



Additional Protocol to the Convention on Human Rights and Biomedicine, concerning Biomedical Research

(CETS No. 195)

Français

Explanatory Report

Introduction

1. This Additional Protocol to the Convention on Human Rights and Biomedicine on Biomedical Research builds on the principles embodied in the Convention, with a view to protecting human rights and dignity in the specific field of biomedical research. The benefits for human health of the acquisition of knowledge from research utilising systematic methodologies in the sphere of biomedicine are widely acknowledged. The distinction between medical research and innovative medical practice derives from the intent behind the intervention. In medical practice the sole intention is to benefit the individual patient, not to gain knowledge of general benefit, though such knowledge may emerge from the clinical experience gained. In an intervention for the purpose of biomedical research the primary intention is to advance knowledge so that patients in general may benefit. An individual research participant may or may not benefit directly.

2. The purpose of the Protocol is to define and safeguard fundamental rights in the field of biomedical research, in particular of those participating in research. Biomedical research is a powerful tool to improve human health. Freedom of research is important in and of itself, but also because of the practical benefits it brings to the healthcare field. At the same time, it is always necessary to protect human beings participating in research. Research participants are contributing their time to the research and may be subjecting themselves to risks and burdens. Particular attention must be paid to ensuring that their human rights are always protected and their altruism is not exploited.

Drafting of the Protocol

3. In Recommendation 1160 in 1991, the Council of Europe Parliamentary Assembly recommended that the Committee of Ministers "envisage a framework convention comprising a main text with general principles and additional protocols on specific aspects." Also in 1991, the Committee of Ministers instructed the CAHBI (*ad hoc* Committee of Experts on Bioethics), re-designated the CDBI in 1992 (Steering Committee on Bioethics) "to prepare,Protocols to this Convention, relating to, in a preliminary phase: organ transplants and the use of substances of human origin; medical research on human beings." The Additional Protocol was drafted with the inclusion of the relevant provisions of the Convention concerning biomedical research. This was done to facilitate its use by practitioners in the field of biomedical research, avoiding the need for them to consult a number of interlinked legal instruments.

4. At its 14th meeting (Strasbourg, 5-8 November 1991) the CAHBI appointed the Working Party on Medical Research, responsible for preparing the draft Additional Protocol. The CAHBI-CO-GT2 chaired by Ms. Paula KOKKONEN (Finland), held its first meeting from 22 to 24 January 1992 beginning its activities concurrently with the CDBI's work on the Convention. It was later re-designated as the CDBI-CO-GT2.

5. However, as the CDBI focused its efforts on the preparation of the Convention itself, work on the draft Protocol was suspended after its second meeting from September 1992 until April 1997.

6. The Convention on Human Rights and Biomedicine was adopted by the Committee of Ministers on 19 November 1996 and was opened for signature on 4 April 1997 in Oviedo, Spain. The CDBI decided, at its 11th meeting in June 1996, to renew the terms of reference of the CDBI-CO-GT2 asking it to take into account the newest advances in the field. The Working

Party was then chaired by Dr. Rosemary BOOTHMAN (Ireland).

7. The draft Protocol was examined by the CDBI at its December 2000 and June 2001 meetings, and was declassified by the CDBI at its June 2001 meeting under the Chairmanship of Dr. Elaine GADD (United Kingdom) for the purposes of consultation. Those consulted, including member States and relevant European non-governmental organisations have contributed to the development of the text. After re-examination, the CDBI finalised the text of the Protocol during its meeting from 17 to 20 June 2003. The Protocol was approved by the CDBI on 20 June 2003 under the chairmanship of Mrs. Ruth REUSSER (Switzerland). The Parliamentary Assembly gave an opinion on the Protocol, Opinion No. 252 (2004) on 30 April 2004, Mrs. Majléne Westerlund PANKE being the rapporteur for the Committee on Culture, Science and Education, and Mr. Claude EVIN and Mr. József GEDEI being the co-rapporteurs for the Committee on Social, Health and Family Affairs, and the Committee on Legal Affairs and Human Rights, respectively. The Protocol was adopted by the Committee of Ministers on 30 June 2004.

The Protocol is accompanied by this Explanatory Report, drawn up under the responsibility of the Secretary General of the Council of Europe. It takes into account the discussions held in the CDBI and its Working Party entrusted with the drafting of the Protocol; it also takes into account the remarks and proposals made by delegations. The Committee of Ministers has authorised its publication on 30 June 2004. The Explanatory Report is not an authoritative interpretation of the Protocol. Nevertheless it covers the main issues of the preparatory work and provides information to clarify the object and purpose of the Protocol and make the scope of its provisions more comprehensible.

Comments on the provisions of the Protocol

Title

8. The title identifies this instrument as the "Additional Protocol to the Convention on Human Rights and Biomedicine, on Biomedical Research."

