Production of informed-consent form in compliance with the clinical trials, post-genomic research and genetic data handling requirements

Project Number: FP6-2005-IST-026996

Deliverable id: D 10.1

Deliverable name: Production of informed-consent form in compliance with the clinical trials, post-genomic research and genetic data handling requirements

Date: 15.03.2007

COVER AND CONTROL PAGE OF DOCUMENT	
Project Acronym:	ACGT
Project Full Name:	Advancing Clinico-Genomic Clinical Trials on Cancer: Open Grid Services for improving Medical Knowledge Discovery
Document id:	D 10.1
Document name:	Production of informed-consent form in compliance with the clinical trials, post-genomic research and genetic data handling requirements
Document type (PU, INT, RE)	INT
Version:	DRAFT
Date:	15.03.2007
Editor: Organisation: Address:	Jean-Marc Van Gyseghem (FUNDP) Belgium

Document type PU = public, INT = internal, RE = restricted

ABSTRACT:

This deliverable contains in the first part an analysis of the relevant ethical and legal requirements for informed-consent forms within ACGT. Special issues such as the scope of the consent with special regard to future research, informed consents of minors and relatives are discussed.

The second part contains the general terms of ACGT, that have to be accepted by every participant, as well as different consent forms and agreements, that have to be concluded between the different participants.

KEYWORD LIST: Informed-consent, Ethic, Data Protection

MODIFICATION CONTROL			
Version	Date	Status	Author
0.1	19.01.2007	Draft	J.-M. Van Gyseghem
0.5	22.01.2007	Draft	R. Kollek; J.-M. Van Gyseghem; N. Forgó
0.7	31.01.2007	Draft	R. Kollek, J.-M. Van Gyseghem; N. Forgó
1.0	06.02.2007	Draft	R. Kollek, J.-M. Van Gyseghem; N. Forgó
2.0	12.03.2007	Final	I. Petersen, J-M Van Gyseghem, F. M Buffa, N. Forgó

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Contents

Executive Summary

Although this deliverable stands by its own, it has to be red in combination with the D10.2 which analyses the ethical and legal, in particular data protection requirements for ACGT..

The main matter of this deliverable is the consent in the ACGT project.

The first part of the document is related to an ethical view of the consent. Today, the doctrine of informed consent is widely acknowledged as one of the main principles in ethics and bioethics by protecting persons concerned and their fundamental rights to integrity and self-determination in medical interventions. In principle, the doctrine states that any medical treatment as well as scientific research involving human subjects is only to be carried with the prior, free, and informed consent of the person concerned. Therefore, it is indispensable that the person concerned will be informed adequately prior to consent. In addition, consent should be explicitly expressed and may be withdrawn at any time and for any reason without disadvantage or prejudice.

Even though the doctrine of informed consent is globally recognized for clinical practice and biomedical research, it is – from a historical point of view – a relatively new phenomenon. In 1964, the General Assembly of the World Medical Association adopted the Declaration of Helsinki strongly emphasizing the need to obtain informed consent in medical treatment and research. Nevertheless, considerable lack of clarity still exists when it comes to the question of how the doctrine can or should be applied in different medical, social and cultural contexts.

The second one deals with the informed consent as one way, among others, to legitimate the data processing needed in the ACGT project in the sense of the European Data Protection Directive 95/46/EC.

There are several preconditions that have to be fulfilled to make an informed consent valid. It has to be explicit, freely given, e.g. not led by external influences, for a specific case and in awareness of the factual situation, which means, it has to be an “informed” consent.

It is difficult to define a specific case for data processing in research projects like ACGT as an abstract consent to the processing of personal data is not possible. On the other hand it is accepted to ask a patient concerned for a consent for the specific project in question and further future projects.

As in ACGT minor patients are involved informed consents by their legal representatives are required. As soon as the minor becomes mature he can exercise his right to withdraw. If this happens, his or her data has to be anonymized by erasing the link for re-identification that was stored at the Trusted Third Party.

The third part contains the general terms for ACGT, consent forms and other agreements to allow and rule the data processing within ACGT.

1 INTRODUCTION

Research in genetic data opens new and far reaching possibilities. But there is no special European legislation governing research in genetic data. Therefore, existing legislation has to be interpreted in a way that it comprises research in genetic data. Due to the enormous amount of information they carry, genetic data is sensitive personal data, which means that data protection legislation is applicable.

Hence research in genetic data presents new challenges for data protection and the content of an informed consent the patient has to give. Research in genetic data can, for example, achieve results that can change the view on information duties and/or information rights of the patient considerably. Furthermore, scientists are interested in storing genetic data for longer periods of time, especially in order to use them for research projects, which are not known at the time of storage. For the storage and use of genetic data to be in accordance with data protection legislation, the informed consent has to present a sustainable and long term solution, especially with regard to the central issues of an informed consent: information of the said person, the consent being given voluntarily and the said person being able to understand.

This deliverable has to be seen in the context of "*The ACGT ethical and legal requirements*" (D 10.2). From a legal point of view, the primary object of the proposed ACGT Data Protection Framework, as stated in D 10.2, was to create a Data Protection architecture that allows by means of anonymization to process as much data as possible outside of the scope of the European Data Protection legislation. In a second step it is planned to bind all participating partners by contracts to the ACGT policies and procedures to ensure their compliance with the Data Protection regulation.

Nevertheless from an ethical as well as from a legal point of view it is essential and of high importance to obtain an informed consent from the participating patients anyway. For firstly, the informed consent is a fall-back-scenario if the Data Protection Directive in some cases should be applicable anyway (e.g. a data processor can re-identify the patient for some reason) and secondly, not less important, from an ethical point of view it is strongly demanded to let patients participate in and have a measure of influence over the processing of their genetic data.

This document gives an overview of the ethical and legal aspects concerning an informed consent and provides the proposed informed consent forms as well as general terms for ACGT, which have to be accepted by every participating party within the project.

However and from a legal point of view, the consent is a way, amongst others, to legitimate the sensitive data processing I the sense of the European data protection Directive. We send back to the deliverable D10.2 (3.3.2.7) where the consent is analyzed.

In general, this deliverable has to be red in accordance with the deliverable 10.2 which gives more explanations about the different principles used in this one.

2 ETHICAL AND LEGAL ASPECTS

2.1 ETHICAL ASPECTS

2.1.1 The importance of the doctrine of informed consent

The doctrine of informed consent is one of the most well known elements of medical ethics and bioethics today. In essence it states that any preventive, diagnostic or therapeutic medical intervention as well as scientific research involving human subjects is only to be carried out 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.

Since medical treatment or research may pose risks to patients or human subjects, they have to be protected from unwanted and unwarranted interventions. Individual consent therefore is an indispensable prerequisite for medical care or biomedical research. It is an expression of respect for autonomy and self determination. 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.

However, this global recognition of informed consent as a condition sine qua non for regular and experimental medical interventions is a relatively new phenomenon. Historically, it is by no means self-evident that a patient or research subject has to be informed about such interventions and to be asked for consent.

2.1.2 Historical background

The history of informed consent is manifold, culturally diverse, rather controversial and cannot be "reduced to linear narration of social events and practices"[1]. What seems to be clear, however, is that the concept of informed consent and its evolution is tightly connected to the physician-patient-relationship and the way it developed through the centuries. The history of informed consent reflects these changes. Furthermore, the idea that patients should be asked for consent before any medical intervention is also closely linked to a secular conception of medicine, which did not develop before the sixth or fifth century of our time in ancient Greece.

In parallel, the first explicit conception of medical ethics can be located. It has been traced back to Hippocrates, one of the founders of this new secular and empirically based medicine. According to this "Hippocratic oath" physicians were obliged to act for the benefit of their patients and to avoid harm. However, this did not entail the obligation to tell

[1] Faden RR & Beauchamp TL (1986): A history and theory of informed consent. New York: Oxford University Press.

the truth to their patients. On the contrary, sometimes it was considered harmful to be to outspoken about their disease, its treatment and prognosis. The physicians regard themselves as knowing best what is good for the patients. In western countries, such paternalistic conceptions of the doctor-patient-relationship prevailed until the second half of the 20th century. In contrast to paternalism, modern conceptions of the physician-patient-relationship are characterized by individualism and self determination. The physician acknowledges that it is the patient who finally authorizes interventions into his or her body. In western countries, this change is at least in part the result of the social emancipation movement of the 1960th and 1970th with its strong rejection of authoritarian structures in all dimensions of societal life.[2] In addition to the strengthening of informed consent for treatment and clinical research, the requirement of informed consent for the use of stored tissue and patient data became a subject of ethical debate in the 1980th.

Obtaining consent for necessary treatment in case of painful and/or progressing illness is but one part of the history of consent. The other, much more recent and controversial part of this history is related to systematic medical research involving healthy volunteers or patients. Such research became an important part of medical practice in the second half of the 19th century, when scientific and experimental methodology was introduced into clinical medicine, and large hospitals were established. Often, research was done "in the service of science and medical progress" without consent of the patients. After it became known that some people suffered injury and harm from non-therapeutic interventions, the ethics of human experimentation became a public and political issue. The first detailed regulations about non-therapeutic research which set forth the legal basis for disclosure and unmistakable consent were issued in Germany in 1900.[3]

However, it was not before the horrible crimes of the Nazi doctors became known, and the publication of the Nuremberg Code in 1947, that the moral duty of physicians and researchers to obtain consent became more widely recognized. In 1964, the "Ethical Principles for Medical Research Involving Human Subjects" strongly emphasizing the need to obtain informed consent for medical treatment and research, became adopted by the General Assembly of the World Medical Association in Helsinki.[4] Today, the doctrine of informed consent has been widely accepted in both clinical practice and biomedical research.

