Guidelines on collection, storage and use of children's biological samples

September 2011

INTRODUCTION

The conduct of research in children carries with it the same ethical obligations as research in adults. However, children comprise an especially vulnerable population and must be provided added protection against violation of their individual rights and exposure to undue risks. This situation imposes special considerations when inviting participation in studies, assessing risks and benefits, and ensuring equitable participation and benefits in clinical research (1).
Medical research involving children is an important means of promoting child health and wellbeing and children are unique as a research group.
Several principles have to be considered when a research is carried out on children/minors:

1. research involving children is important for the benefit of all children and should be supported, encouraged and conducted in an ethical manner
2. children are not small adults; they have an additional, unique set of interests
3. research should only be done on children if comparable research on adults could not answer the same question
4. a research procedure which is not intended directly to benefit the child subject is not necessarily either unethical or illegal
5. all proposals involving medical research on children should be submitted to a research ethics committee
6. legally valid consent should be obtained from the child, parent or guardian as appropriate. When parental consent is obtained, the agreement of school age children who take part in research should also be requested by researchers (2).

Paediatric studies that involve genetic research present even more complex challenges to ensure appropriate protection of children and families as research participants. Long-term studies with a genetic component involve collection, retention and use of biological samples and personal information over many years.
The research with biological samples causes a competition between the duty to protect subjects, adequately (from risks, incorrect use of personal information and from other harms) and the necessity of researchers of carrying out their researches and improving the scientific knowledge.

This issue is obviously more intricate when the research with biological samples involves minors who cannot give an informed consent, but only an assent in fact an informed consent can be defined as a decision made by a competent individual, free of any undue influence, on the basis of all relevant information, while an assent means a child's affirmative agreement to participate in research, so children have their whole future ahead of them, but do not have an impact on the direction of development in research and on the use of samples and data. Moreover identifiable genetic data are ethically in a special category, because it can be permanently attached to a person. Use of such data may have long-term consequences years after the data are generated, and they should thus be treated with more care than other types of health data (3), nevertheless, it is essential to consider that research is especially important in relation to children, given the poor evidence base for much paediatrics (4)

Key ethical, legal, and social issues in genetic research studies involving children include: (I) recruitment, especially the scope of parental authority to permit a child to participate in research; (II) the nature of consent sought, particularly the breadth or specificity of initial consent, and subsequent seeking of assent and/or consent from the child; (III) confidentiality and sample/data protection measures; (IV) handling sensitive information (e.g. signs of child abuse); (V) disclosure of results to participants; and (VI) withdrawal from the cohort (5).
Currently, specific laws or directives which regulate the conduction of genetic research in minors are not available, so it is necessary to refer to specific articles of other laws or guidelines; according

to the Article 15 of the Treaty Series No. 195, Human Rights and Biomedicine. Protocol on Biomedical Research (2005)**,** research on a person without the capacity to consent to research may be undertaken only if all the following specific conditions are met:
i. the results of the research have the potential to produce real and direct benefit to his or her health;
ii. research of comparable effectiveness cannot be carried out on individuals capable of giving consent;
iii. the person undergoing research has been informed of his or her rights and the safeguards prescribed by law for his or her protection, unless this person is not in a state to receive the information;
iv. the necessary authorisation has been given specifically and in writing by the legal representative or an authority, person or body provided for by law, and after having received the information required by Article 16, taking into account the person's previously expressed wishes or objections. The opinion of a minor shall be taken into consideration as an increasingly determining factor in proportion to age and degree of maturity;
v. the person concerned does not object.
Exceptionally and under the protective conditions prescribed by law, where the research has not the potential to produce results of direct benefit to the health of the person concerned, such research may be authorised subject to the conditions laid down above, and to the following additional conditions:
i. the research has the aim of contributing, through significant improvement in the scientific understanding of the individual's condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the person concerned or to other persons in the same age category or afflicted with the same disease or disorder or having the same condition;
ii. the research entails only minimal risk and minimal burden for the individual concerned; and any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden.
3. Objection to participation, refusal to give authorisation or the withdrawal of authorisation to participate in research shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care.

