject.

• secondary collection when the collection of personal data is obtained from sources other than the data subject himself.

ACGT will deal with both primary and secondary collections because a collection will often be re-used for another purpose than the first one.

Organizational measures

Organizational measures must ensure combined with technical measures an appropriate level of security of the data processing, taking into account the state of the art and the costs of their implementation in relation to the risks inherent in the processing and the nature of the data to be protected. Appropriate organizational measures shall be taken by the controller against accidental loss, destruction or alteration of, or damage to, personal data and against unauthorized or unlawful processing of personal data in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing. The controller must, where processing is carried out on his behalf, choose a processor providing sufficient guarantees in respect of the technical security measures and organizational measures governing the processing to be carried out, and must ensure compliance with those measures.

Such appropriate organizational measures to ensure the confidentiality, integrity and accuracy of processed data should be for example:

- control of the entrance to installations
- access control
- authorization control
- transmission control
- input control
- job control
- availability control

Such organizational measures have to be taken by all the ACGT-participants processing personal data.

Patient

Patient means the concerned sick person and will be considered as the data subject in this general terms.

Personal data

Personal data means any information relating to an identified or identifiable natural person ('data subject'). An identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity. Therefore a set of date collected under a certain number or sign “patient xxx”, “tissue YYY” can be personal data.

Physician

The physician is the natural person who is in charge of the patient’s treatment.

Processing/Automated Processing

The concept of processing is very broad. It concerns any operation or set of operations that are performed upon personal data, whether or not by automatic means. Data processing is considered to be the collection, recording, organisation, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available (e.g. by allowing the inspection of data retrieval by a third party), alignment or combination, blocking, erasure or destruction of personal data.

The application of data protection legislation is limited to automated processing and to non-automated processing. Both types of processing operations form part of a filing system or are intended to form part of a filing system, i.e. any structured set of personal data which are accessible according to specific criteria, whether centralised, decentralised or dispersed on a functional or geographical basis.

The processing operations covered by data protection legislation are therefore not limited to electronic files or databases, but also include the processing of data in a manual paper file as soon as this is structured according to certain criteria.

The concept of processing also includes the operations performed by Internet software and hardware without the knowledge of the data subject, and hence invisible to them, such as the use of cookies. The exchange of information related to the use of browser software is also to be considered as processing.

Pseudonymizing

Pseudonymizing means replacing a person's name and other identifying characteristics with a label, in order to preclude identification of the data subject or to render such identification substantially difficult. Pseudonymized data still is “personal data” in the legal sense.

Public Register

A public register is a register which according to laws or regulations is intended to provide information to the public and which is open to consultation either by the public in general or by any person who can demonstrate legitimate interest, to the extent that the conditions laid down in law for consultation are fulfilled in the particular case.

Publish

The controller should refrain from publishing personal data or otherwise making them public. In most cases this will not be necessary to achieve the purpose of the research, or it may create an attempt to the data subject's interests that appears to be disproportionate to the interest of the controller.

The notion of making public is also a criteria to allow the processing. It's the case when the data subject has manifestly made public his personal date concerning, for example, his health, the processing is allowed (article 8.2.e of the Directive 95/46/EC).

Purpose

The purposes for processing of personal data must be adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed.

The purposes must be specified, explicit and legitimate. Personal data must be not further processed in a way incompatible with those purposes. The purpose for the data processing within ACGT is explained in detail in D10.1.

Recipient

The recipient is a natural or legal person, public authority, agency or any other body to whom data are disclosed, whether a third party or not. Authorities that may receive data during a particular inquiry shall not be regarded as recipients (article 2 of the Directive 95/46/EC)

Recording

Recording is a process and a criteria to determine the scope of the Directive 95/46/EC.

The Directive uses it to fix some delay for the execution of obligations. For example, the controller (or their representative) must provide the required information to the data subject at the latest at the time of recording, except when the data subject has already been provided with the information (article 11).

Sensitive (personal data)/Special categories of data

Sensitive personal data is personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and data concerning health (genetic data) or sex life. Member States shall prohibit the processing of these data, except in explicitly stated exceptions.

Statistical processing

Statistical processing is any operation of collection and processing of personal data necessary for statistical surveys or for the production of statistical results.

These statistical results may further be used for different purposes, including a scientific purpose. The statistical purpose cannot lead to the possibility of taking individual decisions.

Storage

Storage of personal data is allowed by the Data Protection Directive 95/46 EC. But when the purpose of processing is achieved, and the data are not required any more for that particular purpose, these personal data must be rendered anonymous or be destroyed.

Most national laws allow personal data to be stored for a longer term, provided that this is in order to use the data exclusively to carry out scientific research or statistics. Nevertheless, some national laws impose supplementary conditions or formalities in order to allow longer storage.

Third Party

The third party is a natural or legal person, public authority, agency or any other body other than the data subject, the controller, the processor and the persons who, under the direct authority of the controller or the processor, are authorized to process the data.

Regarding ACGT third parties will be all the other bodies outside of ACGT, such as researchers and hospitals, which do not take part in ACGT or authorities.

Transfer (also to Third Countries)

The purpose of the Data Protection Directive 95/46 EC is to allow the free flow of personal data between Member States. The other objective of the Directive is to protect the fundamental rights and freedoms of natural persons, and in particular their right to privacy with respect to the processing of personal data.

The Directive defines specific conditions and restrictions guaranteeing the protection of data subjects, but the Member States are not allowed to restrict or prohibit these flows to a greater extent than permitted in the framework of the Directive. A specific regime regarding the transfer of personal data to non-EEA countries has been put in place to protect the data subjects whose data are exported outside the territorial scope of the application of the Directive.

Before transferring data to a third country, the controller must check if the third country allows an adequate level of protection.

If it's not so, the transfer can't take place except some exceptions mentioned in the article 25 of the Directive 95/46 EC:

(a) the data subject has given his consent unambiguously to the proposed transfer; or

(b) the transfer is necessary for the performance of a contract between the data subject and the controller or the implementation of precontractual measures taken in response to the data subject's request; or

(c) the transfer is necessary for the conclusion or performance of a contract concluded in the interest of the data subject between the controller and a third party; or

(d) the transfer is necessary or legally required on important public interest grounds, or for the establishment, exercise or defence of legal claims; or

etc…

Trusted Third Party

The Trusted Third Party is a security authority that performs the security related functions and cryptography methods. Institutions, public authorities or companies which offer trust services can be Trusted Third Parties. Within ACGT the Trusted Third Party will implement appropriate technical and organizational measures to protect personal data against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular if the processing involves the transmission of data via network, and against all other unlawful forms of processing. Having regard to the state of the art and the cost of their implementation, such measures shall ensure a level of security appropriate to the risks represented by the processing and the nature of the sensitive data to be protected.

Using

The use of personal data is considering by the Directive 95/46 EC as part of the processing and is a criteria used to define the processing and the scope.

Appendix 2 – European Regulation

CHARTER OF FUNDAMENTAL RIGHTS OF THE EUROPEAN UNION

The Charter of Fundamental Rights of the European Union was solemnly proclaimed by the European Council in 2000 and was also approved by the European Commission and the European Parliament. It is part of the proposed European Constitution that failed to be ratified. Therefore the Charter contains non-binding law. But nevertheless it is an important guideline of interpretation. The most important provisions concerning ACGT are:

Article 3: Right to the integrity of the person

Article 3, which refers to the right to the integrity of the person, states that:

1. Everyone has the right to respect for his or her physical and mental integrity.

2. In the fields of medicine and biology, the following must be respected in particular:

the free and informed consent of the person concerned, according to the procedures laid down by law,

the prohibition of eugenic practices, in particular those aiming at the selection of persons,

the prohibition on making the human body and its parts as such a source of financial gain,

the prohibition of the reproductive cloning of human beings.

Article 7: Respect for private and family life

The Charter of Fundamental Rights of the European Union protects the right to respect for private life. It echoes in some extent the right to self-determination and to the right to informational self-determination. This legal tool states precisely that:

Everyone has the right to respect for his or her private and family life, home and communications.

Article 8: Protection of personal data

Also in Article 8, related to the protection of personal data, it is stated that:

1. Everyone has the right to the protection of personal data concerning him or her.

2. Such data must be processed fairly for specified purposes and on the basis of the consent of the person concerned or some other legitimate basis laid down by law. Everyone has the right of access to data which has been collected concerning him or her, and the right to have it rectified.

3. Compliance with these rules shall be subject to control by an independent authority.

DIRECTIVE 95/46/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL OF 24 OCTOBER 1995

The Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data created a legal framework common to all the Member States relative to the processing of personal data. This Directive had to be transposed into national law by the Member States.

In a first step, the Directive lays down the rules applicable to every processing of personal data. In a second step, the Directive provides some additional rules for the processing of sensitive data (as medical data). In a third step, the Directive provides special rights of the data subject and control mechanisms. In a fourth and last step, the Directive rules the transfer of personal data to third countries.