2.1.3 Fundamental importance of consent

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. These rights are part of human rights which have been affirmed by the majority of the countries in the world (Conference on Human Rights, Vienna 1993). In ethical terms, the requirement for informed consent is based on the principles of 'respect

[2] Fox RC (1990): The Evolution of American bioethics: a sociological perspective. In: Weisz G (ed): Social science perspectives on medical ethics, Dordrecht: Kluwer, pp. 201–217.
[3] Vollmann J, Winau R. (1996): Informed consent in human experimentation before the Nuremberg code. British Medical Journal 313(7070):1445-9.
[4] World Medical Association (1964): 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.

for persons' and 'respect for human dignity'. They denote that a human being must not be used merely as a means to an end. Instead, one should not act against their wishes, respect their autonomy, their capacity to consider options, make choices, and act without undue influence of others.

It is important to note that the necessity to obtain informed consent for medical interventions and medical research on human subjects sets limits on the ability of the state, of medicine and the community to govern the individual. No interference into the human body must be undertaken without the permission of the person concerned. No matter, how much the family or the wider social group may be involved in such a decision – ultimately, it should be the right of the individual person to decide.

The rights to integrity and self determination, however, are not the only justifications for requirement of informed consent. For example, the duty to inform subjects about key aspects of a treatment, a clinical trial or research involving identifiable blood and/or tissue samples can also be justified by the requirement of common decency or minimal respect which we owe other persons because they are human beings. Since most people do feel violated if others interfere with their bodily integrity without consent, it can also be argued that the necessity to obtain consent has anthropological roots which are at least to a certain extent independent of social and cultural circumstances. These basic feelings extend – although to a lesser extent – to research on one's own tissue samples.

The requirement of consent is of fundamental importance for the protection of the most basic rights of a person in the context of medical treatment and research. However, it also protects physicians against accusations and litigations, and opens up a legitimate domain of biomedical research. Today, informed consent has become "the modern clinical ritual of trust".[5].

2.1.4 Application of the doctrine of informed consent

Although the requirement for informed consent is widely acknowledged, considerable lack of clarity exists when it comes to the question of how the article can or should be applied in practice and in various contexts of application. In order to clarify this issue, elements of informed consent will be identified and questions will may arise in different contexts of application will be discussed.

2.1.4.1 Elements and procedures of informed consent

Consent is not a single act. It is but the last step of a process which involves at least four steps.[6]

a) Disclosure of information to the subject: The first step in the process of obtaining consent is the provision of information. Content of this information as well as method,

[5] Wolpe PR (1998): The triumph of autonomy in American medical ethics. In: DeVries R & Subedi H, eds., Bioethics and Society: Sociological Investigations of the Enterprise of Bioethics, Prentice Hall, New York, pp 38-59.

[6] Beauchamp TL & Childress JF (2001): Principles of biomedical ethics (Fifth Edition). New York: Oxford University Press.

timing and setting of its provision are of overwhelming importance. Disclosure of information involves practical problems concerning the amount and complexity of information provided. For some participants, even simple protocols may be too complicated and too extensive. Formalized and lengthy documents may ask too much of patients and undermine motivation to participate. Secondly, subjects may not be familiar with basic concepts of research and study design elements like randomization or control group. Thirdly, obtaining consent is not only sought out of respect for individual autonomy, but it is also a legal cover for health care providers. Therefore, different information may be relevant for health care providers than for patients or research subjects. And finally, extensive descriptions of uncertainty concerning best treatment may undermine trust.

b) Understanding of information: In order to give valid consent, the individual must have the capacity to understand the information given to her or him. This generates a fundamental problem for research in children or persons without the capacity to consent. Comprehension can also be problematic if information given to the subject is concerned only with medical aspects and therefore may be one-dimensional and not sufficient for understanding and informed decision making. Other dimensions, for example values hold by the prospective participant, have to be considered as well. Furthermore, information relevant to behaviour and decision making may differ from case to case. And finally, it is difficult to assess, whether the patient or subject has indeed understood the information given to him or her. Although some efforts have been made to develop measures of informed consent and choice[7], more research is needed in order to evaluate comprehension in a sound way.

c) Voluntariness of decision: The person must be able to decide freely whether she wants to be treated in a certain manner or participate in research. She must not be subjected to undue influence or intimidation. Furthermore, she must be free to withdraw from consent at any stage, especially of research, without suffering prejudice or disadvantage. There are several factors which may affect a person ability to decide freely. Significant differences in social status between prospective participant and researcher may affect willingness to ask questions and also may affect freedom to decline from taking part in research. Asymmetric relationships between medical personnel and patients may prevent prospective patients to express uncertainty, and social expectations from family or community may force participants to take socially desired choices. Finally, especially in poor countries, economic benefits may act as significant incentives and hence can restrict indirectly voluntariness.

d) Formal consent: It is widely accepted that consent at least to participate in research must be explicit. This means that the consent form has to be signed, or an oral statement has to be given in the presence of a witness. In “first person consent” the participant him-/herself provides consent. However, this may not be appropriate or acceptable in all cultures or groups. In some communities there may be a necessity to consult social leaders before asking individuals. Here the question arises whether this represents a case of inappropriate paternalism and neglects the right of a person to make her own choices, or whether such a practice is in accordance with the required respect for personal autonomy. In “proxy consent” the right to give consent to research is granted to social leaders, marital partners, senior family members, or community leaders. They may have the authority to give consent on behalf of others. However, it is being debated whether such proxy consent involves the danger that participants are

[7] Marteau TM, Dormandy E, Michie S (2001) A measure of informed choice. Health Expect 4(2): 99-108. Michie S, Dormandy E, Marteau TM (2002): The multi-dimensional measure of informed choice: a validation study. Patient Educ Couns 48(1): 87-91.

enrolled in clinical research against their will, and it therefore is in conflict with the fundamental principle of respect for persons.

2.1.4.2 Different practical context of application

Although informed consent has been widely accepted in ethical discourse, its practical application in different medical, social and cultural contexts poses several challenges. In the medical context, the application of the doctrine may differ in treatment and research. Consent for treatment is generally regarded as less critical, since the patient is in need of help and often does not have much choice. Although the patient must in principle consent to treatment and have the right to refuse it, in most cases implicit consent may be sufficient. With respect to consent for research, different types of research have to be distinguished. Whereas clinical research may involve physical risks for patients and subjects involved in such studies, this is for instance not the case in epidemiological or biobank research. Here the informational risk prevails.

Up to now, informed consent has mainly been relevant in the context of clinical studies designed to test new drugs and to analyze the patient's response to it. In such cases, the patient is directly affected and consent usually is sought for clearly defined and limited research purposes. In research on human tissue samples, which usually is done to generate basic knowledge or for public health purposes, the individual is not directly or physically affected. In the context of such research, the paradigm of obtaining specified consent is increasingly regarded as dysfunctional.[8] Since samples are needed for future research and projects cannot be defined clearly at the time consent is being sought, it would be costly and time consuming to obtain qualified individual consent for each new research project. Others reject the idea of a broad consent and suggest a model of tiered consent.[9] Furthermore, in some areas of medicine, like for the selection of health policies or the provision of public health, informed consent is considered to be useless.[10]

Together with new research priorities, objectives and strategies, a competition emerges between two concepts which differ with respect to the meaning and primacy of autonomy: In the context of individualism, individual rights and interests are regarded as most important because they limit the ability of the state, the community, or family to govern the individual.[11] In the context of communitarian concepts, individual rights are regarded as secondary to the needs of the community or the state, who has the obligation to guarantee law and order, stabilize social structures, set health policy goals, and so on.[12]

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[8] Lunshof JE (2006): Ethics watch: Desperate times call for desperate measures. Nature Reviews Genetics 7, 162

[9] Reymond MA, Alla AS, Steinert R, Eder F, Halangk W, Lippert H (2003): Informed Consent for Molecular-Based Diagnostic and Prognostic Studies in the Cancer Patient, Digestive Diseases, 21, 351-6. Williams ED (2001): Informed consent in genetic research, Croatian Medical Journal, 42 (4), 451-457

[10] O'Neill O (2003): Some limits of informed consent. J Med Ethics 29(1): 4-7.

[11] Engelhardt HT: The Foundations of Bioethics. New York: Oxford University Press, Inc., second edition, 1996.

[12] Callahan D (2003): Individual good and common good: a communitarian approach to bioethics. Perspect Biol Med 46(4): 496-507.

First attempts to develop a new normative framework have been made.[13] It questions the primacy of the current individualistic model and emphasizes communitarian values and principles like reciprocity, mutuality, solidarity, and citizenry instead. The aim is, to find a balance between protecting the individual on the one hand, and enabling research for the benefit of society on the other (ibid.). Whether and how this can achieved is currently under discussion. It certainly would be a problem to ask the individual to waive his or her rights without establishing legal safeguards in addition to ethical ones. Initiatives to simplify over-boarding bureaucracy and laborious procedures which may be a hindrance to science are welcomed. At the same time, however, one has to avoid that well founded interest and rights of the individual are traded off for the interest of the society, research and economic development.

2.1.4.3 Different cultural context of application

Beyond practical context, application of the doctrine may also be shaped by the cultural context in which it is applied. The term "culture" refers to the capacity of human beings to classify, codify, and communicate their experiences symbolically. More generally, it refers to patterns of human activity and the symbolic structures that give significance to such activity. Therefore, different cultures reflect different ways to signify and to evaluate human activity. Religions, values, political systems, social structures, appreciation of different professions, relation between the past and the present, the older and younger generations, the family and the individual, men and women, doctors and patients and so on belong to the factors which characterize a specific culture.