9. The term "biomedical research" is used in order to be consistent with the Convention (Convention for the Protection of Human Rights and Dignity of the Human Being with regard to the Application of Biology and Medicine) and in order to stress that the Protocol covers all areas of research involving interventions on human beings in the field of biomedicine, which may also be carried out by biologists and other professionals such as psychologists.

Preamble

10. Protection and guarantees in the fields of biology and medicine, including biomedical research, are provided by 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), hereafter the "Convention".

11. After the Protocol on the prohibition of cloning human beings and the Protocol concerning transplantation of organs and tissues of human origin, this Additional Protocol on biomedical research supplements further the provisions of the Convention. The Protocols are designed to address the ethical and legal issues raised by present or future scientific advances through the further development, in specific fields such as biomedical research, of the principles contained in the Convention. The preamble to this Protocol reaffirms the aims of the Council of Europe and the Convention. It recognises the role of progress in medical and biological sciences and the contribution that it has made to reducing morbidity and mortality and improving the quality of life. It also takes due regard of the previous work of the Committee of Ministers and the Parliamentary Assembly concerning biomedical research and this has been taken into account in the preparation of this Additional Protocol.

12. The preamble affirms the commitment of the Parties to take necessary measures to safeguard human dignity and the fundamental rights and freedoms of human beings with regard to biomedical research. It highlights some of the fundamental principles that underlie that commitment:

- biomedical research shall never be carried out contrary to human dignity;
- the protection of the human being must always be of paramount concern;

- every person has a right to accept or refuse to undergo biomedical research and no one shall be forced to participate; and
- particular protection shall be given to human beings vulnerable in the context of biomedical research.

CHAPTER I – Object and scope

Article 1 (Object and purpose)

13. This article specifies that the object of the Protocol is to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity and other fundamental rights and freedoms with regard to any research in the field of biomedicine involving interventions on human beings. Research should not be carried out in a manner, which, owing to its aim, nature or realisation, would infringe human dignity. It closely follows the approach of Article 1 in the Convention, narrowing its application to a research context. The Convention does not define the term "everyone" (in French "toute personne"). These two terms are equivalent and found in the English and French versions of the European Convention on Human Rights, which however does not define them. In the absence of a unanimous agreement on the definition of these terms among member States of the Council of Europe, it was decided to allow domestic law to define them for the purposes of the application of the Convention on Human Rights and Biomedicine. The Convention also uses the expression "human being" to state the necessity to protect the dignity and identity of all human beings. It was acknowledged that it was a generally accepted principle that human dignity and the identity of the human being had to be respected as soon as life began.

Article 2 (Scope)

14. The scope of the Protocol is set out in this article.

15. In paragraph 1, it states that the Protocol covers the full range of research activities in the health field involving interventions on human beings. This includes all aspects of the research project from start to finish, including selection and recruitment of the participants. It lays out the principles for all types of biomedical research involving interventions on human beings. It is difficult to exactly delimit the health field. The Protocol covers research into molecular, cellular and other mechanisms in health, disorders and disease; and diagnostic, therapeutic, preventive and epidemiological studies involving interventions. This list is not meant to be exhaustive. Insofar as a human being is involved in research, this Protocol applies, notwithstanding the fact that provisions of other protocols could apply to research in specific spheres.

16. The scope of the Protocol does not extend to studies whose purpose is not to gain new scientific knowledge but to collect or to process information for purely statistical purposes such as for audits or monitoring of the healthcare system.

17. Paragraph 3 states that, for the purposes of this Protocol, the term "intervention" covers physical interventions. It covers other interventions in so far as they involve a risk to the psychological health of the person concerned. The term "intervention" must be understood here in a broad sense; in the context of this Protocol it includes all medical acts and interactions relating to the health or well being of persons in the framework of health care systems or any other setting for scientific research purposes. The Protocol covers all interventions performed for the purposes of research in the fields of preventive care, diagnosis, treatment, or rehabilitation. The Protocol merely follows the definition of intervention used by the Convention, applying it here to the specific field of biomedical research. Questionnaires, interviews and observational research taking place in the context of a biomedical research protocol constitute interventions when they involve a risk to the psychological health of the person concerned. Questionnaires or interviews could carry a risk to the psychological health of the research participant, if they include questions of an intimate nature capable of resulting in psychological harm. In this context, slight and temporary emotional distress would not be regarded as psychological harm. However, such questionnaires could be related to enquiries into sexual history or to certain psychiatric disorders. Studies in the field of genetics that involve probing into past and family medical histories are another example of sensitive areas of research. Small groups of patients with rare genetic diseases or patients with discernible, and sometimes sensitive, social markers in an individual or group context could be particularly at risk of discrimination or stigmatisation. Such risk may exist even if the data is anonymised because the group to which the source belongs to is still identifiable. This potential would have to be

evaluated. Member States would be able to choose the criteria for making this distinction. A possible method of doing so would be by the development of guidelines as to the type of questionnaires, interviews and observations which have this potential. It should not be forgotten that even observation, questions or interviews could be profoundly troubling to a patient if they address a sensitive sphere of that person's private life, such as a previous or current illness. One ramification of defining such research as coming within the scope of this Protocol is that it would be reviewed by an ethics committee, which could point out any potential problems in the research project. The Protocol does not address established medical interventions independent of a research project, even if they result in biological materials or personal data that might later be used in biomedical research. However, research interventions designed to procure biological materials or data are covered under this Protocol.