The Directive provides the general rules on the lawfulness of the processing of personal data. This covers:

- the principles relating to data quality (art. 6),
- the criteria for making data processing legitimate (art. 7),
- the special categories of processing (art. 8-9),
- the information to be given to the data subject (art. 10-11),
- the data subject's right of access to data (art. 12) (cf. art. 13 for exemptions and restrictions),
- the data subject's right to object (art. 14-15),
- the confidentiality and the security of processing (art. 16-17),
- the notification to the supervisory authority (art. 18-21),

Then the Directive covers the issues of judicial remedies, liability and sanctions (art. 22-24).

Transfer of personal data to third countries is subject to special rules (art. 25-26).

The Directive also encourages the drafting of Codes of conducts (art. 27).

Finally the Directive creates supervisory authorities and the working party on the protection of individuals with regard to the processing of personal data (art. 28-30).

Some rules concern more directly the ACGT Project and need to be stressed:

With special reference to medical research it is clearly stated that the prohibition of processing of sensitive personal data of Article 8(1) may be lifted for reasons of substantial public interest, by national law or decision of the supervisory authority if Member States provide suitable safeguards (Article 8(4));

Also for medical research the prohibition of processing of sensitive personal data may be lifted, if this medical research could be considered in some special cases to be a subcategory of preventive medicine, medical diagnosis, the provision of care or treatment, or management of health-care services, provided that the processing of sensitive personal data involved is carried out by a health professional or another person subject to an equivalent "obligation of secrecy" per national law or rules established by national competent bodies (Article 8(3)).

Another specific tool for medical research is set by the Codes of conduct: Article 27(1) requires Member States and the Commission to encourage the drawing up of codes of conduct to assist with the implementation of the Directive in specific sectors of processing, representing categories of data controllers and to consult with data subjects or their representatives (Article 27(2)). Article 27(3) provides a role for the Article 29 Working Party in approving draft Community Codes and amendments to existing Community codes.

Member States have to determine the processing operations likely to present specific risks to the rights and freedoms of data subjects and shall check that these processing operations are examined prior to the start thereof (art. 20.1).

Such prior checks have to be carried out by the supervisory authority following receipt of a notification from the controller or by the data protection official, who, in cases of doubt, must consult the supervisory authority (art. 20.2).

Member States may also carry out such checks in the context of preparation either of a measure of the national parliament or of a measure based on such a legislative measure, which define the nature of the processing and lay down appropriate safeguards (art. 20.3).

For the purposes of this Directive:

(a) 'personal data' shall mean any information relating to an identified or identifiable natural person ('data subject'); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity;

(b) 'processing of personal data' ('processing') shall mean any operation or set of operations which is performed upon personal data, whether or not by automatic means, such as collection, recording, organization, storage, adaptation or alteration, retrieval, consultation, use, disclosure by transmission, dissemination or otherwise making available, alignment or combination, blocking, erasure or destruction;

It is very stated very clearly in the directive (Section 1, Article 6) that

personal data must be:

1. processed fairly (in compliance with the announced purposes of the data processing) and lawfully (this latter referring in ACGT notably to the respect of the medical secrecy);

2. collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes (this refers to the proportionality test). Further processing of data for historical, statistical or scientific purposes shall not be considered as incompatible provided that Member States provide appropriate safeguards;

3. adequate, relevant and not excessive in relation to the purposes for which they are collected and/or further processed (this refers also to the proportionality test);

4. kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the data were collected or for which they are further processed (right to oblivion). Member States shall lay down appropriate safeguards for personal data stored for longer periods for historical, statistical or scientific use.

Personal data may only be processed under the conditions described in article 7 for the processing of "simple" personal data. The unambiguously consent of the data subject is the first condition allowing the processing of "simple" personal data.

The processing of personal data revealing racial or ethnic origin, political opinions, religious or philosophical beliefs, trade-union membership, and the processing of data concerning health or sex life, is banned (article 8). This prohibition may be lifted under the conditions described in article 8.2. The explicit consent of the data subject is the first condition allowing the processing of medical data (art. 8.2.a). But Member State may provide that this prohibition may not be lifted by the data subject's consent.

Processing of medical data can be legalised by the Member States, if the data is required for the purposes of preventive medicine, medical diagnosis, the provision of care or treatment or the management of health-care services, and where those data are processed by a health professional subject under national law or rules established by national competent bodies to the obligation of professional secrecy or by another person also subject to an equivalent obligation of secrecy.

The Directive makes additional significant provisions, especially about the data subject's right of information and its right of access to the data, as described below:

Section 4, Article 10: Information in cases of collection of data from the data subject

Member States shall provide that the controller or his representative must provide a data subject from whom data related to him/her are collected with at least the following information, except where he already has it:

(a) the identity of the controller and of his representative, if any;

(b) the purposes of the processing for which the data are intended;

(c) any further information such as - the recipients or categories of recipients of the data, - whether replies to the questions are obligatory or voluntary, as well as the possible consequences of failure to reply, - the existence of the right of access to and the right to rectify the data concerning him o in so far as such further information is necessary, having regard to the specific circumstances in which the data are collected, to guarantee fair processing in respect of the data subject.

Section 4, Article 11: Information where the data have not been obtained from the data subject

The Directive makes the following provisions where the data have not been obtained from the data subject,

1. Member States shall provide that the controller or his representative must at the time of undertaking the recording of personal data or if a disclosure to a third party is envisaged, no later than the time when the data are first disclosed provide the data subject with at least the following information, except where he already has it:

(a) the identity of the controller and of his representative, if any;

(b) the purposes of the processing;

(c) any further information such as - the categories of data concerned, - the recipients or categories of recipients, - the existence of the right of access to and the right to rectify the data concerning him in so far as such further information is necessary, having regard to the specific circumstances in which the data are processed, to guarantee fair processing in respect of the data subject.

2. Paragraph 1 shall not apply where, in particular for processing for statistical purposes or for the purposes of historical or scientific research, the provision of such information proves impossible or would involve a disproportionate effort or if recording or disclosure is expressly laid down by law. In these cases Member States shall provide appropriate safeguards.

Section 5, Article 12

Member States shall guarantee every data subject the right to obtain from the controller without constraint at reasonable intervals and without excessive delay or expense:

(a) confirmation as to whether or not data relating to him are being processed and information at least as to the purposes of the processing, the categories of data concerned, and the recipients or categories of recipients to whom the data are disclosed,

(b) communication to him in an intelligible form of the data undergoing processing and of any available information as to their source,

(c) knowledge of the logic involved in any automatic processing of data concerning him at least in the case of the automated decisions referred to in Article 15 (1);

The confidentiality and the security of the data processing must be guaranteed. There are special rules when the processing is carried out by a processor on behalf of the data controller.

Chapter 4, Article 25: Transfer of personal data to third countries.

The Member States shall provide that the transfer to a third country of personal data which are undergoing processing or are intended for processing after transfer may take place only if, without prejudice to compliance with the national provisions adopted pursuant to the other provisions of this Directive, the third country in question ensures an adequate level of protection.

The adequacy of the level of protection afforded by a third country shall be assessed in the light of all the circumstances surrounding a data transfer operation or set of data transfer operations; particular consideration shall be given to the nature of the data, the purpose and duration of the proposed processing operation or operations, the country of origin and country of final destination, the rules of law, both general and sectoral, in force in the third

country in question and the professional rules and security measures which are complied with in that country.

The Member States and the Commission shall inform each other of cases where they consider that a third country does not ensure an adequate level of protection within the meaning of paragraph 2.

Where the Commission finds, under the procedure provided for in Article 31 (2), that a third country does not ensure an adequate level of protection within the meaning of paragraph 2 of this Article, Member States shall take the measures necessary to prevent any transfer of data of the same type to the third country in question.

Article 26: Derogations

1. By way of derogation from Article 25 and save where otherwise provided by domestic law governing particular cases, Member States shall provide that a transfer or a set of transfers of personal data to a third country which does not ensure an adequate level of protection within the meaning of Article 25 (2) may take place on condition that:

a. the data subject has given his consent unambiguously to the proposed transfer; or

b. the transfer is necessary for the performance of a contract between the data subject and the controller or the implementation of pre-contractual measures taken in response to the data subject's request; or

c. the transfer is necessary for the conclusion or performance of a contract concluded in the interest of the data subject between the controller and a third party; or

2. Without prejudice to paragraph 1, a Member State may authorize a transfer or a set of transfers of personal data to a third country which does not ensure an adequate level of protection within the meaning of Article 25 (2), where the controller adduces adequate safeguards with respect to the protection of the privacy and fundamental rights and freedoms of individuals and as regards the exercise of the corresponding rights; such safeguards may in particular result from appropriate contractual clauses.

3. The Member State shall inform the Commission and the other Member States of the authorizations it grants pursuant to paragraph 2.

DIRECTIVE 2001/20/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 4 April 2001

Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use.

This Directive establishes specific provisions regarding the conduct of clinical trials, including multi-centre trials, on human subjects involving medicinal products and is the most important European directive with respect to clinical trials.