With respect to the application of informed consent in different cultural contexts we are confronted with the challenge that the doctrine is culturally bound. Like medical science and technology and the ethics designed to deal with its impact, it is very much shaped by liberal individualism which has its roots in western culture.[14] For example, in western culture, beliefs about personhood and autonomy inform every aspect of medical transactions, including the notion of informed consent. The individual is the locus of decisional capacity and informed consent is regarded as an expression of personal autonomy. The concept of individual autonomy is deeply embedded in western thought and philosophy. The preoccupation with these concepts in western bioethics is indicative of the extent to which cultural values influence our orientation to biomedical morality. However, individualist assumptions underlying these concepts may not have universal applicability, even in western settings.[15] They may be meaningless in societies that stress overriding importance of an individual's relationship to family and community, or that express decisional capacity socially, and not individually

Although it is increasingly recognized that different strategies of application of the doctrine of informed consent are needed, there is little agreement about what processes and documentation are appropriate in varying cultural and social contexts. The challenge is to establish procedures that are both ethically sound and culturally sensitive, although there may be times when these two requirements appear to be in

[13] Knoppers BM, Chadwick R (2005): Human genetic research: emerging trends in ethics. Nature Reviews Genetic 6(1):75-9.
[14] Pellegrino ED (1992): Intersections of Western biomedical ethics and world culture: problematic and possibility. Camb Q Healthc Ethics 1(3): 191-6.
[15] Barrett RJ, Parker DB (2003): Rites of consent: negotiating research participation in diverse cultures. Monash Bioeth Rev 22(2): 9-26.

conflict. One way of resolving such situations is through careful and sustained community involvement in research[16]

2.2 LEGAL ASPECTS

The informed consent is also subject to several legal provisions. In the following the legal aspects of the informed consent shall be examined.

2.2.1 Regulatory framework

2.2.1.1 Definition

Art. 2(h) of the Data Protection Directive defines 'the data subject's consent' as 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.

In other words, the Directive requires a declaration of intention made by the patient concerned, which is given voluntarily, for a specific case in awareness of the factual situation.

2.2.1.2 Declaration of intention

A declaration of intention is an action being visible from outside for the addressee, which, from an objective point of view, can be seen as consent.

For sensitive data generally an *explicit* declaration is required (Art. 8 para. 2a); otherwise, it is also accepted if consent is given by way of implied conduct. If the said person remains silent, this cannot be interpreted as consent.

A specific form is not required. The declaration can be given orally, in writing or electronically.[17]

2.2.1.3 Freely given

The Directive requires the declaration of intention to be given freely, which means, it has to be a self-determined action, which is not led by external influences. The motivation of the person concerned, e.g. the question, whether the person concerned acts in his/her own interest or for the benefit of others, is not relevant. Relevant is only, if the declaration is a product of a free decision. The wording “freely given indication” makes clear, that the absence of external forces and threats of violence is not enough.

[16] Lindegger G, Bull S: Ensuring valid consent in a developing country context. Science and Development Network. (2002) http://www.scidev.net/

[17] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 115.

The freedom of decision-making can also be restricted in a relation of dependence, which can make a consent invalid.[18]

2.2.1.4 For a specific case

According to the Directive, the declaration must relate to a specific case. That means, that the data and activities in question must be specified as far as their content and extend is concerned. The requirements concerning the degree of specification are higher, the more rights and freedoms of the person concerned are touched.

An abstract consent to the processing of personal data is not possible. From the specific case and the situation must be clear, to which kind of personal data and to which activities the consent relates. This does not mean that the Data Protection Directive makes it impossible to give consent, which is valid for future research (see further under 2.2.2.1).[19] This is of high importance for most studies as it can be difficult for researchers to anticipate all future uses of the data. During the course of a study new areas of interest may be highlighted or novel technologies may arise, which could necessitate further analysis of the data.

2.2.1.5 Informed indication

Finally, the consent has to be given in awareness of the factual situation, which means, it has to be an "informed consent". The Data Protection Directive requires the data processor to inform the person concerned (Art. 10 ff.).

The information to be given to the data subject is at least

- the identity of the controller and of his representative, if any and

- the purposes of the processing for which the data are intended.

Additional information, if necessary, with regard to the specific circumstances could concern 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 and the existence of the right of access to and the right to rectify the data concerning the data subject.

Wrong or incomplete information of the said person by the data processor makes the consent invalid.[20]

2.2.2 Scope of the consent

2.2.2.1 Object of the consent / purpose specification / future research

As stated above, the declaration must relate to a specific case. That means that the data and activities in question must be specified as to their content and extend. The

[18] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 116.
[19] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 115.
[20] Dammann, Ulrich / Simitis, Spiros, EG-Datenschutzrichtlinie, 1997, pp. 116.

requirements concerning the degree of specification are higher, the more rights and freedoms of the person concerned are touched. An abstract consent to the processing of personal data is not possible.

The patient concerned must be informed about the object and the kind of research, which will be conducted with his data. This is the central requirement of all relevant regulations and recommendations concerning medical research. Nevertheless, from this requirement arise most questions concerning the informed consent.

For clinical studies, which usually have a clearly defined purpose, the object for which the consent is given, is obvious.

But when, as in ACGT, the aim of a research project is to set up a database in order to enable various research projects to be performed, the definition of the object is more difficult. Of course, these kinds of projects also focus on a specific area of research. Nevertheless, there is an interest to use the data stored in that database for research purposes, which are not known at the point of time of storage. From this scenario arises the question, of how to define the object of a research project, so that the patient can give an informed consent, which is also valid for future research projects.

An option could be a far reaching definition of "specific case", e.g. medical research including genetic research. In this case, a requirement would be that the person concerned will be informed about the uncertainty of the future use of his/her data. In consequence, this means that an informed consent can also be reached by information about the uncertainty of the future use. The person concerned will be able to keep control about his/her data by the right to revocation and erasure.

Nevertheless, if the object is more specifically defined, e.g. a specific research question or research area, it will more certainly fulfill the generally accepted requirement of the general and appropriate information of the said person about the intended use of his data. But to mention a specific object might result in the situation that, if scientific research later requires an extension of the research question, the extended research object is not covered by the consent.

Therefore, it is recommended to ask the patient concerned for a consent for the specific project in question and further future projects.

In conclusion, the patient concerned should be informed as specifically as possible about the extend in which his personal data will be used. The information can relate to one or more specific research questions or to one or more research areas.

If the object is to set up a database for various research questions, which are maybe not known at the point of time of storage, a more far reaching definition of the object in combinations with a right to erasure would be useful.[21]

The objectives of the ACGT-project are defined as follows:

First, ACGT aims at generating new knowledge with respect to the characterization, classification, prognosis of cancer and prediction of response, since prognostic and predictive markers are different. One of the goals is, to compare the activity of genes in the tumours of patients who responded well to therapy with the activity of genes in the tumours of bad responders.

[21] BMB-Projekt: Ein generisches Datenschutzkonzept für Biomaterialbanken, Version 1.0; April 2006, pp.31-33; Wellbrock, R, Biobanken für die Forschung – Zur Stellungnahme des Nationalen Ethikrates, Datenschutz und Datensicherheit, 2004 (9), pp. 563/564.

Second, it aims at establishing a new, computer based, interconnected infrastructure which helps research groups in different countries to access medical and genomic data from cancer patients and to analyze and compare these data.

Ultimately, the project aims at facilitating data exchange and analysis, and contributing to a more precise description of different cancers, in the moment breast cancer and nephroblastoma.

2.2.2.2 Expected period of usage / temporal scope of the consent

An important principle of data protection legislation is that personal data has to be erased, if it is not necessary anymore for the specified purpose it was collected for. In general, for an informed consent this means, that the said person has to be informed about the point of time of erasure of his personal data. The intended duration of use has to be stated in the consent form.

However, there are no fixed limits on the time of storage to be found in European data protection legislation. As stated above, data protection legislation refers to the necessity of storage for the specified purpose the data was collected for.[22]

For a project aiming at the setting up of a database, the definition of the intended duration of use is naturally more difficult than in the case of a research question with a defined start and end. Also, for a database, a limited time of storage would be counterproductive as many studies rely on the long-term availability of the data.

However, from an ethical point of view, doubts have been raised concerning the applicability of the doctrine of informed consent for future research projects.[23] *Tiered consent* arranging different levels of authorization in the consent procedure is proposed as able to provide an appropriate solution. It 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.[24] 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) may be within the limits of ethical as well as legal considerations. This model also includes the general necessity to ask for reconsent if the scope of consent (clinico-genomic research on cancer/ACGT project) will change and re-identifiable data will be used in further research projects.

The end of the ACGT research project will be around 2010. Due to this temporal limitation in the consent forms, the informed consent given by the patient expires in 2010, because the specified research setting of ACGT is then completed. ACGT is then obliged to ask for reconsent because the scope of consent will change *or* to erase all personal data and to inform the data subject about the erasure.

But the data stored in the ACGT database is de-facto anonymous data. The informed consent relates to personal data. Therefore, when the consent expires, the link between the patient concerned and his/her data, which is needed to inform the patient

[22] Nationaler Ethikrat, Biobanken für die Forschung, 2004, p. 61, http://www.ethikrat.org/themen/pdf/Stellungnahme_Biobanken.pdf

[23] See D10.2, chapter 2.2/Informed consent

[24] See D10.2, paragraph 2.4.1.2/Conclusions: How to design the informed consent process

about research results, has to be erased and the patient has to be informed about the erasure. What remains is a database consisting of anonymous genetic data.