18. This Protocol does not address research on the body or body parts of deceased persons.

19. Research on fetuses and embryos *in vivo*, and pregnant women is covered by the Protocol. As women should not be excluded from the protections envisaged by the Protocol by virtue of the fact they are pregnant, and the impact on the embryo or foetus must always be considered when research is undertaken on such women, it is therefore necessary for both to be covered by this Protocol. However, research on embryos *in vitro* is excluded, this type of research being covered by Article 18 of the Convention. The CAHBI decided at its 15th meeting (24-27 March 1992, Madrid) to exclude the embryo from the draft Protocol on Medical Research. It was foreseen that this type of research would be addressed in another Protocol on the protection of the human embryo and foetus. This Protocol does not address research on archived biological materials or personal data. However, this does not necessarily exclude biomedical research based on archived personal data or biological materials from submission to an ethics committee. The Protocol was not prepared with the intention of regulating interventions to collect biological materials which would be stored for future research, for instance in biobanks.

CHAPTER II – General provisions

Article 3 (Primacy of the human being)

20. This article affirms the primacy of the human being participating in research over the sole interest of science or society. Priority is given to the former and this must as a matter of principle take precedence over the latter in the event of a conflict between them.

21. The whole Additional Protocol, the aim of which is to protect human rights and dignity, is inspired by the principle of the primacy of the human being, and all its Articles must be interpreted in this light.

Article 4 (General rule)

22. Freedom of biomedical research is justified not only by humanity's right to knowledge, but also by the considerable progress its results may bring in terms of the health and well-being of patients and the general population.

23. Nevertheless, such freedom is not absolute. In biomedical research it is limited by the fundamental rights of individuals expressed, in particular, by the provisions of the Additional Protocol and the Convention and by other legal provisions that protect the human being. In this regard, it should be noted that the first Article of the Protocol specifies that its aim is to protect the dignity and identity of all human beings and guarantee everyone, without discrimination, respect for their integrity as well as for other fundamental rights and freedoms with regard to any research involving interventions on human beings in the field of biomedicine.

Article 5 (Absence of alternatives)

24. The Article sets out the requirement that research on human beings can only be undertaken if there is no alternative of comparable effectiveness. Comparable effectiveness refers to the foreseen results of the research, not to individual benefits for a participant. Invasive methods will not be authorised if other less invasive or non-invasive methods can be used with comparable effect. Consequently, research on human beings will not be allowed if comparable results can be obtained by other means unless this is clearly unreasonable. Such alternatives include computer modelling or research on animals. This does not imply that the Protocol authorises using alternatives that are unethical. The Protocol does not evaluate the

ethical acceptability of research on animals or other alternatives. These matters are addressed by other legal instruments, such as the Council of Europe Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (ETS No. 123), national law and professional obligations and standards.

Article 6 (Risks and benefits)

25. The principle that research shall not involve risk and burden disproportionate to its potential benefits is set out in this article. When medical research may be of direct benefit to the health of the person undergoing research, a higher degree of risk and burden may be acceptable provided that it is in proportion to the possible benefit. For example, a higher degree of risk and burden may be acceptable on a new treatment for advanced cancer, whereas the same risk and burden would be quite unacceptable where the aim is to improve the treatment of a mild infection. The notions of risk and burden include not only physical risks and burdens but also social or psychological risks to the participant. A direct benefit to a person's health signifies not only treatment to cure the patient but also treatment that may alleviate his/her suffering thus improving his/her quality of life. However, it must be noted that benefits referred to in this article include not only direct benefits but also the benefits of the research to science or society. This is particularly relevant in the case of research that has not the potential to produce results of direct benefit for the health of the person concerned. It should be recalled that such research may entail, for a person able to consent, only acceptable risk and acceptable burden for the person concerned.

26. An individual may choose to take part in research a number of times or regularly, provided that continued participation in research does not endanger the participant's health.

27. The Article also addresses the participation in research of persons who are able to consent but who would gain no potential direct benefit from the research. This category includes all non-therapeutic research, including that on the so-called "healthy volunteers." The Article sets out the additional preconditions for this type of research. Whether or not the risk and burden are acceptable will be considered carefully by the ethics committee and competent body that approves the research project. The final decision on whether or not the risk and burden are acceptable will be made by the persons concerned when they decide to give or withhold consent. Because these participants are able to consent to research, the level of risk and burden permitted (acceptable) is higher than that allowed for persons not able to consent (minimal risk and minimal burden).