The genetic research on minors is justified only if:

- the studied disease is specific of the minors' population or it is intended to benefit the minor and research has been already carried out on adults
- minor's assent must be obtained, moreover that of parents/legal representative's one, every time is possible (6).

KEY POINTS

Genetic research in minors is justified only if the disease is specific of the minor or it is intended to benefit the minor

Parents/legal guardians are responsible of giving the consent for the collection and treatment of their children's biological samples

Minor's assent is required (if available)

PURPOSE AND SCOPE

"*It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects*" (World Medical Association Declaration of Helsinky, Ethical Principles for Medical Research Involving Human Subjects, Seoul October 2008) .

This document has the aim of improving the practical aspects of ethical issue of paediatric research, especially considering the collection, storage and use of minors' biological samples.

These guidelines are intended to be built up according to the following European and National laws, guidelines and regulations (7):

Council of Europe

(L) Convention for the Protection of Human Rights and Dignity of the Human Being with Regard to the Application of Biology and Medicine (1997)
(L) Treaty Series No. 195, Human Rights and Biomedicine. Protocol on Biomedical Research (2005)
(G) Recommendation (2006) 4 on Research on Biological Materials of Human Origin (2006)

European States

France

(G) Ethical Issues Raised by Collections of Biological Materials and Associated Data: 'Biobanks', 'Biolibraries'—National Consultative Bioethics Committee for Health and Life Sciences (2003)

Germany

(G) Biobanks for Research—National Ethics Council Opinion (2004)

Italy

(G) Biobanks and Research on Human Biological Material—National Bioethics Committee Opinion (2006)
(G) Guideline for Clinical Protocols of Genetic Research—Italian Society of Human Genetics (2006)
(G) Guideline for Genetic Biobanks—Telethon (2003) Specific informed consent
(G) Guideline for the Establishment and Accreditation of Biobanks (2006)

Spain

(R) Royal Decree 411/1996, by which Activities Regarding the Use of Human Tissues are Regulated (1996)

United Kingdom

(L) Human Tissue Act (2004)
(G) Human Tissue and Biological Samples for Use in Research—Medical Research Council (2001)

The Netherlands

(L) Civil code, article 467 (1994)
(G) Code for Proper Secondary Use of Human Tissue in The Netherlands (2002)

L: law
G: guideline
R: regulations

Other relevant documents :
International Ethical Guidelines for Biomedical Research Involving Human Subjects Prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization (WHO), 2002.

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects (Seoul, October 2008).

International Declaration on Human Genetic Data (16 October 2003).

The treatment of personal data has to be according to the Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

ICH Topic E 11 Clinical Investigation of Medicinal Products in the Paediatric Population (2001).

Collection of biological samples for research purposes: informed consent. National Committee for Biosafety, Biotechnologies and Life Sciences (2009).

ICH E6(R1) - Good Clinical Practice (1996).

KEY POINT

Purpose: providing specific knowledge and instruments for the correct collection, storage and use of minors' sample according to European Directives, recommendations and documents.

GENERAL RULES

1. Biological samples: identification, collection and use

A biological sample is every biological materials which contains genotipic information of a subject (e.g. blood, tissues, cells, etc.) (8).
The collection of biological samples for specific research is a collection of samples and clinical data. The data of the genetic database have to be linked with the demographic and clinical data of every subjects. Usually, the subject is identified in the databases with a code and not with his/her name, so the person who has access to databases doesn't know the name of the involved person (5).

Identifiability of biological samples
Biological materials may be identifiable or non-identifiable:
i. *Identifiable biological materials* are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code.
In the latter case, the user of the biological materials may either:
a. have access to the code, referred to as "coded materials"; or
b. not have access to the code, which is under the control of a third party: referred to as "linked anonymised materials".

ii. *Non-identifiable biological materials* referred to as "unlinked anonymised materials", are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned.

Collections of biological materials

i. The person and/or institution responsible for the collection should be designated.
ii. The purpose(s) of a collection should be specified. The principles of transparency and accountability should govern its management, including access to and use and transfer of its biological materials and disclosure of information.
iii. Each sample of biological material in the collection should be appropriately documented, including information on any relevant consent or authorisation.
iv. Clear conditions governing access to, and use of, the samples should be established.
v. Quality assurance measures should be in place, including conditions to ensure security and confidentiality during storage and handling of the biological materials.