The directive provides useful definitions and provisions for clinical trials involving minors:

Article 2: Definitions

(a) 'informed consent': decision, which must be written, dated and signed, to take part in a clinical trial, taken freely after being duly informed of its nature, significance, implications and risks and appropriately documented, by any person capable of giving consent or, where the person is not capable of giving consent, by his or her legal representative; if the person concerned is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

Article 4: Clinical trials on minors

In addition to any other relevant restriction, a clinical trial on minors may be undertaken only if:

(a) the informed consent of the parents or legal representative has been obtained; consent must represent the minor's presumed will and may be revoked at any time, without detriment to the minor;

(b) the minor has received information according to its capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits;

(c) the explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principal investigator;

(d) no incentives or financial inducements are given except compensation;

(e) some direct benefit for the group of patients is obtained from the clinical trial and only where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods; additionally, such research should either relate directly to a clinical condition from which the minor concerned suffers or be of such a nature that it can only be carried out on minors;

(f) the corresponding scientific guidelines of the Agency have been followed;

(g) clinical trials have been designed to minimise pain, discomfort, fear and any other foreseeable risk in relation to the disease and developmental stage; both the risk threshold and the degree of distress have to be specially defined and constantly monitored;

(h) the Ethics Committee, with paediatric expertise or after taking advice in clinical, ethical and psychosocial problems in the field of paediatrics, has endorsed the protocol; and

(i) the interests of the patient always prevail over those of science and society.

Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products (Text with EEA relevance)

laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products

(Text with EEA relevance)

THE COMMISSION OF THE EUROPEAN COMMUNITIES,

Having regard to the Treaty establishing the European Community,

Having regard to Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use [1], and in particular Article 1(3), Article 13(1) and Article 15(5) thereof,

Whereas:

(1) Directive 2001/20/EC requires the adoption of principles of good clinical practice and detailed guidelines in line with those principles, minimum requirements for authorisation of the manufacture or importation of investigational medicinal products, and detailed guidelines on the documentation relating to clinical trials to verify their compliance with Directive 2001/20/EC.

(2) The principles and guidelines for good clinical practice should be such as to ensure that the conduct of clinical trials on investigational medicinal products, as defined in Article 2(d) of Directive 2001/20/EC, is founded in the protection of human rights and the dignity of the human being.

(3) Manufacturing requirements to be applied to investigational medicinal products are provided for by Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use [2]. Title IV of Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [3] contains the provisions applied for the authorisation for the manufacture of medicinal products as part of the requirements needed for the application for a marketing authorisation. Article 3(3) of that Directive establishes that these requirements are not applicable for medicinal products intended for research and development trials. It is therefore necessary to lay down minimal requirements regarding applications for and management of authorisations to manufacture or import investigational medicinal products, as well as for the granting and the content of the authorisations, in order to guarantee the quality of the investigational medicinal product used in the clinical trial.

(4) With regard to the protection of trial subjects and to ensure that unnecessary clinical trials will not be conducted, it is important to define principles and detailed guidelines of good clinical practice whilst allowing the results of the trials to be documented for use in a later phase.

(5) To ensure that all experts and individuals involved in the design, initiation, conduct and recording of clinical trials apply the same standards of good clinical practice, principles and detailed guidelines of good clinical practice have to be defined.

(6) Provisions for the functioning of the Ethics Committees should be established in each Member State on the basis of common detailed guidelines, in order to ensure the protection

of the trial subject while at the same time allowing a harmonised application in the different Member States of the procedures to be used by Ethics Committees.

(7) To secure the compliance of clinical trials with the provisions on good clinical practice, it is necessary that inspectors ensure the practical effectiveness of such provisions. It is essential therefore to provide detailed guidelines on the minimum standards for the qualification of inspectors, in particular as regards their education and training. For the same reason, detailed guidelines on inspection procedures, in particular on the cooperation of the various agencies, and the follow-up to the inspections, should be laid down.

(8) The International Conference on Harmonisation (ICH) reached a consensus in 1995 to provide a harmonised approach for Good Clinical Practice. The consensus paper should be taken into account as agreed upon by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, hereinafter "the Agency", and published by the Agency.

(9) It is necessary that sponsors, investigators and other participants take into account the scientific guidelines relating to the quality, safety and efficacy of medicinal products for human use, as agreed upon by the CHMP and published by the Agency, as well as the other pharmaceutical Community guidelines published by the Commission in the different volumes of The rules governing medicinal products in the European Community.

(10) In conducting clinical trials on investigational medicinal products for human use, the safety and the protection of the rights of trial subjects should be ensured. The detailed rules adopted by Member States pursuant to Article 3(1) of Directive 2001/20/EC, to protect from abuse individuals who are incapable of giving their informed consent should also cover individuals temporarily incapable of giving their informed consent, as in emergency situations.

(11) Non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry may be of great benefit to the patients concerned. Directive 2001/20/EC recognises the specificity of these non-commercial clinical trials. In particular, when trials are conducted with authorised medicinal products and on patients with the same characteristics as those covered by the authorised indication, requirements already fulfilled by these authorised medicinal products, as far as manufacturing or importation are concerned, should be taken into consideration. However, it could also be necessary, due to the specific conditions under which non-commercial trials are conducted, that Member States foresee specific modalities to be applied to these trials not only when conducted with authorised medicinal products and on patients with the same characteristics, in order to comply with the principles imposed by this Directive, in particular as far as the manufacturing or import requirements for authorisation and the documentation to be submitted and archived for the trial master file are concerned. The conditions under which the non-commercial research is conducted by public researchers and the places where this research takes place, make the application of certain of the details of good clinical practice unnecessary or guaranteed by other means. Member States will ensure in these cases, when providing for specific modalities, that the objectives of the protection of the rights of patients who participate in the trial, as well as, in general, the correct application of the good clinical practice principles, are achieved. The Commission will prepare a draft with guidance in this respect.

(12) The measures provided for in this Directive are in accordance with the opinion of the Standing Committee on Medicinal Products for Human Use,

HAS ADOPTED THIS DIRECTIVE:

CHAPTER 1

SUBJECT-MATTER

Article 1

1. This Directive lays down the following provisions to be applied to investigational medicinal products for human use:

(a) the principles of good clinical practice and detailed guidelines in line with those principles, as referred to in Article 1(3) of Directive 2001/20/EC, for the design, conduct and reporting of clinical trials on human subjects involving such products;

(b) the requirements for authorisation of the manufacture or importation of such products, as provided for in Article 13(1) of Directive 2001/20/EC;

(c) the detailed guidelines, provided for in Article 15(5) of Directive 2001/20/EC, on the documentation relating to clinical trials, archiving, qualifications of inspectors and inspection procedures.

2. When applying the principles, detailed guidelines and requirements referred to in paragraph 1, Member States shall take into account the technical implementing modalities provided for in the detailed guidance published by the Commission in The Rules governing medicinal products in the European Union.

3. When applying the principles, detailed guidelines and requirements referred to in paragraph 1 to non-commercial clinical trials conducted by researchers without the participation of the pharmaceutical industry, Member States may introduce specific modalities in order to take into account the specificity of these trials as far as Chapters 3 and 4 are concerned.

4. Member States may take into account the special position of trials whose planning does not require particular manufacturing or packaging processes, carried out with medicinal products with marketing authorisations within the meaning of Directive 2001/83/EC, manufactured or imported in accordance with the same Directive and conducted on patients with the same characteristics as those covered by the indication specified in the marketing authorisation.

Labelling of investigational medicinal products intended for trials of that nature may be subject to simplified provisions laid down in the good manufacturing practice guidelines on investigational medicinal products.

Member States shall inform the Commission as well as the other Member States of any specific modalities implemented in accordance with this paragraph. These modalities will be published by the Commission.

CHAPTER 2

GOOD CLINICAL PRACTICE FOR THE DESIGN, CONDUCT, RECORDING AND REPORTING OF CLINICAL TRIALS

SECTION 1

GOOD CLINICAL PRACTICE

Article 2

1. The rights, safety and well being of the trial subjects shall prevail over the interests of science and society.

2. Each individual involved in conducting a trial shall be qualified by education, training, and experience to perform his tasks.

3. Clinical trials shall be scientifically sound and guided by ethical principles in all their aspects.

4. The necessary procedures to secure the quality of every aspect of the trials shall be complied with.

Article 3

The available non-clinical and clinical information on an investigational medicinal product shall be adequate to support the proposed clinical trial.

Clinical trials shall be conducted in accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects, adopted by the General Assembly of the World Medical Association (1996).

Article 4

The protocol referred to in point (h) of Article 2 of Directive 2001/20/EC shall provide for the definition of inclusion and exclusion of subjects participating in a clinical trial, monitoring and publication policy.

The investigator and sponsor shall consider all relevant guidance with respect to commencing and conducting a clinical trial.

Article 5

All clinical trial information shall be recorded, handled, and stored in such a way that it can be accurately reported, interpreted and verified, while the confidentiality of records of the trial subjects remains protected.

SECTION 2

THE ETHICS COMMITTEE

Article 6

1. Each Ethics Committee established under Article 6(1) of Directive 2001/20/EC shall adopt the relevant rules of procedure necessary to implement the requirements set out in that Directive and, in particular, in Articles 6 and 7 thereof.