Article 7 (Approval)

28. Article 16 of the Convention sets out the conditions that must be met before research on a person may be undertaken, and includes the condition that the research project has been approved by the competent body after independent examination of its scientific merit, including assessment of the importance of the aim of the research, and multidisciplinary review of its ethical acceptability. This article of the Protocol sets out the requirements for such approval. It is acknowledged that in some countries, the ethics committee could also act as the competent body while in other cases or in other countries, the competent body might be a Ministry or a regulatory agency (for pharmaceuticals, for instance), which would take the opinion of the ethics committee into account. Research must comply with the relevant legal requirements. The Article does not set out a specific procedure or sequence for the submission of research projects to the relevant bodies.

29. This provision does not contradict the principle of freedom of research. In fact, Article 4 of this Protocol states that biomedical research shall be carried out freely. However, this freedom is not absolute. It is qualified by the legal provisions ensuring the protection of the human being. Independent examination of the ethical acceptability of the research project by an ethics committee, and the approval of that project is one such protective provisions. Allowing unethical research to utilise human beings would contravene their fundamental rights. It is the responsibility of Parties to designate within the framework of their legal system the ethics committee or a different competent body as the decision making organ in order to protect the participants taking part in the research.

30. The relevance of the research to the health needs of the local community may be relevant to the ethical assessment of a research project. In most cases, such relevance, along with the fulfilment of the other conditions, will be a factor in a positive opinion on the research project by an ethics committee and approval by the competent body. However, this does not mean

that only research that is relevant to local health needs can be approved. The example may be given of a phase of research undertaken in an urban European setting where the results may be of relevance to a cure for a tropical disease; especially where the research would involve volunteers capable of giving consent, there should be no strict prohibition on participating in such research out of solidarity. However, the aim of considering this issue is to prevent the "export" of research in order to avoid stringent ethical standards or in order to find volunteers in another country when they cannot be found in the country where the research would be relevant to local health needs.

Article 8 (Scientific quality)

31. This article applies to all researchers in the biomedical field, including doctors and other healthcare professionals. It is understood that researchers engaging in biomedical research may also be biologists, psychologists, computer experts, medical students or members of other professions outside of the health care field (sociologists, educationalists etc.). The requirement of supervision by an appropriately qualified researcher makes it clear that the suitability of the person supervising must be assessed in relation to the particular project concerned. It is intended not to foreclose on the possibility of students, for example, being part of a biomedical research team as long as their work is supervised by an appropriately qualified researcher.

32. The term "research" must be understood here as corresponding to the scope set out in Article 2.

33. All research must be carried out in accordance with the law in general, as supplemented and developed by professional standards.

34. The current state of the art of scientific knowledge and clinical experience determines the professional standards and skill to be expected of professionals in the performance of research. In following the progress of biology and medicine, it changes with new developments and eliminates methods that do not reflect the state of the art. Nevertheless, it is accepted that professional standards do not necessarily prescribe one line of action as being the only one possible or foreclose research seeking to improve or replace an intervention.

35. Furthermore, in cases where the research has the possibility of producing a real and direct benefit for the health of a research participant, a particular course of action must be judged in the light of the participant's specific health problem.

36. In particular, an intervention must meet criteria of relevance and proportionality between the aim pursued and the means employed. This is particularly relevant in the case of research that does not have the potential of producing a real and direct benefit for the health of a research participant. The issue of proportionality is addressed specifically in Article 6 of this Protocol.

37. The Article states that research must be scientifically justified and meet generally accepted criteria of scientific quality. This would ordinarily be done by independent peer review or scientific advisors. The assessment of scientific quality will in particular take into account the appropriateness of the research design, the objectives of the research, the technical feasibility, statistical methods (including sample size calculation where relevant), and the potential for reaching valid conclusions with the smallest possible number of research participants. It has to be recognised that there may be different types of research projects requiring their own kind of assessment, e.g. a study to develop new methods or a pilot study proving the suitability of a project, which may include tools such as questionnaires. The scientific design of such a study has to be appropriate in respect to its limited aim, e.g. only to derive a statistically based tendency or probability, so that a subsequent study to prove or refute a scientific hypothesis could be justified. However, for a study to be able to reach valid conclusions, there must be a sufficient number of participants to demonstrate, for example, that there is a statistically significant difference between the outcome for the group of patients who

received a new drug treatment compared to those who received standard treatment. It is considered that research that does not meet these criteria is, by definition, unethical and should not be approved by the ethics committee or competent body reviewing the research. The participation of persons in research of sub-standard scientific quality is not considered permissible. Scientific quality must be present in the project before its approval and throughout the implementation of the research.