Use of biological materials in research projects

Research on biological materials should only be undertaken if it is within the scope of the consent given by the person concerned. The person concerned may place restrictions on the use of his or her biological materials**.**

Identifiable biological materials

1. i. If the proposed use of identifiable biological materials in a research project is not within the scope of prior consent, if any, given by the person concerned, reasonable efforts should be made to contact the person in order to obtain consent to the proposed use.
ii. If contacting the person concerned is not possible with reasonable efforts, these biological materials should only be used in the research project subject to independent evaluation of the fulfilment of the following conditions:
a. the research addresses an important scientific interest;
b. the aims of the research could not reasonably be achieved using biological materials for which consent can be obtained; and
c. there is no evidence that the person concerned has expressly opposed such research use.
2. The person concerned may freely refuse consent for the use in a research project of his or her identifiable biological materials, or withdraw consent, at any time. Refusal to give consent or the withdrawal of consent should not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care, or participation to the principal clinical trial.

Unlinked anonymised biological materials

1. Unlinked anonymised biological materials may be used in research provided that such use does not violate any restrictions placed by the person concerned prior to the anonymisation of the materials.
2. Anonymisation should be verified by an appropriate review procedure.

Independent review

1. Research should only be undertaken if the research project has been subject to an independent examination of its scientific merit, including assessment of the importance of the aim of the research, and verification of its ethical acceptability.

KEY POINTS

Biological sample is every biological materials which contains genotipic information of a subject

Identifiable biological materials **are those biological materials which, alone or in combination with associated data, allow the identification of the persons concerned either directly or through the use of a code.**

Non-identifiable biological materials **referred to as "unlinked anonymised materials", are those biological materials which, alone or in combination with associated data, do not allow, with reasonable efforts, the identification of the persons concerned**
The person and/or institution responsible for the collection should be designated.

The purpose(s) of a collection should be specified

SPECIFIC RULES

2. Legitimacy of collecting and using biological materials.

"Legal comparisons between regulations in different countries are laborious and defy generalizations'' (9).
According to the International Ethical Guidelines for Biomedical Research Involving Human Subjects Issues of confidentiality in genetic research (CIOMS, 2002), an investigator who proposes to perform genetic tests of known clinical or predictive value on biological samples that can be linked to an identifiable individual must obtain the informed consent of the individual or, when indicated, the permission of a legally authorized representative. Conversely, before performing a genetic test that is of known predictive value or gives reliable information about a known heritable condition, and individual consent or permission has not been obtained, investigators must see that biological samples are fully anonymized and unlinked; this ensures that no information about specific individuals can be derived from such research or passed back to them.
When biological samples are not fully anonymized and when it is anticipated that there may be valid clinical or research reasons for linking the results of genetic tests to research subjects, the investigator in seeking informed consent should assure prospective subjects that their identity will be protected by secure coding of their samples (encryption) and by restricted access to the database, and explain to them this process.
When it is clear that for medical or possibly research reasons the results of genetic tests will be reported to the subject or to the subject`s physician, the subject should be informed that such disclosure will occur and that the samples to be tested will be clearly labelled.
Investigators should not disclose results of diagnostic genetic tests to relatives of subjects without the subjects` consent. In places where immediate family relatives would usually expect to be informed of such results, the research protocol, as approved or cleared by the ethical review committee, should indicate the precautions in place to prevent such disclosure of results without the subjects`consent; such plans should be clearly explained during the process of obtaining informed consent.

The biological material may be processed only if the subject has given his/her consent.