2. The Ethics Committees shall, in every case, retain the essential documents relating to a clinical trial, as referred to in Article 15(5) of Directive 2001/20/EC, for at least three years after completion of that trial. They shall retain the documents for a longer period, where so required under other applicable requirements.

3. Communication of information between the Ethics Committees and the competent authorities of the Member States shall be ensured through appropriate and efficient systems.

SECTION 3

THE SPONSORS

Article 7

1. A sponsor may delegate any or all of his trial-related functions to an individual, a company, an institution or an organisation.

However, in such cases, the sponsor shall remain responsible for ensuring that the conduct of the trials and the final data generated by those trials comply with Directive 2001/20/EC as well as this Directive.

2. The investigator and the sponsor may be the same person.

SECTION 4

INVESTIGATOR'S BROCHURE

Article 8

1. The information in the investigator's brochure, referred to in Article 2(g) of Directive 2001/20/EC, shall be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician or potential investigator to understand it and make an unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial.

The first subparagraph shall apply also to any update of the investigator's brochure.

2. If the investigational medicinal product has a marketing authorisation, the Summary of Product Characteristics may be used instead of the investigator's brochure.

3. The investigator's brochure shall be validated and updated by the sponsor at least once a year.

CHAPTER 3

MANUFACTURING OR IMPORT AUTHORISATION

Article 9

1. Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall be required for both total and partial manufacture of investigational medicinal products, and for the various processes of dividing up, packaging or presentation. Such authorisation shall be required even if the products manufactured are intended for export.

Authorisation shall also be required for imports from third countries into a Member State.

2. Authorisation, as provided for in Article 13(1) of Directive 2001/20/EC, shall not be required for reconstitution prior to use or packaging, where those processes are carried out in hospitals, health centres or clinics, by pharmacists or other persons legally authorised in the Member States to carry out such processes and if the investigational medicinal products are intended to be used exclusively in those institutions.

Article 10

1. In order to obtain the authorisation the applicant must meet at least the following requirements:

(a) specify in his application the types of medicinal products and pharmaceutical forms to be manufactured or imported;

(b) specify in his application the relevant manufacture or import operations;

(c) specify in his application, where relevant as in the case of viral or non-conventional agents' inactivation, the manufacturing process;

(d) specify in his application the place where the products are to be manufactured or have at his disposal, for their manufacture or importation, suitable and sufficient premises, technical equipment and control facilities complying with the requirements of Directive 2003/94/EC as regards the manufacture, control and storage of the products;

(e) have permanently and continuously at his disposal the services of at least one qualified person as referred to in Article 13(2) of Directive 2001/20/EC.

For the purposes of point (a) of the first subparagraph, "types of medicinal products" include blood products, immunological products, cell therapy products, gene therapy products, biotechnology products, human or animal extracted products, herbal products, homeopathic products, radiopharmaceutical products and products containing chemical active ingredients.

2. The applicant shall provide with his application documentary evidence that he complies with paragraph 1.

Article 11

1. The competent authority shall issue the authorisation only after verifying the accuracy of the particulars provided by the applicant pursuant to Article 10 by the means of an inquiry carried out by its agents.

2. Member States shall take all appropriate measures to ensure that the procedure for granting an authorisation is completed within 90 days of the day on which the competent authority receives a valid application.

3. The competent authority of the Member State may require from the applicant further information concerning the particulars supplied pursuant to Article 10(1), including in particular information concerning the qualified person at the disposal of the applicant in accordance with point (e) of Article 10(1).

Where the competent authority concerned exercises that right, the application of the time-limits laid down in paragraph 2 shall be suspended until the additional data required have been supplied.

Article 12

1. In order to ensure that the requirements laid down in Article 10 are complied with, authorisation may be made conditional on the carrying out of certain obligations imposed either when authorisation is granted or at a later date.

2. An authorisation shall apply only to the premises specified in the application and to the types of medicinal products and pharmaceutical forms specified in that application pursuant to point (a) of Article 10(1).

Article 13

The holder of the authorisation shall at least comply with the following requirements:

(a) to have at his disposal the services of staff that comply with the legal requirements existing in the Member State concerned both as regards manufacture and controls;

(b) to dispose of the investigational/authorised medicinal products only in accordance with the legislation of the Member State concerned;

(c) to give prior notice to the competent authority of any changes he may wish to make to any of the particulars supplied pursuant Article 10(1) and, in particular, to inform the competent authority immediately if the qualified person referred to in Article 13(2) of Directive 2001/20/EC is replaced unexpectedly;

(d) to allow agents of the competent authority of the Member State concerned access to his premises at any time;

(e) to enable the qualified person referred to in Article 13(2) of Directive 2001/20/EC to carry out his duties, for example by placing at his disposal all the necessary facilities;

(f) to comply with the principles and guidelines for good manufacturing practice for medicinal products as laid down by Community law.

Detailed guidelines in line with the principles referred to in point (f) of the first paragraph will be published by the Commission and revised where necessary to take account of technical and scientific progress.

Article 14

If the holder of the authorisation requests a change in any of the particulars referred to in points (a) to (e) of Article 10(1), the time taken for the procedure relating to the request shall not exceed 30 days. In exceptional cases, this period of time may be extended to 90 days.

Article 15

The competent authority shall suspend or revoke the authorisation, as a whole or in part, if the holder of the authorisation fails at any time to comply with the relevant requirements.

CHAPTER 4

THE TRIAL MASTER FILE AND ARCHIVING

Article 16

The documentation referred to Article 15(5) of Directive 2001/20/EC as the trial master file shall consist of essential documents, which enable both the conduct of a clinical trial and the quality of the data produced to be evaluated. Those documents shall show whether the investigator and the sponsor have complied with the principles and guidelines of good clinical practice and with the applicable requirements and, in particular, with Annex I to Directive 2001/83/EC.

The trial master file shall provide the basis for the audit by the sponsor's independent auditor and for the inspection by the competent authority.

The content of the essential documents shall be in accordance with the specificities of each phase of the clinical trial.

The Commission shall publish additional guidance in order to specify the content of these documents.

Article 17

The sponsor and the investigator shall retain the essential documents relating to a clinical trial for at least five years after its completion.

They shall retain the documents for a longer period, where so required by other applicable requirements or by an agreement between the sponsor and the investigator.

Essential documents shall be archived in a way that ensures that they are readily available, upon request, to the competent authorities.

The medical files of trial subjects shall be retained in accordance with national legislation and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

Article 18

Any transfer of ownership of the data or of documents shall be documented. The new owner shall assume responsibility for data retention and archiving in accordance with Article 17.

Article 19

The sponsor shall appoint individuals within its organisation who are responsible for archives.

Access to archives shall be restricted to the named individuals responsible for the archives.

Article 20

The media used to store essential documents shall be such that those documents remain complete and legible throughout the required period of retention and can be made available to the competent authorities upon request.

Any alteration to records shall be traceable.

CHAPTER 5

INSPECTORS

Article 21

1. The inspectors, appointed by the Member States pursuant to Article 15(1) of Directive 2001/20/EC, shall be made aware of and maintain confidentiality whenever they gain access to confidential information as a result of good clinical practice inspections in accordance with applicable Community requirements, national laws or international agreements.

2. Member States shall ensure that inspectors have completed education at university level, or have equivalent experience, in medicine, pharmacy, pharmacology, toxicology or other relevant fields.

3. Member States shall ensure that inspectors receive appropriate training, that their training needs are assessed regularly and that appropriate action is taken to maintain and improve their skills.

Member States shall also ensure that the inspectors have knowledge of the principles and processes that apply to the development of medicinal products and clinical research. Inspectors shall also have knowledge of applicable Community and national legislation and guidelines applicable to the conduct of clinical trials and the granting of marketing authorisations.

The inspectors shall be familiar with the procedures and systems for recording clinical data, and with the organisation and regulation of the healthcare system in the relevant Member States and, where appropriate, in third countries.

4. Member States shall maintain up-to-date records of the qualifications, training and experience of each inspector.

5. Each inspector shall be provided with a document setting out standard operating procedures and giving details of the duties, responsibilities and ongoing training requirements. Those procedures shall be maintained up to date.

6. Inspectors shall be provided with suitable means of identification.

7. Each inspector shall sign a statement declaring any financial or other links to the parties to be inspected. That statement shall be taken into consideration when inspectors are to be assigned to a specific inspection.

Article 22

In order to ensure the presence of skills necessary for specific inspections, Member State may appoint teams of inspectors and experts with appropriate qualifications and experience to fulfil collectively the requirements necessary for conducting the inspection.

CHAPTER 6

INSPECTION PROCEDURES

Article 23

1. Good clinical practice inspections may take place on any of the following occasions:

(a) before, during or after the conduct of clinical trials;

(b) as part of the verification of applications for marketing authorisation;

(c) as a follow-up to the granting of authorisation.

2. In accordance with Article 15(1) and (2) of Directive 2001/20/EC, inspections may be requested and coordinated by the European Medicines Agency within the scope of Regulation (EC) No 726/2004 of the European Parliament and of the Council [4], especially in connection with clinical trials relating to applications through the procedure established by this Regulation.