The safeguards set up by ACGT to prevent misuse and de-anonymization of the genetic data will remain in place, e.g. prohibition on publication, no un-encrypted transmission.

The only purpose the ACGT database, now consisting of anonymous data, may be used for after 2010, is research. The only persons allowed to access the database are those partners taking part in ACGT up to 2010, which means, those, who were allowed to access the databases up to 2010. There will be no new partners or third parties, who are allowed to access the database. This conclusion might be different, if there is a legal successor of ACGT, who takes over all its rights and duties. Any transmission and disclosure of the data is forbidden.

2.2.2.3 Death of the patient

Another problem arises in case of the death of the person concerned. Data protection legislation is only applicable to living persons. But in Germany for example the basic right to protection of personal rights has its effects even after the death of the person concerned – with a declining intensity the more time passes after the death of the person concerned.[25] The doctor-patient confidentiality is also extended to the time after the death of the patient by German Criminal Law (§ 203 IV StGB). Therefore a consent, defined purpose or access limitation given by the patient does not become invalid after his death. Relatives, heirs and other third persons can make arrangements in the medical field, if these arrangements comply with the wishes of the person concerned. The right to information might vest to the relatives of the person concerned, as far the information to be collected may be helpful to detect hereditary diseases or to answer questions of descent.[26]

Within ACGT, as stated above, anonymous data will be used. As the informed consent to participate in ACGT given by the patient concerned does not become invalid after his/her death, the anonymous data stored in the ACGT data bases can be stored even after the death of the patient. The question, if the right to erasure of the link can vest to the heir of the person concerned, does not affect the database itself.

2.2.2.4 Data transfer to third parties / third countries

As described in D10.2 genetic data has to be regarded as personal data in case of transfer as the recipient might re-establish the link by using a matching procedure. As ACGT cannot know, whether the recipient has a database to carry out such a matching procedure the privacy of the data subject concerned may be at risk, so that data protection legislation such as the Data Protection Directive 95/46/EC must be applicable in order to provide sufficient protection for the data subjects concerned. Therefore a permission is required if genetic data shall be transferred to third parties. As a statutory permission for the transfer is not available the concerned data subject has to give his or her informed consent for the transfer of his or her genetic data.

[25] BVerfGE 65, 1; BVerfGE 30, 173, 194 „Mephisto“.
[26] Datenschutz Berlin, Stellungnahme zu Fragen der Enquete-Kommission „Recht und Ethik der modernen Medizin vom 19.12.2000, p. 7.

If the recipient is situated in a third country outside of the EU, additional rules and conditions for the transfer apply. They are described in detail in D10.2.

2.2.3 The right to know and the duty of notification

Each patient taking part in ACGT would like to decide whether he wants to get informed about the results of the research that is done with his or her genetic data or not. Therefore it has to be examined whether the patient has a statutory right to know or not to know these results.

According to Art. 12 of the Directive, each data subject has the right to know from the data controller if personal data is processed, for what purposes it is processed, which categories of data are concerned and who the recipient(s) of the data is/are. But this right to know is only guaranteed by the Directive, if the Directive is applicable at all.

As described in D10.2, genetic data within ACGT is pseudonymized twice and has to be regarded as de-facto anonymized data, so that the Directive is not applicable. Therefore, the data subject has no statutory right to know what happens with his or her genetic data within ACGT, as long as the data is not disclosed or transferred, since the quality of the genetic data changes in these cases as described in detail in D10.2. In these cases the genetic data has to be regarded as personal data, so that the data subject concerned might have the right to know the described facts.

Even in these cases, it is questionable whether the data subject has such a statutory right, as Art. 13 para 2 of the Directive states an important exemption. According to that and subject to adequate legal safeguards, Member States may, where there is clearly no risk of breaching the privacy of the data subject, restrict by a legislative measures the rights provided for in Article 12 when data is processed solely for purposes of scientific research or is kept in personal form for a period which does not exceed the period necessary for the sole purpose of creating statistics.

In the ACGT scenario there might be no risk of breaching the privacy of the data subject, as the genetic data is pseudonymized twice and has to be regarded as de-facto anonymous data. But in case of disclosure or transfer of genetic data the risk of breaching the privacy of the data subject cannot be excluded as a recipient might re-establish the link and de-anonymize the genetic data by using a matching procedure. Therefore the exemption stated in Art. 13 para 2 of the Directive is not applicable whenever genetic data is disclosed or transferred, so that the data subject has a statutory right according to Art. 12 to know from the data controller if personal data is processed, for what purposes they are processed, which categories of data are concerned and who the recipient(s) of the data is/are.

But this right does not include a statutory right to get to know the results of the research done with the genetic data of the concerned data subject anyway.[27]

According to Art. 10 no. 2 of the Convention 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 everyone is entitled to know any information collected about his or her health. However, the wishes of individuals not to be

[27] See Antonow, p. 90; Simitis/Dammann, EG-Datenschutzrichtlinie, Art. 12 marginal number 4

so informed shall be observed. In this context genetic data has to be regarded as information about health.[28] But this right only grants access to the collected data or not to be informed about the collected data and not to results of a research, too. That is why this statutory right does not entitle the concerned patient to get to know the results of the research that was done with his or her data.[29]

A right (not) to get to know these results might be developed from the personal rights of the concerned patients.[30] The concerned patient has the right to be informed by the data controller or data processor about his or her genetic disposition.[31] This genetic disposition and the consequences have to be explained to the patient by an expert, so that the patient understands what a particular genetic disposition means for him. As this knowledge might cause harm to the patient, he or she must also have the right not to get to know these results, since the patient as a person must be able to choose what he wants to know about himself or herself and what facts he or she doesn't want to know, as it is granted by the personal rights.

The information procedure must be designed in a way that the researcher cannot re-establish the link of the genetic data, as the genetic data would no longer be de-facto anonymous for the researcher, if he gets to know, that a particular patient would like to be informed about a particular genetic data set with a certain pseudonym. Therefore in ACGT this request would have to be submitted from the patient via his physician either via the Data Protection Board to the Trusted Third Party or directly to the Trusted Third Party. The Trusted Third Party would then have to request the data with the corresponding pseudonym from the researcher or the ACGT database and then provide the results to the patient's physician, who could explain the results to the patient.

One opinion even grants the patient concerned the right to be informed about how the research with the genetic data was done and what means were used for the analysis, as otherwise the researcher would have too much power over the patient as nobody else would be able to verify the analysis.[32] Another argument for that opinion is that Art. 12 lit. a of the Data Protection Directive states the right of the data subject to obtain from the controller the 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).

But this right of knowledge must be limited. The researcher has intellectual property rights regarding the tools and means used for the analysis and therefore, he cannot be forced to publish them just because of that rule.[33] Therefore the concerned patient has no statutory right to be informed about the tools and means used for the analysis of his or her genetic data.

Furthermore, it can be doubted that a patient participating in ACGT has a statutory right of (non) knowledge that can only be concluded from his or her personal rights. As only de-facto anonymous data will be used during the research within ACGT the personal rights may not be applicable in this case.

[28] Antonow, p. 80
[29] Compare Antonow, p. 80
[30] See Weichert, DuD 2002, p. 133 (141), Wellbrock , CR 1989, p. 204 (209)
[31] See for example: Weichert, DuD 2002, p. 133 (141)
[32] Weichert, DuD 2002, p. 133 (142)
[33] See Antonow, p. 90

Therefore a contractual right should guarantee the participating patients in ACGT to get the right to be informed about their genetic disposition. This right should be included in the contract the patient has to conclude with ACGT before entering the trial. Furthermore this right should not only be a pull procedure. ACGT should also inform the patient (if he or she wants that), whenever results are achieved that could be important for the treatment of the patient. The patient would also be granted a right of notification then. So whenever a researcher achieves results from that patients having a certain genetic disposition could benefit, in the ACGT database should be searched for the data sets with that disposition. The Trusted Third Party can then de-anonymize the pseudonymized data and send the results to the particular physician who can inform the participating patient and explain the results to him or her. It is of vital importance for ACGT to guarantee these patient's rights, as a lot of more patients will take part in ACGT in this case. Also for dissemination purposes it must be recommended to grant the participating patients these rights.

2.2.4 Consent of relatives needed?

Another important issue in the context of the informed consent is the problem, who has to consent in case of genetic research. As explained in detail in D10.2 the genetic data contains information not only about the concerned data subject, but also about his or her relatives. Whenever genetic data is examined, information can be gathered about the participating patient him- or herself and also about his or her 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 other words: Who is the data subject of the genetic data?

On the other hand this would make genetic research much more complicated, if the consent from each relative is needed 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.

Art. 2 lit (a) of the Data Protection Directive 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.[34] But this provision must be interpreted restrictively. The consent is only needed of first-grade relatives (such as the parents or children), as only their data sets contain enough similarities to the data set of the patient that their privacy is affected.[35] In all other cases, a consent of the relatives is not needed because of the marginal similarities and the missing

[34] See Weichert, DuD 2002, p. 133 (138)
[35] See Weichert, DuD 2002, p. 133 (138)

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.

This interpretation corresponds also with the Data Protection Directive. 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.

2.2.5 The consent of the minor patient or person under disability needed?

Some data exploited in the ACGT project concern patient who are minor or person under disability and, therefore, represented by their legal representative in the exercise of his rights.