According to the Declaration of Helsinky some research populations are particularly vulnerable and need special protection. These include those who cannot give or refuse consent for themselves, such as children and adolescents. In fact as a rule, a paediatric subject is legally unable to provide informed consent.
Referring to research informed consent is defined by the Good Clinical Practice (ICH Topic E 6 (R1)) as a process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.
Instead children/adolescents are dependent on their parent(s)/legal guardian to assume responsibility for the use of their data. Fully informed consent should be obtained from the legal guardian in accordance with regional laws or regulations. All participants should be informed to the fullest extent possible about the use of their data in language and terms they are able to understand.
Where appropriate, participants should assent to the use of their data. Participants of appropriate intellectual maturity should personally sign and date either a separately designed, written assent form or the written informed consent.(ICH Topic E 11).
If an adolescent aged 16 to 18 is no longer a minor as defined in national law, or is an "emancipated minor", then written informed consent is required from these individuals as for any adult capable of giving consent. Under these conditions, informed consent is no longer required from the parents/legal representative, although an adolescent is still vulnerable and may require additional discussions and explanations and every effort should be made to understand and respect differences of opinion between the child and his/her parents or legal representative.
Strong and definitive objections from the child should be respected.

So it is important to provide to parents/legal guardian all the information referring the collection and the processing of their children's biological materials.
Minors will be provided all the information referring the collection and processing of their biological materials according to their level of maturity, in order to give their assent.

Consent models designed to appropriately regulate research with biological materials are characterized by a maze of laws, policies and ethical recommendations that range from strict (specific informed consent) to basically unrestricted use (broad consent) (10).
Current literature defines four different types of informed consent referred to the collection of biological materials:

Model of informed consent	**Definition**
Broad consent	Allows the use of biological specimens and related data in immediate and future investigations of any kind at any time
Partially restricted consent	Allows the use of biological specimens and related data in specific immediate research and in future investigations directly or indirectly associated with them
Multi-layered consent	Requires several options to be explained to the research subject in a detail form
Specific informed consent	Allows the use of biological specimens and related data only in immediate research, forbids any future study that is not foreseen at the time

	of the original consent

At the European level, both legislation and ethical recommendations tend towards requiring the consent to be as strict as possible. The Council of Europe (CE), in its Convention for the Protection of Human Rights and Dignity of the Human Being, states that, "consent for using body parts for purposes other than that for which they were originally removed should be appropriate according to national laws", but declares in the Additional Protocol to the Convention that consent for such uses should be specific (CE, 1997, 2005). Similarly, the CE recommendation about research on biological materials of human origin requires specific consent for any foreseen research use and as specific a consent form as possible for unplanned research studies (COE, 2006) (7).

Biological samples of minors may be used for research only if:

- research is directly connected with subject's disease
- parents/legal representative have given a valid informed consent
- risks for subject are irrelevant

Risks may be estimated as minimal, low or high

Minimal (the least possible) risk describes procedures such as questioning, observing, and measuring children, provided that procedures are carried out in a sensitive way, and that consent has been given. Procedures with minimal risk include collecting a single urine sample (but not by aspiration), or using blood from a sample that has been taken as part of treatment.

Low risk describes procedures that cause brief pain or tenderness, and small bruises or scars. Many children fear needles and for them low rather than minimal risks are often incurred by injections and venepuncture.

High risk procedures such as lung or liver biopsy, arterial puncture, and cardiac catheterisation are not justified for research purposes alone. They should be carried out only when research is combined with diagnosis or treatment intended to benefit the child concerned.

That research in which children are submitted to more than minimal risk with only slight, uncertain or no benefit to themselves deserves serious ethical consideration.

The most common example of such research involves blood sampling. Where children are unable to give consent, by reason of insufficient maturity or understanding, their parents or guardians may consent to the taking of blood for non-therapeutic purposes, provided that they have been given and understand a full explanation of the reasons for blood sampling and have balanced its risk to their child. Many children fear needles, but with careful explanation of the reason for venepuncture and an understanding of the effectiveness of local anaesthetic cream, they often show altruism and allow a blood sample to be taken. This has to be the child's decision. It is completely inappropriate to insist on the taking of blood for nontherapeutic reasons if a child indicates either significant unwillingness before the start or significant stress during the procedure.

Despite careful selection, children in clinical trials have social and emotional problems that are mainly unpredictable. Provision for necessary, continuing, emotional support should be built into the research design (11).