3. Inspections shall be conducted in accordance with the inspection guidance documents developed to support the mutual recognition of inspection findings within the Community.

4. Improvement and harmonisation of inspection guidance shall be achieved by the Member States, in collaboration with the Commission and the Agency, through joint inspections, agreed processes and procedures and sharing of experience and training.

Article 24

Member States shall make publicly available within their territories the documents relating to the adoption of good clinical practice principles.

They shall establish the legal and administrative framework within which their good clinical practice inspections operate, with definition of the powers of inspectors for entry into clinical

trial sites and access to data. In so doing they shall ensure that, on request and where appropriate, inspectors of the competent authority of the other Member States also have access to the clinical trial sites and data.

Article 25

Member States shall provide for sufficient resources and shall in particular appoint an adequate number of inspectors to ensure effective verification of compliance with good clinical practice.

Article 26

Member States shall establish the relevant procedures for verification of good clinical practice compliance.

The procedures shall include the modalities for examining both the study management procedures and the conditions under which clinical trials are planned, performed, monitored and recorded, as well as follow-up measures.

Article 27

Member States shall establish the relevant procedures for the following:

(a) appointing experts for accompanying inspectors in case of need;

(b) requesting inspections/assistance from other Member States, in line with Article 15(1) of Directive 2001/20/EC and for cooperating in inspections in another Member State;

(c) arranging inspections in third countries.

Article 28

Member States shall maintain records of national and, if applicable, international inspections including the good clinical practice compliance status, and of their follow-up.

Article 29

1. In order to harmonise the conduct of inspections by the competent authorities of the different Member States, guidance documents containing the common provisions on the conduct of those inspections shall be published by the Commission after consultation with the Member States.

2. Member States shall ensure that national inspection procedures are in compliance with the guidance documents referred in paragraph 1.

3. The guidance documents referred to in paragraph 1 may be updated regularly according to scientific and technical development.

Article 30

1. Member States shall lay down all necessary rules to ensure that confidentiality is respected by inspectors and other experts. With regard to personal data, the requirements of Directive 95/46/EC of the European Parliament and of the Council [5] shall be respected.

2. Inspection reports shall be made available by the Member States only to the recipients referred to in Article 15(2) of Directive 2001/20/EC, in accordance with national regulations of

the Member States and subject to any arrangements concluded between the Community and third countries.

CHAPTER 7

FINAL PROVISIONS

Article 31

1. Member States shall bring into force the laws, regulations and administrative provisions necessary to comply with this Directive by 29 January 2006 at the latest. They shall forthwith communicate to the Commission the text of those provisions and a correlation table between those provisions and this Directive.

When Member States adopt these provisions, they shall contain a reference to this Directive or be accompanied by such a reference on the occasion of their official publication. Member States shall determine how such reference is to be made.

2. Member States shall communicate to the Commission the text of the main provisions of national law which they adopt in the field covered by this Directive.

Article 32

This Directive shall enter into force on the twentieth day following that of its publication in the Official Journal of the European Union.

Article 33

This Directive is addressed to the Member States.

DIRECTIVE 98/79/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 27 October 1998 on in vitro diagnostic medical devices

Article 1: Scope, definitions

For the purposes of this Directive, the following definitions shall apply:

(a) ‘medical device’ means any instrument, apparatus, appliance, material or other article, whether used alone or in combination, including the software necessary for its proper application, intended by the manufacturer to be used for human beings for the purpose of:

diagnosis, prevention, monitoring, treatment or alleviation of disease,

diagnosis, monitoring, treatment, alleviation or compensation for an injury or handicap,

investigation, replacement or modification of the anatomy or of a physiological process,

control of conception,

and which does not achieve its principal intended action in or on the human body by pharmacological, immunological or metabolic means, but which may be assisted in its function by such means;

(b) 'in vitro diagnostic medical device' means any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment, or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information:

concerning a physiological or pathological state, or

concerning a congenital abnormality, or

to determine the safety and compatibility with potential recipients, or

to monitor therapeutic measures.

CONVENTION OF THE COUNCIL NO. 05 FOR THE PROTECTION OF HUMAN RIGHTS AND FUNDAMENTAL FREEDOMS

This Convention was not ratified by the European Union itself, but by all of the Member States. According to Art. 6 para. 2 of the Treaty on European Union the Union shall respect the Convention as general principles of Community Law. The most important provision concerning ACGT is:

Article 8 – Right to respect for private and family life

1. Everyone has the right to respect for his private and family life, his home and his correspondence.

2. There shall be no interference by a public authority with the exercise of this right except such as is in accordance with the law and is necessary in a democratic society in the interests of national security, public safety or the economic well-being of the country, for the prevention of disorder or crime, for the protection of health or morals, or for the protection of the rights and freedoms of others.

CONVENTION NO. 108 OF THE COUNCIL OF EUROPE FOR THE PROTECTION OF INDIVIDUALS WITH REGARD TO AUTOMATIC PROCESSING OF PERSONAL DATA

The Convention was not ratified by the European Union itself, but by all Member States. It obliges the signing Member States to transpose the provisions into national law. The most important provisions concerning ACGT are:

Article 1 – Object and purpose

The purpose of this convention is to secure in the territory of each Party for every individual, whatever his nationality or residence, respect for his rights and fundamental freedoms, and in particular his right to privacy, with regard to automatic processing of personal data relating to him ("data protection").

Article 2 – Definitions

For the purposes of this convention:

(a) "personal data" means any information relating to an identified or identifiable individual ("data subject");

(b) "automated data file" means any set of data undergoing automatic processing;

(c) "automatic processing" includes the following operations if carried out in whole or in part by automated means: storage of data, carrying out of logical and/or arithmetical operations on those data, their alteration, erasure, retrieval or dissemination;

(d) "controller of the file" means the natural or legal person, public authority, agency or any other body who is competent according to the national law to decide what should be the purpose of the automated data file, which categories of personal data should be stored and which operations should be applied to them.

Article 4 – Duties of the Parties

1. Each Party shall take the necessary measures in its domestic law to give effect to the basic principles for data protection set out in this chapter.

2. These measures shall be taken at the latest at the time of entry into force of this convention in respect of that Party.

Article 5 – Quality of data

Personal data undergoing automatic processing shall be:

(a) obtained and processed fairly and lawfully;

(b) stored for specified and legitimate purposes and not used in a way incompatible with those purposes;

(c) adequate, relevant and not excessive in relation to the purposes for which they are stored;

(d) accurate and, where necessary, kept up to date;

(e) preserved in a form which permits identification of the data subjects for no longer than is required for the purpose for which those data are stored.

Article 6 – Special categories of data

Personal data revealing racial origin, political opinions or religious or other beliefs, as well as personal data concerning health or sexual life, may not be processed automatically unless domestic law provides appropriate safeguards. The same shall apply to personal data relating to criminal convictions.

Article 7 – Data security

Appropriate security measures shall be taken for the protection of personal data stored in automated data files against accidental or unauthorised destruction or accidental loss as well as against unauthorised access, alteration or dissemination.

Article 9 – Exceptions and restrictions

1. No exception to the provisions of Articles 5, 6 and 8 of this convention shall be allowed except within the limits defined in this article.

2. Derogation from the provisions of Articles 5, 6 and 8 of this convention shall be allowed when such derogation is provided for by the law of the Party and constitutes a necessary measure in a democratic society in the interests of:

(a) protecting State security, public safety, the monetary interests of the State or the suppression of criminal offences;

(b) protecting the data subject or the rights and freedoms of others.

3. Restrictions on the exercise of the rights specified in Article 8, paragraphs b, c and d, may be provided by law with respect to automated personal data files used for statistics or for scientific research purposes when there is obviously no risk of an infringement of the privacy of the data subjects.

Article 10 – Sanctions and remedies

Each Party undertakes to establish appropriate sanctions and remedies for violations of provisions of domestic law giving effect to the basic principles for data protection set out in this chapter.

Article 11 – Extended protection

None of the provisions of this chapter shall be interpreted as limiting or otherwise affecting the possibility for a Party to grant data subjects a wider measure of protection than that stipulated in this convention.

Article 12 – Transborder flows of personal data and domestic law

1. The following provisions shall apply to the transfer across national borders, by whatever medium, of personal data undergoing automatic processing or collected with a view to their being automatically processed.

2. A Party shall not, for the sole purpose of the protection of privacy, prohibit or subject to special authorisation transborder flows of personal data going to the territory of another Party.

3. Nevertheless, each Party shall be entitled to derogate from the provisions of paragraph 2:

(a) insofar as its legislation includes specific regulations for certain categories of personal data or of automated personal data files, because of the nature of those data or those files, except where the regulations of the other Party provide an equivalent protection;

(b) when the transfer is made from its territory to the territory of a non EU belonging State through the intermediary of the territory of another Party, in order to avoid such transfers resulting in circumvention of the legislation of the Party referred to at the beginning of this paragraph.