CHAPTER III – Ethics committee

Article 9 (Independent examination by an ethics committee)

38. The Article requires that all research projects within the scope of this Protocol be submitted for independent examination of their scientific merit and ethical acceptability in each State in which any research activity is to take place. This may include States from which research participants are to be recruited for research physically carried out in another State. Best practice is to also submit research projects to an ethics committee in every research location within each State. Although each committee will reach an independent view on the appropriateness of carrying out the research in that particular location, it is acceptable for such committees to endorse the conclusions of one “lead” ethics committee within that State on the science and ethics of the research project.

39. Due to the differing systems in use in various States, the Article refers to ethics committees. It is considered that this term covers ethics committees or other bodies authorised to review biomedical research involving interventions on human beings. In many States this would refer to a multidisciplinary ethics committee but review by a scientific committee might also be required. The Article does not require a positive assessment by the ethics committee being that the role of such bodies or committees in many States is advisory. The conclusion of this assessment may have legal force in some jurisdictions while in others it serves to advise the competent body (for example, a regulatory body) which will rule on the commencement of the research project.

40. The second paragraph sets out the purpose of the multidisciplinary examination after the precondition of scientific quality has been met. This purpose, in accordance with the aim of the Convention and Protocol to protect the dignity and identity of all human beings, is to protect the dignity, rights, safety and well being of the research participants. If participants are to be included during the reproductive stage of their lives, care should be taken, within the framework of the ethics committee opinion, that if the research project could have an impact on reproductive health or on a future child (for example, in a project concerning the use of a new drug, the effect of which on an unborn child is not known) the duty of the researcher to provide birth control advice, is fulfilled. Both paragraphs 1 and 2 of this article refer to the examination of the “ethical acceptability” of the research project. The requirement for multidisciplinary review of the ethical acceptability of research projects was first set out in the Convention’s Article 16, indent iii, and a number of the provisions of this Protocol develop this principle by establishing more precise rules.

41. Further, the second paragraph of the Article states that the assessment of the ethical acceptability shall draw on an appropriate range of expertise and experience adequately reflecting professional and lay views. This combination of different types of expertise, experience, and viewpoints gives an ethics committee its multidisciplinary character, though the specific competences to be included may differ, for example in accordance with the type of research to be reviewed. The existence of an independent ethics committee ensures that the interests and concerns of the community are represented, and the participation of laypersons is important in ensuring that the public can have confidence in the system for oversight of biomedical research. Such laypersons will be neither healthcare professionals nor have experience in carrying out biomedical research. The fact that a person is an expert in an unrelated field, such as engineering or accountancy, does not preclude a person from being able to express lay views within the meaning of this article. Thus this paragraph further details what is meant by the term “multidisciplinary” In order to satisfy the spirit of the requirement of multidisciplinary, thought should also be given to gender and cultural balance in the bodies carrying out the assessment. In creating this body, the nature of the projects that are likely to be presented for review should also be taken into account. The ethics committee may need to invite experts to assist it in evaluating a project from a specific sphere of biomedicine. It may be appropriate for ethics committees to consult with patients’ organisations familiar with a particular condition and/or situation.

42. Paragraph 3 requires that after the multidisciplinary review of the ethical acceptability of a research project, the ethics committee give clearly stated reasons for its positive or negative conclusions. This is a general principle of administrative law. Whether the reasoning and conclusions are further considered by the competent body in granting or denying approval, or they are regarded as the final say on the research project, the basis for the conclusion should be clearly comprehensible both to specialists in the field and to laypersons. Clear reasoning and

conclusions are also necessary if an appeals process is provided for.

Article 10 (Independence of the ethics committee)

43. The Article first addresses the independence of the ethics committee on the group level. Parties to the Protocol shall take measures to assure the operational independence of their ethics committees, ensuring that they are not subject to undue external influences to come to a specific conclusion.

44. Next, in the second paragraph, the article addresses the independence of the individuals making up the ethics committee. It requires members to declare any direct or indirect conflicts of interest related to submitted research projects and requires that members with such conflicts shall not participate in the discussion and decision making related to the project in question. A conflict arises when a person's judgement concerning a primary interest, such as scientific knowledge, could be unduly influenced by secondary interests, which may include financial gain, personal advancement, or personal, family, academic or political interests. It is not inherently unethical to find oneself in a position of conflict of interest; what is required is to recognise the fact and deal with it appropriately. Potential conflicts of interest, as well as the perception of the existence of such conflicts, may be as important as actual conflicts, to the point that they may affect the credibility of ethical review.

45. The independence of the ethics committee as a whole and its individual members may be reinforced by provision of insurance for the ethics committee and its members for civil liability. Such insurance could be particularly important for lay members, who would not be covered by insurance that might already cover the participation of employees of universities or research institutes or medical professionals.

Article 11 (Information for the ethics committee)

46. The Article requires that all information that is necessary to the ethical assessment of the research project must be submitted in written form to the ethics committee. This information is necessary for the proper evaluation of biomedical research projects by the entrusted committee in order to protect the dignity, rights, safety and well-being of those participating.