KEY POINTS

Minor is legally unable to provide informed consent

Informed consent must be written, signed and dated by both parents/ legal guardian

Minor should assent for the use of their biological materials from the intellectual age of 7 years

Assent means the acceptance of an approach or action that is offered without a full and comprehensive exploration of the alternatives and it is given by a person who may not be fully capable of consent but may be clear about his or her wishes

Strong and definitive objections from the child should be respected

3. Security of biological materials

No norms have been issued by the European Union (like a Directive) regulating the use of human biological samples in *scientific research*.
It has been argued that genetic data are different from other health data, because they have some unique characteristics that make them require specific ethical and legal treatments (this position is known as genetic exceptionalism (12).
In 2004, the European Commission published a document with 25 recommendations on ethical, legal and social implications of genetic testing. It stated that "genetic exceptionalism should be avoided internationally, in the context of the EU, and at the level of its Member States. However, the public perception that genetic testing is different needs to be acknowledged and addressed; all medical data, including genetic data, must satisfy equally high standards of quality and confidentiality".

In this sense, the UNESCO Declaration on genetic data establishes that genetic data have a special status because:
(i) they can be predictive of genetic predispositions concerning individuals;
(ii) they may have a significant impact on the family, including offspring, extending over generations, and in some instances on the whole group to which the person concerned belongs;
(iii) they may contain information the significance of which is not necessarily known at the time of the collection of the biological samples;
(iv) they may have cultural significance for persons or groups.

The genetic information or biological sample that it is necessary to protect is the one linked to an identified or an identifiable subject (for example, when all identifying information about that person is replaced by a code, but that identity could be known by some procedure).
The threat of violations of privacy and non-discrimination rights disappears only when the data cannot be linked to an identifiable person through the destruction of the link to any identifying information.

For genetic information and biological samples have to be followed the same rules expected for personal data. So according to the Directive 95/46/EC :
the controller must implement appropriate technical and organizational measures to protect genetic information and biological against accidental or unlawful destruction or accidental loss, alteration, unauthorized disclosure or access, in particular where the processing involves the transmission of data over a network, and against all other unlawful forms of processing.
Having regard to the state of the art and the cost of their implementation, such measures shall ensure a level of security appropriate to the risks represented by the processing and the nature of the data to be protected**.**

Appropriate security measures must be taken against unauthorised access to, or alteration, disclosure or destruction of, the data and biological sample and against their accidental loss or destruction. The security of personal information is all-important, but the key word here is appropriate, in that it is more significant in some situations than in others, depending on such matters as confidentiality and sensitivity and the harm that might result from an unauthorised disclosure.
High standards of security are, nevertheless, essential for all personal information. The nature of security used may take into account what is available technologically, the cost of implementation and the sensitivity of the data in question. (13).

KEY POINTS

Genetic data and biological samples have to be protected according to the Directive 95/46/EC
A minimum standard of security would include the following:

- **access to laboratories to be restricted in a secure location to a limited number of staff with appropriate procedures for the accompaniment of any non-authorised staff;**
- **access to any genetic data and biological samples within an organisation to be restricted to authorised staff on a 'need-to-know' basis in accordance with a defined policy;**
- **access to computer systems should be password protected with other factors of authentication as appropriate to the sensitivity of the information;**
- **information on computer screens and manual files to be kept hidden;**
- **all reasonable measures to be taken to ensure that staff are made aware of the organisation's security measures, and comply with them;**
- **all waste papers, printouts, etc. to be disposed of carefully;**
- **a designated person should be responsible for security and for periodic reviews of the measures and practices in place.**

4. Rights of Data subject

At an international level, especially at an European level, essential information for the subject/patient that has to be registered for the documentation of the consent/dissent are: the willingness to participate, the possible transfer of the samples to another laboratory, or to another different group of research, the possibility or not of knowing the results of the research (the absence of this possibility is present when the analysis of the genetic materials don't have a clinic significance), the possible consequences of the results of the research for the subject and his/her relatives, the possibility to anonymise the data and to codify the data, the methods used for protecting personal data, the possibility for the subject to withdraw, in every moment, the consent, the destiny of the sample at the end of the research, the possibility for the subject to receive diagnostic/ therapeutic benefits from the research.