In a lot of countries in Europe, to be more precise in Napoleonic law, the legal representative is empowered to represent the minor or person under disability until he gets his majority (usually at the age of 18).

That means that the legal representation covers the administration of the person and the goods of the minor. In other words, the minor or person under disability can benefit from his rights but cannot exercise them by himself (except with special and legal authorization) but only through his legal representative. It's a general prohibition of exercise.[36]

However, the national law and Courts are beginning to introduce the possibility for the minor, at least, to be associated in the decision concerning his rights. Even, in some matters like medical law (therapeutic or sexual life), he can take the decision by himself without being represented by his legal representative. Those matters must be interpreted

[36] P. – Y. Leleu, Droit des personnes et des familles, Bruxelles, Larcier, 2005, pp. 217 and following.

on a very restrictive way and some time (medical treatment), the appreciation of the minor's capacity to act by himself is in the hands of the medical doctor.

In the ACGT project, we have to pay attention to the fact that the capacity of the minor or person under disability is regulated by the national laws and can be different from one country to another. The general terms and agreement forms will have to be modified in each country to fit the national regulation.

However, we should have a look on the position of the minor or person under disability in the ACGT project. As saying before, the minor can benefit from 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 or person under disability is certainly the data subject from the beginning but his rights (acceptance, withdraw, etc…) will be exercised by his legal representative until he reaches the majority. After reaching this majority or a person under disability getting back the exercise of his rights, he will be empowered to exercise his rights by himself amongst which is the right of withdraw. Asking a new consent from the minor would be a real non sense relating to the concept of the legal representation and hardly feasible for the practitioner.

However, there is no reason to avoid an association of the minor or person under disability to the decision to enter the trial or not. From a legal point of view, it's feasible and won't infringe any regulation.

The World Medical Association 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."[37]

Keeping in mind that this settlement is not constraining, it's a way to involve the minor in his medical life through his association to the consent.

We can consider that, at least, a 14-years old can be considered responsible and mature enough to be associated to the decision. The capacity to understand of a person under disability will be under the physician assessment.

2.2.6 The right to withdraw and right to erasure

Each data subject has the right to withdraw his or her consent. According to Art. 12 lit b of the Directive the stored personal data of the data subject concerned must be erased.

If the data concerned is stored in an anonymized form, it is not personal data anymore, because the link to the patient concerned is not known to the researchers working with the data stored in the database.

[37] WMA 2004, paragraph 25; see also D10.2, 2.2.2.2.3

As recommended in Deliverable D10.2, within ACGT all data is anonymous data. The participating hospitals will transmit pseudonymized patient data to the Trusted Third Party, which will pseudonymize the data it receives for a second time. After this double pseudonymization process, the data will be stored in the databases. For the researchers working with the data, it is anonymous data. The link between the data and the patient, which can transform the de facto anonymous data into personal data is exclusively held by the Trusted Third Party.

When the patient concerned signs the consent form to take part in ACGT, he/she consents to the anonymization and the processing of his/her data.

As within ACGT all data is anonymous, which means, within ACGT, there is no personal data, the patient concerned has no right to erasure of his data. Nevertheless, he has a claim to erasure of the link which is held by the hospital and the Trusted Third Party. But this right does not affect the database itself. Therefore the de-facto anonymous data stored in the ACGT database can still be used for the research within ACGT. But as the concerned patient has withdrawn his or her consent the data must not longer be disclosed or transferred, as for these processing operations an informed consent of the concerned data subject is needed as described in detail in D10.2. The withdrawal of the consent has only future consequences. The processing operations for which a consent is needed and that already took part have still to be regarded as lawful operations. Only the future processing of the concerned data is forbidden when the consent is withdrawn by the data subject and the consent is needed for the lawfulness of the processing.[38] Therefore the transfer and the disclosure of the concerned data would no longer be lawful, whereas all other data processing operations such as the use of the genetic data would still be lawful, as the genetic data within ACGT has to be regarded an anonymous data and no consent is needed for the processing of anonymous data.

The request of withdraw or another exercise of his right will be formulated to his medical doctor of which identity is written in the consent form and will concern the only hospital in charge of the non pseudonymized data. Actually, he is the link between the patient and hospital which is the data controller.

[38] See Ehmann/Helfrich, EG-Datenschutzrichtlinie, Art. 12 marginal number 72 f.

3 GENERAL TERMS

To be as flexible as possible, the suggestion is to create general terms document in a form which can be stored by the contractors.

We must pay attention to the fact that those general terms will have to be translated in the patient's, hospital's, physician's and user's language in respect of the national law of those parties. These general terms constitute a "standard" which correspond to the Directive.

The main purpose of the general terms is to set duties and rights of the parties as the secrets, no use of the data outside of the purpose defined by the project, etc… Then, to achieve this goal of flexibility and to allow new parties (hospital, patient) to integrate the project, it will through an acceptance of the general rules by them through a consent form. It's a way to avoid an important number or "bilateral" contracts. Actually, we have to keep in mind that the ACGT project will grow and include researchers or physicians who are not partner of the project at the present time and will never be part of it (we may believe that this ACGT project will continue over 2010 or another one with the same purpose will be created).

The TTP will be – in cases in which the TTP receives personal data from the hospital/investigator – data controller itself to ensure total independency from both ACGT and the hospital/investigator.

The consequences of this status of data controller is that in these cases the TTP has to respect the duties stipulated by the Directive 95/46/EC.

Even if the TTP can receive anonymous data, the ones transmitted to it are often not. Actually, the TTP receives, most of the time, data directly and without any intermediary organisation from the legal or physical person who knows the identity of the data subject. Therefore, the TTP can indirectly make the link between the data subject and the data. That means that, even if the data are pseudonymized or coded, the TTP can not benefit of the principle of "de facto anonymous data" as ACGT does (see D10.2) in many cases.

However, some possible duties cannot be performed as the information, the access for the data subject, as the consequence of the kind of data processed by the TTP (see above). Let's remind that the TTP doesn't know directly the identity of the patient linked to the data.

GENERAL TERMS

Preamble:

The project "Advancing Clinico-Genomic Clinical Trials on Cancer: Open Grid Services for improving Medical Knowledge Discovery", abbreviated ACGT in this present document, aims at creating clinico-genomic databases on cancer. The ACGT project will start up by collecting data on breast cancer (BRCA) and paediatric nephroblastoma (PN), but it is projected to involve further cancer types in the future.

At run-time of the research project, the data are available to researchers working in the European Union and involved in scientific researches on cancer.

The project ACGT is within the scope of the Directive 95/46 EC of the 24.10.1995 on the protection of individuals with regard to the processing of personal data.

The final purpose of such scientific research is to improve cure and management of future cancer patients by putting together the results of several researches running in Europe.

The database(s) within ACGT will consist of data transferred by the hospital/investigator collected from the patient after having received his or his legal representative's explicit, unambiguous and informed consent. This/those database(s) won't host nothing else than data (excluding, for example, biomaterial)

All the data collected by the hospital/investigator will be pseudonymized by the hospital itself and sent to a trusted third party (TTP) which will pseudonymize the data again. The data can also be pseudonymized through a special and dedicated software provided by this TTP and hosted in the hospital. The key used by the TTP or its software in the pseudonymization process will be kept only by the TTP. That means that the user (researcher) using the data will be unable to identify the patient whom the data refers to. Account is taken of all the means likely reasonably to be used either by the data controller or by the user to identify the patient. The anonymity of the data is coming from the context of use of the data by the user which is guaranteed by ACGT[39] and the TTP.

The TTP will be responsible for the pseudonymization of the data transmitted to ACGT. Its independence from both ACGT and the hospital/investigator will be guaranteed., therefore the cryptographic keys will be kept safely.

The data will be archived for a length no longer than the ACGT project itself or a similar project with the same purpose, finality and objective if the data remain anonymous for the user.

The patient's data are considered as sensitive data.

[39] ACGT grants the user. That's means that there is a previous control of the quality of the user by ACGT.

The data controller is the hospital/investigator where the patient's data is collected in accordance with the Directive 95/46/EC mentioned above.

These general terms will apply to ACGT (as a legal person), patients, physicians, users as researchers and data processor.

Definitions:

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. We assume that most data processed in ACGT is aliased. Aliased data still is “personal data” in the legal sense.

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, we guess 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. Concerning ACGT we assume that the specification of the consent will be critical and might create large databases that have to be managed. 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 (which will be the regular case in the Nephroblastoma-studies), 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 CE, the natural or legal person who alone, or jointly with others, determines the purposes and means of the processing of personal data. It is important to identify who the controller of any processing is, since this 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 Subject

The data subject is the subject of personal data, i.e. an identified or identifiable person about whom the personal data refers. 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.

Hospital

Hospitals are health institutions where patients are treated and their personal data are collected for the purpose of the ACGT project.

Investigator

The legal or natural person who gathers and manages the patient's data from the hospitals, laboratories, etc… and keeps the trial/study database.

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.

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
- control of data media
- memory control
- control of utilization
- access control
- control of communication
- control of data introduction
- control of transport

availability control

Such organizational measures have to be taken by all the ACGT-participants processing personal data.

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.

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 data 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.

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 (genomic data) or sex life. Member States shall prohibit the processing of these data, except in explicitly stated exceptions.

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. In ACGT, the third party will be the other centers of researches, administration, other hospitals, etc…

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 defense of legal claims; or etc… The word "transfer" concerns also the disclosure of the data to a recipient or third person (see those words).

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.

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 of the Directive 95/46/EC).