CONVENTION No. 164 OF THE COUNCIL OF EUROPE FOR THE PROTECTION OF HUMAN RIGHTS AND DIGNITY OF THE HUMAN BEING WITH REGARD TO THE APPLICATION OF BIOLOGY AND MEDICINE (Convention on Human Rights and Biomedicine)

Relevant Text Excerpts:

Chapter 2, Article 5 - General rule

An intervention in the health field may only be carried out after the person concerned has given free and informed consent to it. This person shall beforehand be given appropriate information as to the purpose and nature of the intervention as well as on its consequences and risks. The person concerned may freely withdraw consent at any time.

Chapter 2, Article 6 - Protection of persons not able to consent

Subject to Articles 17 and 20 below, an intervention may only be carried out on a person who does not have the capacity to consent, for his or her direct benefit.

Where, according to law, a minor does not have the capacity to consent to an intervention, the intervention may only be carried out with the authorisation of his or her representative or an authority or a person or body provided for by law.

The opinion of the minor shall be taken into consideration as an increasingly determining factor in proportion to his or her age and degree of maturity.

The representative, the authority, the person or the body mentioned in paragraphs 2 and 3 above shall be given, under the same conditions, the information referred to in Article 5.

Chapter 4, Article 12 - Predictive genetic tests

Tests which are predictive of genetic diseases or which serve either to identify the subject as a carrier of a gene responsible for a disease or to detect a genetic predisposition or susceptibility to a disease may be performed only for health purposes or for scientific research linked to health purposes, and subject to appropriate genetic counselling.

Recommendations

Apart from the EC Directives above, ACGT will also take into account also the following provisions:

Council of Europe, Recommendation No. R(97)5 on the protection of medical data adopted of 13 February 1997.

ACGT will be strictly compliant to the provisions of article 4, in particular Medical data will be collected and processed (…) for preventive medical purposes or for diagnostic or for therapeutic purposes.

Council of Europe, Recommendation on human rights and biomedicine, concerning biomedical research, Strasbourg 25th of January 2005.

Additional protocol to the convention on human rights and biomedicine, concerning biomedical research, Strasbourg 25th of January 2005 of the Council of Europe (CETS No 195) covering the full range of research activities in the health field involving interventions on human being and in particular the primacy of the human being (Chapter II article 3), Chapter III ethics committee , Chapter IV Information and consent, Chapter V (protection of persons not able to consent to research), Chapter VII (Safety and Supervision) Chapter VIII (Confidentiality and right to information).

Relevant International Instruments and Documents

At the international level, a number of documents and instruments exist which have been issued by professional bodies or international organisations. Although they are not legally binding they are nevertheless important, since in most cases they are the result of a consensus process involving numerous individuals and groups concerned with the rights and the wellbeing of patients taking part in clinical trials and/or biomedical research.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

The World Medical Association Declaration of Helsinki (Ethical Principles for Medical Research Involving Human Subjects) adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, as amended by various Assemblies, last in Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004.

In particular, part B (The Basic Principles for All Medical Research) contains some fundamental guidelines in terms of medical research and data treatment:

Section 10: "It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject."

Section 21: "The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject."

Section 25: "When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative".

UNESCO DECLARATIONS

Important relevant documents and legislations have been also produced by UNESCO's Internationals Bioethics Committee (IBC) and adopted by the General Conference of

UNESCO. Three of them are especially important in the context of ACGT and will be considered:

the Universal Declaration on the Human Genome and Human Rights (1997)

http://portal.unesco.org/en/ev.php-URL_ID=13177&URL_DO=DO_TOPIC&URL_SECTION=201.html,

and the International Declaration of Human Genetic Data (2003)

http://portal.unesco.org/shs/en/file_download.php/6016a4bea4c293a23e913de638045ea9Declaration_en.pdf, and

Universal Declaration on Bioethics and Human Rights (2005).

http://portal.unesco.org/shs/en/file_download.php/46133e1f4691e4c6e57566763d474a4dBioethicsDeclaration_EN.pdf

Especially the International Declaration on the Human Genome and Human Rights contains many Articles (3 through 23), which cover issues raised in the context of ACGT. Although declarations of UNESCO are legally not binding (similar to the World Medical Association Declaration of Helsinki), they have been accepted by the member states of UNESCO and therefore are relevant for most European countries as well.

ARTICLE 29 DATA PROTECTION WORKING PARTY. WORKING DOCUMENT ON GENETIC DATA. Adopted on March 17, 2004.

The Art. 29 Data Protection Working Party was established by Art. 29 of the Data Protection Directive 95/46/EC and is an independent advisory body. It can make recommendations on all matters relating to the protection of persons on it's own initiative, advice the Commission on any amendment or specific measure to safeguard the rights and freedoms of natural persons with regard to the processing of personal data and on any other proposed Community measures affecting such rights and freedoms and give the Commission an opinion on the level of protection in the Community and in third countries according to Art. 30 of the Directive 95/46/EC and Art. 14 of Directive 97/66/EC.

This Working Paper contains the authoritative interpretation of the DIRECTIVE 95/46/EC with respect to genetic data and the purposes for which the collection and processing of such data may take place.

Relevant text excerpts of the Working Document on Genetic Data of the Art. 29 Data Protection Working Party:

Section II. DEFINITIONS AND MAIN CHARACTERISTICS OF GENETIC DATA

Definitions:

All data of whatever type concerning the hereditary characteristics of an individual or concerning the pattern of inheritance of such characteristics within a related group of individuals (Council of Europe Recommendation N°R(97)5)

Any data concerning the hereditary characteristics of an individual or group of related individuals (Art 2 (g) of the 2 August 2002 law of Luxembourg on the protection of persons with regard to the processing of personal data)

Non-obvious information about heritable characteristics of individuals obtained by analysis of nucleic acids or by other scientific analysis (International Declaration on Human Genetic data, UNESCO)

Genetic data thus present a number of characteristics which can be summarised as follows:

while genetic information is unique and distinguishes an individual from other individuals, it may also at the same time reveal information about and have implications for that individual's blood relatives (biological family) including those in succeeding and preceding generations, Furthermore, genetic data can characterise a group of persons (e.g. ethnic communities);

genetic data can reveal parentage and family links;

genetic information is often unknown to the bearer him/herself and does not depend on the bearer's individual will since genetic data are non modifiable;

genetic data can be easily obtained or be extracted from raw material although this data may at times be of dubious quality;

taking into account the developments in research, genetic data may reveal more information in the future

and be used by an ever increasing number of agencies for various purposes.

The Working Party also discusses whether genetic data are “personal data” and “sensitive data”:

Section III. APPLICABILITY OF THE 95/46/EC DIRECTIVE

According to Art 2 (a) of the Directive: "personal data" shall mean any information relating to an identifiable natural person (data subject); an identifiable person is one who can be identified, directly or indirectly, in particular by reference to an identification number or to one or more factors specific to his physical, physiological, mental, economic, cultural or social identity."

There is no doubt that genetic information content is covered by this definition. Indeed, a link to a specific person, i.e. the fact that the person concerned is identified or identifiable, is clear in the majority of cases. Nevertheless in some cases it is less clear, e.g. samples of DNA taken in a given place, such as traces at the scene of a crime. However, such samples may constitute a source of personal data in so far as it may be possible to associate samples of DNA with a given person, in particular once their origin has been confirmed by a court upon the forensic evidence. Therefore, in regulating genetic data, consideration should also be given to the legal status of DNA samples.

According to Article 8(1) of the Directive, categories of personal data whose sensitivity requires a higher level of protection includes "data concerning health". Genetic data may provide to an extent a detailed picture of a person's physical disposition and health condition and therefore could be considered as "data concerning health". Furthermore, genetic data

may also describe specific forms of a wide range of physical characteristics. Thus, genetic data which determine the colour of someone's hair, for example, may not be regarded as data directly concerning health. In this context, genetic data can contribute e.g. to assess the ethnic origin of an individual and should as well be considered as falling within the scope of Art 8 (1).

Considering the extremely singular characteristics of genetic data and their link to information that may reveal the health condition or the ethnic origin, they should be treated as particularly sensitive data within the meaning of Article 8 (1) of the Directive and therefore be subject to the reinforced protection provided for in the Directive and the national laws transposing it.

Section IV: PURPOSES FOR WHICH THE COLLECTION AND PROCESSING OF GENETIC DATA MAY TAKE PLACE AND RELEVANT ISSUES

Due to the special nature and characteristics of genetic data and the impact their use may have on the individual's life and on the members of his family, it is very important to determine the purposes for which genetic data may be processed.

Health care/ medical treatment

…..

Medical and scientific research.

Section V: CONCLUDING REMARKS

In Member States where the purposes and the appropriate safeguards for the processing of genetic data are not established by law, the data protection authorities (DPAs) are encouraged to play an even more active role in ensuring that the finality and proportionality principles of the Directive are fully respected.

In this respect, the Working Party recommends that Member States should consider submitting the processing of genetic data to prior checking by DPAs, in accordance with Article 20 of the Directive. This should in particular be the case with regard to the setting up and use of bio banks.