KEY POINTS

Main features of informed consent for research with biological samples:
1) the collection and storage of biological samples may be done only if the subject gives a free an informed consent (except for legal reasons)

2) the collection of biological sample has to be done for specific and explicit purposes, unless the sample is anonymous

3) it is necessary to indicate the period of storage

4) in the possibility of commercial exploitation of the research it necessary to inform the subject and to explain him/her that he/she doesn't have any rights on them.

* Adolescent aged 16 to 18 is no longer a minor as defined in national law, or is an "emancipated minor", then written informed consent is required from these individuals as for any adult capable of giving consent. (ICH E11)
** excluding the cases for which
processing is necessary for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller or in a third party to whom the data are disclosed; or processing is necessary for the purposes of the legitimate interests pursued by the controller or by the third party or parties to whom the data are disclosed, except where such interests are overridden by the interests for fundamental rights and freedoms of the data subject which require protection.

Appendix 1

ASPECTS TO CONSIDER FOR WRITING A GENETIC RESEARCH'S PROTOCOL:

1. RESEARCH'S RATIONALE: has been the rationale of the genetic research elucidated?
2. OBJECTIVES OF THE RESEARCH: are sufficiently clarified the objectives of the research? Have been clarified the possible future results of the research at the scientific, clinical and social level (if applicable)?
3. DESIGN OF THE STUDY: is the design of the study correct?
4. POPULATION: NUMBER AND FEATURES: are the number and the features of the population sufficient?
5. INFORMATION ABOUT THE PLANNED GENETIC ANALYSIS: have been the genetic analysis clarified?
6. BIOLOGICAL SAMPLES: have been clarified:
    - method of collection
    - type of identification
    - period of storage
    - planned uses for the samples
    - destiny of the samples after the planned period for their storage
    - guarantee of safe storage
    - opportunity for the subject of requesting the destruction of the sample (except for the anonymous sample) and opportunity for the sample to be mailed to other laboratories and that it is guaranteed the same protection described in the protocol and in the informed consent
7. CONFIDENTIALITY OF INFORMATION: is correctly described the guarantee of privacy? In the eventuality of not anomymous data, is it clearly explained who, in the different phases, is responsible of the treatment and the handling of data? Is it explained which are the people who have access to data?
8. METHODOLOGY FOR THE WITHDRAWAL OF THE CONSENT: has been clarified the right of the subject to withdraw from the study and the subsequent hereafter of the sample and of obtained information?
9. RESULTS OF THE RESEARCH, PERSONAL AND GLOBAL RESULTS:
    - has been explained whether the results of the research will be useful for the subject's health?
    - has been explained whether the subject may have the results of the research (even if doesn't useful for his/her health, except when the results are unlinked anonymised)?
    - is the dissemination of the genetic results of the subject in accordance with the protection of the subject's health and of his/her privacy?

Appendix 2

ASPECTS TO CONSIDER FOR WRITNG A GENETIC RESEARCH'S INFORMED CONSENT:

OBJECTIVES OF THE RESEARCH: is the objective of the research clear and understandable?

WILLINGNESS TO PARTECIPATE: is it clear the right for the subject not to participate and to withdraw from the research? In the eventuality the samples are unlinked anonymised, have been clarified the consequences of the withdrawal from the study?

WHAT IS REQUESTED TO PARTECIPATE: have been clarified the procedures of the research? Has been described the scientific or moral value of the participation? In the eventuality the study involves also the family of the subject, have been explained the probable implications for his/her family?

BIOLOGICAL SAMPLES: COLLECTION, USES AND STORAGE: has been explained the methodology for the samples' collection? Has been explained what will be done with the sample?
Has been guaranteed that the samples will be used only for the uses described in the consent?
Has been described how the sample is directly linked with the subject (identifiability) and the consequences for the subject?
Has been explained how long samples will be collected and what will be done at the end of the collection? Has been clarified that the subject may ask the destruction of the sample?
Has been clarified that the sample may be sent to other laboratories? In this eventuality, has been described in the consent the guarantee of protection of the subject and of the sample?