Patient:

Patient means the concerned sick person and will be considered like the data subject in these general terms.

Legal representative of the patient ("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).

Article 1: Patient's rights

1.1. Information

The patient or his legal representative must be informed, in an intelligible form and fully, before giving his consent.

The information given to the patient or his legal representative will consist (non exhaustive list) in describing and explaining:

- the identity of the data controller;
- the purpose of the processing of his data;
- his rights;
- the security of the data processing;
- the categories of data concerned;
- the recipients or categories of recipients;

The information will be given by the physician. He is considered like the representative of the hospital towards the patient.

1.2. Access

The patient has, directly or through his legal representative, access to the data processed by or on behalf of the data controller.

This access concerns also the right to have the communication:

- in an intelligible form of the data undergoing processing and of any available information as to their source;
- of the identities of the persons who have had access to his/her data and the moment of this access (log file).

The demand of access is addressed to the hospital through the patients´ physician.

This access is free of charge

1.3. Object and withdrawal of consent

The patient or his legal representative has the right to object to the processing and to withdraw his former consent without giving reasons and at any time. In this last case, all the data which have not been pseudonymized yet by the TTP can't be used anymore and the data already pseudonymized by the TTP have to be completely anonymized (the TTP must erase the key used for the pseudonymization).

The exercise of these rights is free of charge.

1.4. Right to rectify

In case of inaccuracy the patient or his legal representative has the right to demand the modification of his data from the data controller through his physician.

The exercise of this right is free of charge.

1.5. In case of death

If the patient dies, his data can be used for research, but the TTP must erase the key used for the pseudonymization.

1.6. Feed back

The patient or his legal representative will receive a feed back from the research regarding his personal data if:

- the feed back is useful to his therapy

and

- he is physically and psychologically able to receive this feed back.

He may refuse this feed back by letter or secured Email sent to his physician which is the representative of the hospital.

Article 2: Patient's obligation

The patient or his legal representative has the obligation to give complete and useful information to the physician.

This obligation of information will be fulfilled by answering a questionnaire given to him by the physician. This questionnaire will permit the physician to know the situation of the patient relating to his health, medical history, etc… which are needed information for the physician in the context of the ACGT's database.

Article 3: ACGT's, hospital/investigator and physician's Rights

ACGT and the hospital/investigator – after having received the agreement of the patient's physician - have the right to withdraw from the project any patient who (non exhaustive list):

- has given false information in the questionnaire mentioned in article 2;
- is subject of pressure from relatives or other third persons;

In this case, all the data from the concerned person will be erased or will be completely anonymized in the same way provided in 3.2 and 3.3. It's the right of ACGT to choose between the alternatives.

ACGT has the right to stop the project of research without motivation or explanation. In this case, all the data will be erased from the ACGT database and no penalty has to be paid from ACGT.

ACGT has the right to exclude a physician, hospital/investigator or user (researcher) from the project in case of violation of the general terms, contracts, agreements or informed consents of ACGT or national and international legislation.

The physician, hospital/investigator or user has the right to quit the program without giving reasons or any explanation and without any payment of penalty. In this case, his/its grant will be stopped and claimed back, if paid in advance.

If the physician quits or has to quit the project the patient, whose data is stored in the hospital, can stay in the project by choosing another physician of the hospital taking part in the project. Otherwise his data will be completely anonymized in the same way provided in 3.2 and 3.3.

Article 4: ACGT's, Hospital/investigator, user, physician's and trusted third party's obligations

The user's access to the ACGT database must be granted by ACGT. The grant can only be given by ACGT.

ACGT is responsible for the security of its database(s) whereas the hospital is responsible for its own database(s) and the processing of the patient's data, the TTP is responsible for the pseudonymization, until the data is stored in the ACGT database(s). ACGT, the TTP and the hospitals/investigator have to ensure confidentiality of the patient's data as long as they are responsible for the data processing.

In order to be in accordance with the Directive 95/46/EC, the hospital/investigator will enter a contract with a Trusted Third Party (TTP), which will be in charge of the pseudonymization of the patients' data before sending them to the ACGT database[40]. The contract will mention that the TTP 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 if 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 sensitive data to be protected.

From the moment the TTP receives pseudonymized data, the processing of those data won't be made 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.

Article 5: Resolution of litigation

This article will, regarding the applicable **national** law, describe the procedure for the settlement of disputes regarding.

Article 6: Applicable legislation

The applicable legislation regarding the contract has to be the **national** law of the patient.

[40] The pseudonymization will be done either by the TTP itself or through a special and dedicated software provided by the TTP and hosted by the hospital.

4 PATIENT INFORMATION SHEET AND CONSENT FORM

To achieve the goal of flexibility underpinning the general terms, it's needed to write consent forms as explained above (point 4).

The different forms will refer explicitly to the general terms form where all the legal terms are explained. The different parties will accept those general terms through these consent forms.

We remind that ACGT will never know the identity of the patient entering on the project for a question of secrecy. Relating to this principle of secrecy, ACGT will never centralize the patient consent form.

On the other hand, ACGT will centralize all the consent forms coming from the hospitals, the physician and the users to trace them and to be able to give to them an access to the ACGT database or deny it.

At the present time, the consent forms are written for a paper support but it will have to migrate to electronic means with electronic signature to be feasible and more compatible with the electronic environment which ACGT is created in.

Attention must be paid to the fact that, in some countries in Europe as in United Kingdom, the person (legal or natural) collecting all the data coming from several hospitals (NHS/university) is the "investigator". Therefore, the consent forms will anticipate this.

We must pay attention to the fact that those consent forms will have to be translated in the patient's, hospital's/investigator's, physician's and user's language in respect of the national law of those parties. These consent forms constitute a "standard" which correspond to the Directive .

Patient information sheet

Explanation of the research project ACGT

(**A**dvancing **C**linico-**G**enomic Clinical **T**rials on Cancer)

1. Invitation:

You are being invited to take part in a clinical research project involving patients with cancer. The study is called ACGT for short. The full name is: “Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery”. It is a European Union funded project (EU number FP6-IST-026996).

This project is designed to create and assess a Europe-wide infrastructure for the conduct of large trials in cancer patients where new tests of the genes in each patient’s cancer are used

to improve treatment. There are new ways of scanning cancers, using magnets (called MRI for short) and nuclear particles (called PET) to improve the detection of early cancers and see if they have spread, and if so to which parts of the body. The information from genes and scans will be combined in a computer programme so that doctors can match each patient to the correct treatment, whether surgery, radiotherapy or new medicines (hormones, antibodies, chemo drugs, and even new vaccines). The development of a suitable computer programme to process all this information is a major aim of this project.

If you decide to take part, you will be asked to provide your data anonymously to this project. Before you make this decision, it is important for you to understand why the research is being done and what it will involve.

This document describes the project in order to help you to make your decision. Please read the information provided carefully and discuss it with others if you wish. Feel free to ask your medical doctor and other members of your healthcare team if there is anything unclear or if you would like more information.

Take time to decide whether or not you wish to take part. You must not feel obliged to participate in this research project. If you do decide to participate, you can withdraw your consent at any time without any disadvantages. Also, if you decide not to volunteer for the project, it will not affect your treatment in any way.

Thank you for reading this.

2. Purpose of the project

ACGT project has two main objectives.

- to develop a way of using mathematics, statistics and high powered computer technology to help doctors decide on treatments, particularly using the new information called “genomics”, which is the study of which genes go wrong in which cancers. The clinical studies considered in ACGT use advanced molecular biology, genetic and scanning techniques before, during and after treatment to study the way each patient’s genes and scans change as a result of a given treatment. In this context, a new, computer-based, network will be developed and assessed. This will help clinicians and researchers throughout cancer hospitals in Europe to share data and knowledge, and to analyze and compare results.

- to improve outcomes of cancer therapy by tailoring each treatment to individual patients. The project itself will not necessarily develop a new specific treatment but the knowledge gained within the project may eventually improve our understanding of which patient is most likely to benefit from it. It will also help to predict cancer prognosis and the chance of the cancer coming back.

ACGT is sponsored by the European Union. The ACGT research consortium consists of 25 cancer hospitals and institutions located in different European countries and working in a variety of disciplines.

The tools and scientific knowledge produced by this project will be publicly available.

3. Why have you been chosen?

You have been chosen because your cancer is one of the types that are being considered in the ACGT project.

ACGT will involve several hundreds of cancer patients. Currently, it targets breast cancer in women and kidney cancer called nephroblastoma in children, and is being carried out at different hospitals in Belgium, Germany, Greece, Italy, and the United Kingdom. It is envisaged that more cancer diseases will be considered and that more hospitals will become involved over the next few years.

4. Do you have to take part?

Your participation to this study is entirely voluntary. If you decide to take part you will be asked to sign a consent form. By signing the consent form, you will confirm that you were properly informed about this project and that all your questions have been answered. A copy of the patient information sheet and of the consent form will be given to you to keep.

If you decide to take part, you are free to withdraw your consent at any time and leave the study without giving any reason. This, or the decision not to take part, will not affect your medical care or the relationship with your medical doctor or medical staff.

5. What will happen to you if you take part?

If you have decided to take part your tumour and/or blood will be analyzed by your medical doctor or medical staff with respect to different characteristics, such as cell types present, characteristics of proteins, and patterns of gene function or malfunction (e.g. gene activity).

These data will be sent to ACGT in an anonymous way for the computer analysis and experiments, and compared with those of other patients which are also processed in an anonymous way (see below).

Since research is being done on blood and tumour samples which have already been collected from you in relation to the clinical trial or study in which you are enrolling, participation in this project does not imply extra visits to the hospital, nor extra examinations.