47. The Article states that, in so far as it is relevant for the research project, the information listed in the Appendix shall be provided. The Appendix is an integral part of the Protocol. It is noted that, in conformity with paragraph 2 of this article, amendments to the items of information found in the Appendix can be made if adopted by a two-thirds majority of the Committee foreseen by Article 32 of the Convention. These amendments will enter into force following their adoption.

Appendix

48. Indent i of the Appendix to this article requires submission of the name of the principal researcher. In the case of there being a single researcher, that person is logically the principal researcher. In cases of multiple researchers being involved, this would be the responsible researcher to whom the collaborators report. The other researchers should provide information on issues related to the research project to the principal researcher, who will usually maintain contacts with the ethics committee regarding the project. However, all the researchers are responsible for the implementation of the research project, particularly concerning safety and ethical issues.

49. The information required in indent ii is necessary in order to prevent the unethical utilisation of human beings in research that unnecessarily duplicates research or which is otherwise scientifically inadequate. The latest state of scientific knowledge may include the results of any previous relevant studies on human beings or animals, meta-analyses and systematic reviews.

50. Indent iii requires that information on the methods and procedures envisaged be provided to the ethics committee. Chemical substances to be used in a research project are one example of an item of information that could be relevant to the review of the project.

51. Indent iv, which requires the submission of a comprehensive summary of the research project in lay language, underscores the trend in member States to have more and more lay representation in their ethics committees. If the lay representatives are to be able to effectively fulfil their role on the committee, they require sufficient information in a form that is

comprehensible to them to enable them to reach an informed opinion. Lay language will also contribute to the transparency concerning the project.

52. Indent v requires the submission of a statement of previous and concurrent submissions of the research project to one or more ethics committees and, if any, the outcome of those submissions as known at the time of the submission of this project. Nevertheless, if after submission of the research project relevant and important points arise in another ethical review, they should be communicated to the ethics committee. The ethics committee reviewing the research project may then seek further information if any doubts are or have been raised about the ethical acceptability of the research project. This might include concerns that the proponents of the project might be engaging in "forum shopping" (i.e. looking for a venue to accept a research project considered unethical in other jurisdictions). At the same time, the possibility of appeal or a different review should not be discounted entirely, as a previous or concurrent decision might be based on local conditions or culture, or even have been capricious. Such appeals should take place within a previously agreed framework for appeals.

53. Indent vii requires that the ethics committee be informed of the criteria for inclusion or exclusion of any categories of persons and how they are to be selected and recruited. This is both to protect against the inappropriate inclusion of categories of persons in research, such as carrying out research on persons unable to consent which could be carried out on persons able to consent, as well as to protect against the deliberate exclusion of categories of persons from research to whom the research itself or the end product could be beneficial. Examples could be exclusion due to gender or age. Particular care should be taken with respect to persons during the reproductive stage of their lives, and to the possible negative impact on an embryo or foetus.

54. Indent viii asks for the reasons for the use or absence of control groups. This is often essential to ensure the scientific validity of the research project, particularly in most therapeutic research. Treatment is considered to include preventive and diagnostic procedures. As required by Article 23, those in control groups should receive a proven method of prevention, diagnosis or treatment. The use of a placebo is justified if there is no method of proven effectiveness or where withdrawal or withholding of such methods will not expose participants to unacceptable risk or burden.

55. Indent xii refers to timing of the information in the sense of it being essential that the information be provided prior to the consent procedure, as well as to a period of time for reflection that should be given to the potential participant in order to take his/her decision on whether to give consent.

56. Indent xiii specifies that documentation to be used to seek consent or authorisation be submitted. The ethics committee should also be informed of the procedure to be used to obtain consent. This would include information on procedures to seek authorisation in emergency situations in order to ensure protection of persons in such a situation.

57. Indent xv requires researchers to inform the ethics committee of arrangements foreseen for information that might be relevant to the present or future health of potential research participants and their family members. Research may uncover information that would warn participants of a health risk or otherwise be of assistance to them in planning their healthcare or lifestyles. Article 27 of this Protocol sets out the requirement that conclusions of research of relevance to the current or future health or quality of life of participants must be offered to them. The ethics committee should be informed if foreseen anonymisation of data would prevent the transmission of such relevant information. Individuals have the right not to receive such communications if they so wish. Best practice requires that the wish of the participant to know or not to know should be established prior to commencement of the research. Because proper counselling and other healthcare assistance may be necessary to explain the nature of the results and the options available to the participant, the foreseen provision of such assistance should also be described to the ethics committee.

58. Indent xvi addresses payments and rewards to be made to participants, researchers or institutions in the context of the research project. Such information is important to ethics committees in the interests of transparency and for proper evaluation of the research project. For example, unusually large payments or rewards might influence decisions on the risks that participants are willing to undertake, and could influence the behaviour of researchers in regard to such risks.

59. Indent xviii addresses two sets of issues: further potential uses of research results that are already foreseen by the researchers, and foreseen further uses that may be based on biological materials or personal data from a research intervention being archived after the intervention and then utilised later.