Moreover, closer cooperation and exchange of best practices between DPAs could prove to be an efficient way to compensate the present absence of regulatory framework in the field of the on-line "genetic testing direct to the public".

ARTICLE 29 DATA PROTECTION WORKING PARTY Opinion 6/2000 on the Human Genome and Privacy

The decoding of the DNA blueprint paves the way to new discoveries and uses in the field of genetic testing. On the other hand, the information can identify individuals, link them to others, and reveal complex data about the future health and development of those individuals and other people to whom they are genetically related. The Working Party wishes to emphasise the importance of privacy as a fundamental right and the consequent necessity of deploying new genetic technologies with safeguards adequate to protect that right.

OPINION OF THE EUROPEAN GROUP ON ETHICS IN SCIENCE AND NEW TECHNOLOGIES TO THE EUROPEAN COMMISSION, No. 11, 21 July 1998

Ethical Aspects of Human Tissue Banking [Relevant Text Excerpts]

Main ethical issues

Wherever tissues are removed from human beings, and possibly transplanted into other human beings, the activities involved in the collection and use of such tissues are subject to ethical requirements intended to safeguard respect for human beings, their dignity and autonomy, and for the common good.

INTERNATIONAL GUIDELINES FOR BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS.

Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO). CIOMS, Geneva, 2002.

According with these Guidelines, the full respect of three basic ethical principles must be guaranteed: namely justice, respect for persons, and beneficence (maximizing benefits and minimizing harms and wrongs) or non-malevolence (doing no harm).

Appendix 3 – Overview of national legislation within the European Union

ACGT involves pilots in Belgium, Germany, Greece and the UK as shown in the following figure.

The relevant laws and regulations in the countries where the research will be carried out are listed below.

UK

Data Protection Act 1998 Chapter 29. It contains all the regulations and, as far as research is concerned, Part IV specifies the Exemptions: 33 (4) Personal data which are processed only for research purposes are exempt from section 7 if:

(a) they are processed in compliance with the relevant conditions, and

(b) the results of the research or any resulting statistics are not made available in a form which identifies data subjects or any of them.

In the UK there is a national ethical approval application process as governed by COREC (Central Office for Research Ethics Committees). Individual Ethics Committees in the UK use the COREC processes to administer Ethics applications. ACGT will seek approvals from the Local Research Ethics Committee (LREC). http://www.corec.org.uk/applicants/apply/apply.htm.

With regard to informed consent the situation in the UK, and Oxford University in specifically, particularly relating to the samples we want to use in ACGT is as follows.

In Oxford hospital, using the nationally approved consent forms for surgery, there is a section specifically asking for excess tissue to be donated for research. Tissue samples for which a patient has declined consent are specifically earmarked. These will not be used.

With regard to analysis of agreed samples, they can only be used when the COREC approval has been obtained. This is a national scheme of research ethics committees and submission is to your local ethics committee which is monitored by national standards. The ethics committees function according to the new European regulations.

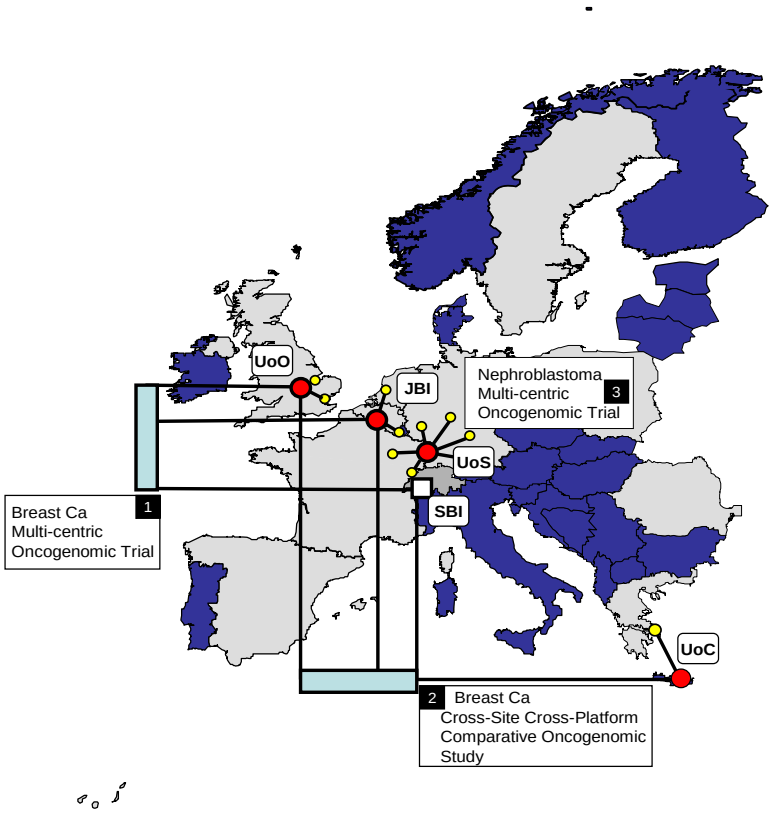

Figure: The ACGT clinical pilot sites

The ethics committee can give permission for the use of retrospective stored samples provided they are not linked to the patient directly. Also, we have been collecting tissues for patients signing their consent on the surgical consent forms. All projects have been submitted to the COREC (Research Ethics Committee) to obtain approval before proceeding with the research. As a condition of obtaining approval the security information, links to patients, how the information will be used and confidentiality need to be described and approved by the ethics committee.

Informed consent for tissue donation is obtained by giving the patient a written information sheet which they have time to consider for at least 24 hours before being requested to sign the consent form. This consent sheet is approved by the local ethics committee as part of the overall ethics application. The Oxford group in ACGT has recently had an MHRA audit relating to patients in clinical trials which was approved.

Samples are given an accession number which can link a pathology number to the sample, but when samples are handled all that is known is the accession number so the scientists and statisticians analysing the sample cannot relate this back to the patient. A specific tissue bank manager organizes the tissue banks and the allocation of samples for research, once ethics committee approval has been obtained.

Clearly, to be of value in terms of new markers, prediction of sensitivity, response to treatment and outcome, there must be a link to clinical follow up. This is maintained in a separate database in a separate hospital and routine follow up on all patients with cancer is obtained for audit purposes in clinical management. These are maintained on a separate database and organized by a separate data manager funded by the National Health Service. The patients' identifiers on this database will include their pathology number. Thus, it will be possible to link the biological variables analyzed in the laboratory, e.g. gene array, using the coded numbers to the pathology.

However, this would not be done by the scientist doing the assays but by the tissue manager. It would be possible to link the data then to outcome, but this is from a separate database and would be linked by the clinical data manager in the National Health Service. No patient names would be used but it would then be possible to link the biological assay to the outcome. The ethics committee has approved this method of confidentiality and security. In the two sites where the databases are kept there is a backup using University or NHS computers and access is through password controlled computers in locked offices in swipe card controlled areas.

As new projects are undertaken then the new project needs to be approved by the ethics committee. There is a time limit on all projects and if a project goes beyond the time then an extension needs to be requested from the ethics committee or the project must halt.

This is bound by the national guidelines on research ethics committees published by the British government and which follows the new European regulations.

The standard form of consent for research trials and sample collection does involve requesting agreement individually for issues such as collaboration with other centres, lack of financial reward to the volunteer, access to relevant government agencies for inspection, collaborations in the future, right to withdraw consent at any time in the future, the knowledge of who is carrying out the research and how to contact them if they want advice on it, the agreement is that if relevant medical information became available form this it could be passed on to their practitioner. These are standard recommendations from the Medical Research Council and followed by all ethics committees in the UK in obtaining tissue consent.

Germany

In Germany, clinical trials are ruled by the German Drug Law (Arzneimittelgesetz). Of special importance are Articles 40, 41 and 42, which ensure the protection of human beings involved in clinical trials. The law has been amended last year, now allowing under very special conditions that children can be enrolled into clinical trials. This is also the case if the trial is not of direct benefit for the child involved, but possibly for the group the child belongs to.

The amendment also implements the Directive 2001/20/EC of the European Parliament and the Council of 4 April 2001 (good clinical practice in the conduct of clinical trials) into German law. According to this law, all clinical trials have to be approved by an official ethics committee. In order to gain approval, consent of the patient or – in the case of children – his or her legal representative has to be obtained after thorough information about the goals, procedures and possible side effects of the treatment to be tested.

Genetic data which are derived from patients are regarded as medical data, and therefore as sensitive data, which require protection equivalent to that of other sensitive data. In Germany, data protection in the private sector and concerning national public bodies is

governed in general by the German Federal Data Protection Act (Bundesdatenschutzgesetz, BDSG), which entered in force on May 23, 2001. By this act, the old data protection law was amended, and with these amendments the provisions of the EU Data Protection Directive 95/46/EC of October 1995 have finally been implemented into national law. This law also contains many provisions, amongst others on the transfer of personal data abroad, as well as collection of data for research purposes.

Personal data such as names, birth dates and addresses collected for research must only be used and processed for this purpose. They should be anonymized as soon as the intended purpose allows it. In the meantime, personal data must be stored separately from medical information, which should not be linked to personal identifiers, but to a code instead.