6. How is your data protected?

The data that will be transmitted to ACGT are your socio-demographic data (sex, age, marital status, number of children, profession, region, etc.), clinical data (type and stage of your cancer as well as other information related to your health and disease), biological data (characteristics of cells and proteins, etc.), and genomic data (for example, data on the genes which are typical of your cancer).

Personal information such as your name or address will never be disclosed to ACGT. Before any data is sent to ACGT, any personal identifiers will be removed by the hospital. This procedure is called pseudonymization.

Before the data can be used for the research purposes described above (see point 1), they will be pseudonymized a second time by a trusted third party. This makes them doubly-anonymous for the scientist of ACGT. The second key will be stored by the trusted third party until the present project is completed, which is at the earliest 2010, but it is likely to be later, or until a follow-up project with the same purpose and objective is completed.

If you decide to withdraw your consent to this project, no more data will be transmitted to ACGT. In this case, the data which have already been sent to ACGT can only be further used if they are anonymized even for your medical doctor or medical staff. In that case, they can no longer be linked back to your person.

7. Will you be informed about the results of the project?

ACGT is aiming to generate a support scaffold or infrastructure for conducting basic and clinical scientific research in cancer. However, the results generated by ACGT are at this stage unlikely to be relevant for the treatment of any individual single patient. Thus, in general you will not be personally informed about the results of the research conducted on you in the context of ACGT. It is of course to be hoped that the results of the ACGT will help improve treatment of future patients who get cancer.

It is possible, albeit unlikely, that research conducted in the context of ACGT may yield results which are of direct relevance for your own treatment or for the prevention of future ailments. If you consent to participating in this project, you may choose whether or not you want to be informed of such results by your medical doctor.

This does not affect your right provided by law to access your processed data and ask for rectification of these data, if any inaccurate information is stored.

8. Risks and benefits of this project:

The data transmitted to ACGT will be extracted from your patient file and the blood and tissue samples which have been collected by your medical doctor or medical staff before diagnosis and during treatment. Therefore, there will not be any extra procedure, examination or visit involving any risk.

Before your data can be used for research, personal information (e.g. name, address, etc.) is disconnected from data identifiers by a two-step procedure which complies with the safety standards requested by law. There is a residual, albeit extremely small risk that these data might be linked back to your person.

You will receive no direct benefit from agreeing to participate in the study. However, the availability of such data for research use is important to the advancement of knowledge about cancer and the future development of new and better treatments for others.

9. Genetic data

Your genetic data also concerns your relatives. In the case that information regarding your close relatives (parents and/or children) would be beneficial to the project, you have to be aware that your physician is allowed to disclose information about you to your relatives exclusively for the purpose of requesting consent from your relatives to the processing of their data in the purpose of the ACGT project.

11. Costs

There will not be any additional costs for you if you decide to participate in the ACGT project.

CONSENT FORM

I, undersigned ……, born on the……, in ……., and living in…….., accept by signing this consent form to take part in the project: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery" (EU number FP6-IST-026996), called ACGT in this document.

(Patient to initial box)

☐ I confirm that I have read and that I understand the patient information sheet (version dated…….).

☐ I confirm that I was given the opportunity to ask my attending physician and the medical staff any questions regarding the ACGT project, the general terms, the information sheet, and the present consent form; and I confirm that I am satisfied with their answers.

☐ I understand that the data controller is the hospital/"the investigator" …….. ……. (please delete as appropriate and introduce the name of the hospital/investigator)and that the supervisory authority reference is…….

☐ I understand that my attending physician, Dr……., is my contact person for all questions that I might have regarding the ACGT project and the use of my rights towards the data controller.

☐ I understand that I am free to decide whether or not to participate in the ACGT project and that refusing to participate will not affect the quality of my medical care or my legal rights.

☐ I understand that I am free to withdraw my consent at any time without giving any reasons and that this will not affect the quality of my medical care or my legal rights.

☐ I understand that I have all the rights described in the general terms form above to access my processed data, correct my processed data, and object to their processing. My requests concerning these rights will be transmitted to the hospital via my attending physician by letter or secured Email.

☐ I understand that this consent form refers to the general terms which are an integral part of the present form, and to European law (namely the Directive 95/46/EC of the 24.10.1995) on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

☐ I understand and I agree that samples from my tumour, blood, tissue and other biological samples will be analysed.

☐ I understand that information about me, about my disease, about genetic tests performed on my tissue samples, and information contained in my medical records will be transferred to ACGT databases which are located in member states of the European Union, and that it will be used for the purposes of the ACGT research project. I understand that to guarantee anonymity of my data two pseudonymization procedures will be undertaken; the

first by the hospital/investigator and the second by a trusted third party (TTP) or through special and dedicated software provided by this TTP and hosted by the hospital/investigator. I understand that the TTP is……..

☐ I understand and agree that, from the moment the TTP receives pseudonymized data, the processing of those data won't be made 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.

☐ I understand that genetic data can not be disconnected from information concerning my close relatives (parents and/or children). Therefore, I allow my physician to disclose information about me for the sole purpose of requesting consent from my close relatives for the processing of their data in the ACGT project. I understand that this will be done only if it is allowed by, and in compliance with, the law of this country.

☐ I **do/do not** agree that DNA material from my tumour, blood, tissue and other biological samples can be analysed using genetic and other tests (delete as appropriate).

☐ I understand that it may be possible, although unlikely, that results from the research conducted in the context of ACGT may be of direct relevance for my treatment or for the prevention of future ailment. I **do / do not** want to be informed of such results by my doctor (delete as appropriate).

☐ I understand that three original copies of this consent form will be produced and will be kept by me, my physician and the hospital respectively.

Name of the patient:……..

Signature of the patient:…….

Date (please date your own signature):……

Patient information sheet (if minor or under disability patient)

Explanation of the research project ACGT

(**A**dvancing **C**linico-**G**enomic Clinical **T**rials on Cancer)

1. Invitation:

You are being invited, as legal representative of the minor or the person under disability mentioned below, to take part in a clinical research project involving patients with cancer. The study is called ACGT for short. The full name is: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery". It is a European Union funded project (EU number FP6-IST-026996). This project is designed to create and assess a Europe-wide infrastructure for the conduct of large trials in cancer patients where new tests of the genes in each patient's cancer are used to improve treatment. There are new ways of scanning cancers, using magnets (called MRI for short) and nuclear particles (called PET) to improve the detection of early cancers and see if they have spread, and if so to which parts of the body. The information from genes and scans will be combined in a computer programme so that doctors can match each patient to the correct treatment, whether surgery, radiotherapy or new medicines (hormones, antibodies, chemo drugs, and even new vaccines). The development of a suitable computer programme to process all this information is a major aim of this project.

If you decide to take part, you will be asked to provide the data of the patient anonymously to this project. Before you make this decision, it is important for you to understand why the research is being done and what it will involve.

This document describes the project in order to help you to make your decision. Please read the information provided carefully and discuss it with others if you wish. Feel free to ask your medical doctor and other members of your healthcare team if there is anything unclear or if you would like more information.

Take time to decide whether or not you wish to take part. You must not feel obliged to participate in this research project. If you do decide to participate, you can withdraw your consent at any time without any disadvantages. Also, if you decide not to volunteer for the project, it will not affect the treatment of the patient in any way.

Thank you for reading this.

2. Purpose of the project

ACGT project has two main objectives.

• to develop a way of using mathematics, statistics and high powered computer technology to help doctors decide on treatments, particularly using the new information called "genomics", which is the study of which genes go wrong in which cancers. The clinical

studies considered in ACGT use advanced molecular biology, genetic and scanning techniques before, during and after treatment to study the way each patient's genes and scans change as a result of a given treatment. In this context, a new, computer-based, network will be developed and assessed. This will help clinicians and researchers throughout cancer hospitals in Europe to share data and knowledge, and to analyze and compare results.

- to improve outcomes of cancer therapy by tailoring each treatment to individual patients. The project itself will not necessarily develop a new specific treatment but the knowledge gained within the project may eventually improve our understanding of which patient is most likely to benefit from it. It will also help to predict cancer prognosis and the chance of the cancer coming back.

ACGT is sponsored by the European Union. The ACGT research consortium consists of 25 cancer hospitals and institutions located in different European countries and working in a variety of disciplines.

The tools and scientific knowledge produced by this project will be publicly available.

3. Why have you been chosen?

You have been chosen because the cancer of the patient is one of the types that are being considered in the ACGT project.

ACGT will involve several hundreds of cancer patients. Currently, it targets breast cancer in women and kidney cancer called nephroblastoma in children, and is being carried out at different hospitals in Belgium, Germany, Greece, Italy, and the United Kingdom. It is envisaged that more cancer diseases will be considered and that more hospitals will become involved over the next few years.

4. Do you have to take part?

Your participation to this study is entirely voluntary. If you decide to take part you will be asked to sign a consent form. By signing the consent form, you will confirm that you were properly informed about this project and that all your questions have been answered. A copy of the patient information sheet and of the consent form will be given to you to keep.

If you decide to take part, you are free to withdraw your consent at any time and leave the study without giving any reason. This, or the decision not to take part, will not affect the provided medical care or the relationship with your medical doctor or medical staff.

5. What will happen to you if you take part?

If you have decided to take part, the tumour and/or blood will be analyzed by your medical doctor or medical staff with respect to different characteristics, such as cell types present, characteristics of proteins, and patterns of gene function or malfunction (e.g. gene activity), genetic testing on DNA.