60. Indent xx requires the submission of information on any insurance or indemnity to cover damage arising in the context of the research project. This provision does not require that such arrangements exist but that the ethics committee be informed whether such insurance or indemnity exists or not. Many jurisdictions require the existence of such arrangements while some ethics committees will not approve certain types of research without arrangements for insurance and compensation.

61. The final paragraph of the Appendix makes clear that even if all the other information required by the article has been provided the ethics committee is not precluded from requesting additional information if it regards it as necessary for proper evaluation of the research project.

Article 12 (Undue influence)

62. The first sentence of this article requires the ethics committee assessing the ethical acceptability of a research project to satisfy themselves that no undue influence, including that of a financial nature, will be exerted on persons to encourage participation in research. The usual legal concept of undue influence involves coercion. The coercion need not involve confinement or violence. It may be exerted in particular on a person in a weak or feeble condition, so that very little pressure will overbear the person's will, and make the individual feel that he or she must agree, although it is not the individual's wish to do so. Payments made to research participants are not prohibited by the Protocol but are subject to the scrutiny of the ethics committee.

63. This understanding of undue influence may also be relevant to situations where one party is in a position of trust toward another and may therefore exercise influence on the latter. Such situations may occur where there is a doctor/patient relationship and the doctor is also the researcher. In such cases, having a neutral third person ask for consent or receive the answer regarding participation in the research has been identified as best practice.

64. If any compensation to the research participants, and where appropriate their representatives, is provided, it would not be considered undue influence if it is appropriate to the burden and inconvenience. However, compensation should not be provided at a level that might encourage participants to take risks that they would not otherwise find acceptable. This should be evaluated by the ethics committee. Reimbursement for any expenses or financial loss shall not be regarded as undue influence. While it is permissible to compensate research participants for expenses or lost time, it is not permissible to pay them to accept a higher level of risk than would otherwise be the case. While financial gain is mentioned, the Article does not exclude consideration of other types of undue influence. For example, it would be inappropriate to suggest to potential employees that their promotion prospects or continued employment depended on participating in research; or that the grades a university student might receive could depend on whether or not they participated in research. Other types of undue influence could include limiting or increasing access to medical care.

65. If the ethics committee is not satisfied that undue influence, broadly defined to include inducements such as those mentioned above, is not being exerted on potential participants of a research project then the project should not receive a positive assessment unless changes are made to address the problem.

66. The second sentence lays out the principle that particular attention must be given to dependent persons and vulnerable persons to ensure that they will not be subjected to undue influence.

67. Dependent persons are those whose decision on participation in a research project may be influenced by their reliance on those who may be offering them the possibility of participation in the research. Such persons could be those deprived of their liberty, recipients of health care dependent on their health care provider for continued care, medical or other students, those in military service, health care workers (particularly those in junior positions) or employees to give just a few examples.

68. It can be said that all human beings enrolled in research are vulnerable to harm, since

research, by definition, involves uncertainty and the utilisation of human beings in order to further the goal of gathering knowledge. However, some human beings may be more vulnerable than others to the risk of being treated unethically in the context of biomedical research. This can be true even in the case of participants who have given their informed consent to taking part in the research project.

69. Human beings asked to take part in research can be classified as being vulnerable due to cognitive, situational, institutional, deferential, medical, economic, and social factors. Persons with cognitive vulnerability may not have the capacity to come to an informed decision on whether to give consent or not. Such persons might be minors or persons suffering from dementia. Persons with situational vulnerability may have the capacity to make a decision, but are deprived of their ability to exercise their capacity by the situation at hand (for example during an emergency or due to a lack of fluency in the language being used to inform and request the consent). Persons subject to institutional vulnerability could be individuals with full cognitive capacity to consent, but who find themselves subject to the authority of persons or bodies who could have their own, and possibly conflicting, interests in relation to a research project. Examples of those subject to this type of vulnerability could be persons fulfilling their service in the military or other uniformed services, prisoners or medical students. Persons subject to institutional vulnerability could also be described as being dependent. Deferential vulnerability is similar to institutional vulnerability, but in contrast to institutional vulnerability, it is characterised by informal, rather than formal, hierarchies. These hierarchies can be based on social frameworks or on subjective deference to the opinion of a family member. It could also be the deference of a patient to the wishes (perceived or real) of his/her physician. Medical vulnerability affects

those suffering from ailments for which there is no satisfactory standard treatment. This type of patient may be vulnerable to exploitation by someone promising him/her a "miracle cure." Economic vulnerability affects those with the cognitive ability to consent to participation but who might easily be induced to take part in research in order to obtain a financial gain or in order not to lose access to some benefits, even if they would not otherwise participate in the research. Social vulnerability arises from the position of certain groups in a given society. Such groups may be stereotyped, may have been historically discriminated against, may have recently arrived in the community, may not speak the language, and may be economically disadvantaged (like the economically vulnerable). Economic, social and educational disadvantage may be more prevalent in some regions or States than in others. In this respect, attention shall be paid to the requirements of Article 29 regarding research in States not party to this Protocol. As the last example shows, membership of these groups can be overlapping.