When personal data are collected in the context of clinical trials, it is required according to German law which rules the conduct of clinical trials on medicinal products for human use (Arzneimittelgesetz) that patients give informed consent not only to the clinical trial, but – separately – also to the collection, storage, processing, transfer and analysis of personal data. Consent is legally effective only if it is given voluntarily and the subject has been informed of the purpose, nature, significance and implications of that use. The subject must know what he or she is agreeing to.

As a rule, information on the specific research project is necessary. However, restriction to a specific purpose may give rise to problems when blood or other tissue samples are collected prospectively for research purposes and stored in "biobanks". As infrastructure facilities for an indefinite number of research projects, they are unsuitable for their purpose if consent is to narrow. Therefore, a more broadly worded consent has been accepted by many ethics committees in Germany.

However, up to now, there is no specific regulation in place with respect to sample and data collection in biobanks. Up to now, several bodies have issued opinions on the use of human biological samples, amongst other the German National Ethics Council (March 17, 2004 "Biobanks for research", http://www.ethikrat.org/_english/publications/opinions.html) – by the way, in close cooperation with the French National Ethics Council (No 77 – March 20, 2003: "Ethical problems raised by the collected biological material and associated information data: 'Biobanks', 'Biolibraries'." http://www.ccne-ethique.fr/english/start.htm).

Currently it is debated in Germany – but certainly not only there – that it could be helpful to have an independent trustee who holds the key which provides the link between personal data and medical information. As a model case a data processing infrastructure has been established by the pharmaceutical company Schering, which includes different coding steps and an independent, third party trustee, providing a high level of privacy protection throughout the research process. Unfortunately, up to now there are only publications in German available which describe this model (http://www.tembit.de/fileadmin/PDFs/Datenschutz_in_der_pharmakogenetischen_Forschung_-_eine_Fallstudie.pdf). Similar considerations may become relevant for the ACGT-project in the future.

Regarding the transnational transfer of samples there are also no clear specific legal regulations available. But it is generally accepted, if the patients are informed about the fact that samples could be handed over to researchers in other countries, and they have consented to it. When the identity of cooperating partners is known at the time of data collection, the patients should be informed about this. Whether patients could also consent to transfer to unknown partners, has to be examined.

According to the German National Ethics Council, such broadly framed consent must, however, be offset by a requirement that the samples and data, if they cannot be anonymized, may leave the area of control of the biobank only in coded form, except in circumstances provided by law. Personal data must not be passed on to third parties. In cases where external researchers require additional relevant data on subjects for their research, the data may be supplied only by an officer of the biobank to which the donors originally entrusted their samples and data, so that the external workers cannot identify individuals. Furthermore, full records should be kept of any transfer to third parties, to maximize transparency and to ensure that donors can withdraw their samples and data at any time. Donors' rights of withdrawal must be guaranteed whenever samples and data are transferred.

Belgium

The clinical partner from Belgium is the coordinator of the TransBIG project, aiming at translating molecular knowledge into early breast cancer management. TransBIG is partially funded by the European Commission under its Framework Programme VI.

The clinical research undertaken will fully obey existing national, European and International regulations. Patients participating in the research will be previously fully informed about the scope of the research and will be asked to give their explicit and written consent about it, as this required by currently legislation which is mentioned below. Tumour samples will be "leftover" tumour breast tissue obtained during diagnostic or therapeutic procedures. Blood samples will be, in the majority of cases, extra samples collected for research purposes only. Both tissues and blood samples will come from women suffering from breast cancer enrolled in a clinical trial run through the ACGT network. All human tissues are used for the identification of prognostic and predictive molecular markers. This implies that no hereditary genetic research is planned. What is to be examined is whether the human biological material may or may not be predictive of the efficacy of a specific treatment in each individual patient.
The Project will comply with the Law of August 22, 2002 relative to the patient's rights.

ACGT research in Belgium will fully comply with the Belgian Law regulating the operation of hospitals (7 August 1987 6), the Royal Decree (R.D.) n° 78 of November 10, 1967, the R.D. of August 12, 1994, the R.D. of 23 October 1964 that sets the standards to which the hospitals and their services must comply with.

The clinical trials are subject to the procedures of the Ethical Committees as these are regulated by the existing law on drugs of March 25, 1964 (that requires that a favourable opinion of an ethics committee is obligatory before the beginning of any clinical trial), as it was modified by the law of the 24 of December 2002 and complies with the Directive 2001/20/EC. It must be also mentioned that the recommendations of the Advisory Ethics Committee of Belgium (No 23 – 8/9/2003 – relating to the Ethics Committees) will be followed (the Law of May 7, 2004 rules the experiments on the human being, executed by the R.D. of June 20, 2004).

Clinical research will also comply with the directives of the "Conseil National de l'Ordre des Médecins" concerning research on human subjects, issued on the 22nd of August 1992, 17th of February 1996, 13th of December 1997, 19th of September 1998, 24th of April 1999, 15th of January 2000 and 19th of February 2000, and 19 2000. Of particular importance will also be the recommendations of the Advisory Ethics Committee of Belgium (No 13 -19/7/2001 - relating to experiments involving human subjects), (No 2 – 7/7/1997 – concerning the convention of the human rights and biomedicine of the Council of Europe).

Clinical and genetic data collected are subject to the legislation about personal data and in particular the law of December 8, 1992 relating to the protection of the private life with regard to the processing of personal data , the Royal Decree (R.D.) of the 13.02.2001 (M.B. 13.03.2001) executing the Privacy Law. Furthermore related to the management of clinical information is the R.D. of December 15, 1987 and the R.D. of May 3, 1999 which determines the minimal general conditions for the medical file of an individual.

In case of problems with any new legislation relating to human biological sample collection and transfer, the Ethical-Legal Committee will evaluate the situation and will take appropriate action.

Greece

In Greece storage and processing of sensitive personal data is primarily governed by the following legislation:

Law No 2068 /1992 validating the European Convention 108/1981 for the Protection of Individual from the Automated Processing of Personal data in Strasbourg 28th of January 1981.

Greek Law No 2619 /1998 validating the Convention for the Protection of Human Rights and Dignity of the Human being with regard to the Application of Biology and Medicine: Convention of Human Rights and Biomedicine (Oviedo, 4th of April 1997) and in particular related to the issues raised by the EC Chapter II Consent, Article 5 (general rule), Article 6 Paragraph 2 (consent about children), Chapter IV (Human Genome), Article 12 (genetic examinations able to predict), and Chapter V (Scientific Research) Article 15 (general rule), Article 16 (Protection of Individual subjects to the Research) and Article 17 (Protection of Individuals Unable to Consent to the Research).

Greek legislation about the consent to diagnostic practice is regulated by Law 2071/1992 and in particular Article 47 paragraphs 3, 4 and 5.

According to the Greek legislation genetic data are “sensitive personal data” and in that sense protected according to Law 2472/1994 and Law No 2068 /1992, in compliance with Directive 95/46/EC on the protection of personal data.

Laws about the Modernization of the National Health System article 57 for the Greek laws 2519/1997 and 2071/1992 article 57 regulate in particular the rights of patients, laws 2889/2001 (article 2 and 5) and 2071/1992 (article 61) the operation of the local ethical committees in hospitals and 2071/1992 (article 62) the code of medical practice.

The Greek Drug Organization operates a National Committee for Clinical Trials according to ministerial decision 89292/2003 in compliance with Directive 2001/20

Of specific importance are the Recommendations of the National Bioethics Committee, operating according to Law 2667/1998 for the collection and management of genetic data (2002) and the recent recommendation for the operation of review ethics committees for biomedical research (2005).

Directive 2002/58/EC on privacy and electronic communications sector (Draft legislation to incorporate this directive into Greek Law is to be discussed soon before Parliament).

The processing of sensitive personal data is generally prohibited. By exception, the processing and recording of sensitive medical data is allowed, provided the Greek Data Protection Authority grants the required authorisation and one or more of the following requirements exists:

1. the data subject has consented in writing to the processing;

2. the processing is necessary for the preservation of the data subject's vital interest;

3. the processing concerns health related issues and is executed by a person who provides by profession medical services and is subject to a confidentiality duty or to related codes of conduct provided that the processing is necessary for the medical prevention, diagnosis, cure or management of health services;

4. the processing is executed exclusively for research and scientific purposes and provided that anonymity is secured and all the necessary measures for the protection of the rights of the individuals to which the data refer are taken.

Of relevance is also the fact that the nationally funded research project "Prognochip", focusing on clinico-genomic breast cancer clinical study (which is a predecessor to the clinical pilot foreseen in ACGT) has been reviewed and approved on the 8th of October 2003 by Ethical Review Committee the International Agency for the Research on Cancer (IARC) applying in it assessments the International Guidelines for Ethics Review of Epidemiological Studies" (CIOMS1991) and the "International Ethical Guidelines of Biomedical Research Involving Human Subjects (CIOMS2002).

Especially with respect to the conduct of clinical trials, it would be useful to get more information.