POTENTIAL RISKS AND DISCOMFORTS: have been described the possible risks which may arrive from the dissemination of the genetic information outside and the methodologies used for protecting the confidentiality of information? Has been clarified the possible risks for their relatives?

INDIVIDUAL DIRECT BENEFITS OR BENEFITS FOR THE COMMUNITY: has been clarified which are the possible benefits for the subject? Has been clarified the possible benefits for the community?

CONFIDENTIALITY OF THE INFORMATION: has been clarified who may and in which conditions it will be possible to connect the link between data and subject?
Has been explained who, except for the subject, may have the individual results? If the data are not anonymous, is it clear who, in the different phases of the research, will be the responsible of the handling of data? Has been requested the permission for their handling?

METHOD FOR THE WITHDRAWAL OF THE SUBJECT'S CONSENT: has been explained the right of the subject to withdraw from the study and the subsequent hereafter of samples and of obtained information? In the eventuality the unlinked anonymised, has been clarified which are the consequences of the withdrawal from the study and about the destruction of the sample?

RESEARCH'S RESULTS, GLOBAL AND INDIVIDUAL RESULTS: has been explained if the results of the research could be useful for the subject's health?
Has been explained that the subject, after requesting, may have its results (even if not useful for his/her health, except the condition in which the data are unlinked anonymised)?
Is it clear which other people may have the individual results of the subject (e.g. investigator of the study, relatives….)?
The dissemination of the individual genetic results of the subject is coherent with the protection of the health of the subject and of his/her privacy?

COMMERCIAL USES: has been explained the possibility for the commercial exploitation of the results and the rights of the subject?

References

1. Savita Malhotra & Subodh B.N. Informed consent & ethical issues in paediatric psychopharmacology. *Indian J Med Res* 129, January 2009, pp 19-32.
2. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2000 82: 177-182.
3. D F Merlo, L E Knudsen, K Matusiewicz, L Niebrój, K H Vähäkangas. Ethics in studies on children and environmental health. *J Med Ethics* 2007; 33:408–413.
4. A Dawson, S. A. Spencer. Informing children and parents about research. *Arch Dis Child* 2005; 90:233-235.
5. Nola M Ries, Jane LeGrandeur, and Timothy Caulfield. Handling ethical, legal and social issues in birth cohort studies involving genetic research: responses from studies in six countries. *BMC Med Ethics*. 2010; 11: 4.
6. Linee Guida per i protocolli clinici di Ricerca Genetica Raccomandazioni per la realizzazione e la valutazione dei protocolli di ricerca clinica in campo genetico. Fondazione Smith Kline e Società Italiana di Genetica Umana (2006).
7. Elena Salvaterra, Lucilla Lecchi, Silvia Giovanelli, Barbara Butti, Maria Teresa Bardella, Pier Alberto Bertazzi, Silvano Bosari, Guido Coggi, Domenico A. Coviello, Faustina Lalatta, Maurizio Moggio, Mario Nosotti, Alberto Zanella & Paolo Rebulla. Banking together. A unified model of informed consent for biobanking. EMBO Rep . 2008 Apr;9(4):307-13.
8. Autorizzazione al trattamento dei dati genetici - 22 febbraio 2007. Gazzetta Ufficiale n. 65 del 19 marzo 2007
9. Knoppers, B. M. (2005). Biobanking: international norms. Journal of Law, Medicine & Ethics, 33(1), 7–14.
10. Boggio A, Adorno NB, Bernice E, Mauron A, Capron AM Comparing Guidelines on Biobanks: Emerging Consensus and Unresolved Controversies. Geneva, Switzerland: Réseau Universitaire International de Genève (2007).
11. Royal College of Paediatrics and Child Health: Ethics Advisory Committee. Guidelines for the ethical conduct of medical research involving children. *Arch Dis Child* 2000 82: 177-182
12. Michael J. Green and Jeffrey R. Botkin. "Genetic Exceptionalism" in Medicine: Clarifying the Differences between Genetic and Nongenetic Tests. Ann Intern Med. 2003;138:571-575.
13. Pilar Nicolás. Ethical and juridical issues of genetic testing: A review of the international regulation. Critical Reviews in Oncology/Hematology 69 (2009) 98–107.