These data will be sent to ACGT in an anonymous way for the computer analysis and experiments, and compared with those of other patients which are also processed in an anonymous way (see below).

Since research is being done on blood and tumour samples which have already been collected from you in relation to the clinical trial or study in which you are enrolling, participation in this project does not imply extra visits to the hospital, nor extra examinations.

6. How is the data protected?

The data that will be transmitted to ACGT are socio-demographic data (sex, age, marital status, number of children, profession, region, etc.), clinical data (type and stage of your cancer as well as other information related to your health and disease), biological data (characteristics of cells and proteins, etc.), and genomic data (for example, data on the genes which are typical of your cancer).

Personal information such as your name or address will never be disclosed to ACGT. Before any data is sent to ACGT, any personal identifiers will be removed by the hospital/investigator. This procedure is called pseudonymization.

Before the data can be used for the research purposes described above (see point 1), they will be pseudonymized a second time by a trusted third party. This makes them doubly-anonymous for the scientist of ACGT. The key which allows to re-identify you will be stored by the trusted third party until the present project is completed, which is at the earliest 2010, but it is likely to be later, or until a follow-up project with the same purpose and objective is completed.

If you decide to withdraw your consent to this project, no more data will be transmitted to ACGT In this case, the data which have already been sent to ACGT can only be further used if they are anonymized even for your medical doctor or medical staff. In that case, they can no longer be linked back to the patient.

7. Will you be informed about the results of the project?

ACGT is aiming to generate a support scaffold or infrastructure for conducting basic and clinical scientific research in cancer. However, the results generated by ACGT are at this stage unlikely to be relevant for the treatment of any individual single patient. Thus, in general you will not be personally informed about the results of the research conducted on the patient in the context of ACGT. It is of course to be hoped that the results of the ACGT will help improve treatment of future patients who get cancer.

It is possible, albeit unlikely, that research conducted in the context of ACGT may yield results which are of direct relevance for the treatment of the patient or for the prevention of future ailments. If you consent to participating in this project, you may choose whether or not you want to be informed of such results by your medical doctor.

This does not affect your right provided by law to access the processed data and ask for rectification of these data, if any inaccurate information is stored.

9. Risks and benefits of this project:

The data transmitted to ACGT will be extracted from the patient file and the blood and tissue samples which have been collected by your medical doctor or medical staff before diagnosis and during treatment. Therefore, there will not be any extra procedure, examination or visit involving any risk.

Before the data can be used for research, personal information (e.g. name, address, etc.) is disconnected from data identifiers by a two-step procedure which complies with the safety standards requested by law. There is a residual, albeit extremely small risk that these data might be linked back to the patient.

The patient will receive no direct benefit from agreeing to participate in the study. However, the availability of such data for research use is important to the advancement of knowledge about cancer and the future development of new and better treatments for others.

10. Genetic data

The genetic data of the patient also concerns his/her relatives. In the case that information regarding his/her close relatives (parents and/or children) would be beneficial to the project, you have to be aware that your physician is allowed to disclose information about the person concerned to his/her relatives exclusively for the purpose of requesting consent from his/her relatives for the processing of their data.

.11. Costs

There will not be any additional costs for you if you decide to participate in the ACGT project.

CONSENT FORM

I, undersigned ……, born on the……., in ……, and living in…….., as legal representative of ……, born on the……,in……. and living in…….., accept by signing this consent form to take part in the project: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery" (EU number FP6-IST-026996), called ACGT in this document.

(Legal representative of the patient to initial box)

☐ I confirm that I have read and that I understand the patient information sheet (version dated…….).

☐ I confirm that I was given the opportunity to ask the patient's attending physician and the medical staff any questions regarding the ACGT project, the general terms, the information sheet, and the consent form; and I confirm that I am satisfied with their answers.

☐ I understand that the data controller is the hospital/"the investigator" …….. ……. (please delete as appropriate and introduce the name of the hospital/investigator)and that the supervisory authority reference is…….

☐ I understand that the patient's attending physician, Dr……, is my contact person for all questions that I might have regarding the ACGT project and the use of my rights.

☐ I understand that I am free to decide whether or not to participate in the ACGT project and that refusing to participate will not affect the quality of the medical care for the patient or my legal rights.

☐ I understand that I am free to withdraw my consent at any time without giving any reasons and that this will not affect the quality of the medical care for the patient or my legal rights.

☐ I understand that I have all the rights described in the general terms form above to access the processed data, correct the processed data, and object to their processing. My requests concerning these rights will be transmitted to the data controller via my attending physician by letter or secured Email.

☐ I understand that this consent form refers to the general terms form, and to European law (namely the Directive 95/46/EC of the 24.10.1995) on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

☐ I understand and I agree that samples from the patient's tumour, blood, tissue and other biological samples will be analysed.

☐ I understand and I agree that information about the patient, about his/her disease, about genetic and other tests performed on his/her tissue samples, and information contained in his/her medical records will be transferred to ACGT databases which are located in member states of the European Union, and that it will be used for the purposes of the ACGT research project. I understand that to guarantee anonymity of his/her data two pseudonymization procedures will be undertaken; the first by the hospital/investigator and the second by a trusted third party (TTP) or through special and dedicated software provided by this TTP and hosted by the hospital/investigator. I understand that the TTP chosen is……

☐ I understand and agree that, from the moment the TTP receives pseudonymized data, the processing of those data won't be made 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.

☐ I understand that genetic data can not be disconnected from information concerning his/her close relatives (parents and/or children). Therefore, I allow my physician to disclose information about him/her for the sole purpose of requesting consent from his/her close relatives for the processing of their data in the ACGT project.. I understand that this will be done only if it is allowed by, and in compliance with, the law of this country.

☐ I **do/do not** agree that DNA material from the patient's tumour, blood, tissue and other biological samples can be analysed using genetic and other tests (delete as appropriate).

☐ I understand that it may be possible, although unlikely, that results from the research conducted in the context of ACGT may be of direct relevance for the treatment of the patient or for the prevention of future ailment. I **do / do not** want to be informed of such results by my doctor (delete as appropriate).

☐ I understand that three original copies of this consent form will be produced and will be kept by the legal representative of the patient, the physician and the hospital/investigator respectively.

Name of the legal representative of the patient:……..

Signature of the legal representative of the patient:…….

Date (please date your own signature):……

5 Minor's agreement

AGREEMENT

I, undersigned …….. born on the……., in……. and living in……., declare by the present consent form to subscribe to the project: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery" (EU number FP6-IST-026996), called ACGT in this document.

I have read and I understand the information sheet and the general terms, which are part of the present document and I agree to subscribe to the general terms.

I understand that, at the present time, I am represented by my legal representative who is……

I understand that when I will reach the age of majority I won't be represented anymore by my legal representative and I will be legally empowered to exercise all my rights described in the general terms and in the patient consent.

I understand that four original copies of this agreement will be produced and will be kept by me, one of my representative, the physician and the hospital/investigator respectively.

Name of the minor patient:……..

Signature of the minor patient:…….

Date (please date your own signature):……

6 HOSPITAL´S/INVESTIGATOR'S AGREEMENT

AGREEMENT

I, undersigned ……., born on the……,in …… and living in……, declare to be the legal representative of the hospital/investigator …… (the statute giving this power must be annexed).

I subscribe by signing this form to the project: “Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery” (EU number FP6-IST-026996), called ACGT in this document.

I have read, I understand and I agree with the general terms - which are part of this document (version dated……..).

In order to be in accordance with the Directive 95/46/EC, the hospital/invesigator will code or pseudonymize all the data of the patients who take part in the ACGT project. The hospital/investigator will enter into a contractual arrangement with a trusted third party (TTP). The TTP is……

The TTP will be in charge of a second pseudonymization of the patients' data before sending them to the ACGT database. The contract will mention that the TTP 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 if 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 sensitive data to be protected.

I'm aware that the hospital/investigator is in charge of the security of its own database(s) and the processing of the patients' data, including the pseudonymization in the hospital/investigator, until the transmission to the ACGT database(s) via the TTP.

I understand that two original copies of this agreement will be produced and they will be kept by ACGT and the hospital/investigator respectively.

Name of the hospital/investigator legal representative:……..

Signature of the hospital/investigator legal representative:…….

Date (please date your own signature):……

7 PHYSICIAN´S AGREEMENT

AGREEMENT

I, undersigned Dr. ……., born on the……, in …….. and living in ……, declare by the present consent form to subscribe to the project: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery" (EU number FP6-IST-026996), called ACGT in this document.

I have read, I understand and I subscribe to the general terms - which are part of this document (version dated……..).

I agree to be the representative of the hospital/investigator towards the patient or his legal representative. I will provide him with all the information requested and needed. I agree to receive his requests relating to his rights described in the general terms or the Directive 95/46/EC.

I understand that two original copies of this agreement will be produced and will be kept by me and ACGT respectively.

Name of the physician:……..

Signature of the physician:…….

Date (please date your own signature):……

8 USER´S AGREEMENT (Researcher, etc…)

AGREEMENT

I, undersigned ……, born on the……, in…… and living in ……, declare by the present consent form to subscribe to the project: "Advancing Clinico-Genomic Trials on Cancer: Integrated Services Improving Medical Knowledge Discovery" (EU number FP6-IST-026996), called ACGT in this document.

I have read, I understand and I agree to subscribe to the general terms - which part if this document (version dated……..)

I understand that two original copies of this agreement will be produced and will be kept by me and ACGT respectively.

Name of the user:……..

Signature of the user:…….

Date (please date your own signature):……

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