70. Other examples of undue influence could be in the form of veiled threats to deny access to services to which the person would otherwise be entitled, the insinuation of looking favourably on academic work to be submitted in the future, veiled threats of punishment that the person would otherwise receive or that refusal will diminish the likelihood of career advancement, or the offer of amounts of money large enough to influence the giving or denial of consent.

CHAPTER IV – Information and consent

Article 13 (Information for research participants)

71. This article states that persons being asked to participate in a research project shall be given adequate information in a comprehensible form on the purpose, the overall plan and the possible risks and benefits. The opinion of the ethics committee shall be included. The specific information that potential participants in research are to receive where it is relevant is listed in this article. Information on the risks involved in the intervention or in alternative courses of action must cover not only the risks inherent in the type of intervention contemplated, but also any risks related to the individual characteristics of each participant, such as age or the presence of other disorders or conditions. Requests for additional information made by potential participants must be answered as fully as possible. The Article does not require that the information be given to the research participant by a specific person. This should be determined by the nature of the research, the needs of the potential participant, national practice and/or law.

72. Moreover, this information must be sufficiently clear and comprehensible to the person who is to take part in the research. The potential participant must be put in a position, through the use of terms he or she can understand, to reach a valid judgement on the necessity and usefulness of the aim and methods of the research intervention, both in relation to the

individual and in relation to others who might benefit, weighing these against any risks or burden it may impose. The information should be provided in a way to make it understandable taking into account the level of knowledge, education and psychological state of the potential participant, be this a patient or a healthy volunteer. Additionally, the information given must be documented, meaning it must be recorded. Whenever possible, the information should be given to the potential participant in its documented form, such as in writing or in the form of a video, a tape, or CD-ROM. Where necessary, the information should be provided in a different language appropriate to a participant/group of participants or in a form appropriate to those with sensory disabilities. It may sometimes be impossible to provide the participant with comprehensible written information because he or she is illiterate. In such cases, the information should be explained to the potential participant and be documented for record keeping purposes and in order to provide it to the potential participant if he/she so wishes. The use of audio tapes and videos can be helpful in imparting information to people who are illiterate. The potential participant should be given sufficient time to review the information, consider his/her participation, and consult with others. Although information listed in the article should be offered to all participants, if the person concerned wishes not to receive detailed information on any area this should be respected so long as he or she has received sufficient information to enable informed consent to be given. The wish of a participant not to receive certain information should be recorded.

73. The second paragraph of the article refers to the "opinion" of the ethics committee. While the conclusion of the ethics committee is referred to as an opinion because it is advisory in many countries, it is considered that this term also includes positive or negative opinions (or decisions) of a binding nature in those countries whose law envisions this. In those States that allow for an appeal of an ethics committee opinion, "opinion" refers to both the initial opinion rendered and the opinion resulting from the appeal.

74. Indent vii requires the researcher to disclose to the potential participant any foreseen commercial use of data, research results or biological materials to be obtained from the potential participant during, or prior to, the research. The requirement in this indent does not reflect any endorsement or condemnation of research conducted with commercial applications in mind. Rather, it acknowledges the fact that the motivation for participation in biomedical research for many persons may be out of solidarity, and information on foreseen commercial uses of their contribution to the research may be important to them in making a decision on whether to take part or not. Additionally, recital 26 of Directive 98/44/EC of the European Parliament and of the Council of 6 July 1998 on the legal protection of biotechnological inventions states that, "whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law."

75. The third paragraph requires that in addition, the persons being asked to participate in a research project shall be informed of the rights and safeguards prescribed by law for their protection, and specifically of their right to refuse consent or to withdraw consent at any time without being subject to any form of discrimination, in particular regarding the right to medical care.

Article 14 (Consent)

76. The Article lays out the requirements for consent to participation in research involving interventions on persons. It affirms at the international level an already well-established rule, which is that no one may, as a matter of principle, be forced to participate in research involving an intervention on him or her without his or her consent. This rule emphasises the autonomy of research participants in their relationship with researchers and health care professionals and states that paternalistic approaches that might ignore their wishes are unacceptable.

77. The person's consent is considered to be free and informed if it is given on the basis of objective information from the responsible researcher or other responsible person as to the nature and potential consequences of the planned intervention or its alternatives, in the absence of pressure from anyone which is of such a degree that the patient is no longer able to make an independent choice. As well as the information that must be provided to the participant about the particular research project, it is also good practice to inform the person of any possible alternatives. The second paragraph states that refusal to participate in research shall not prejudice the right of the individual to receive medical care. Any downgrading of the

medical care offered to an individual because of his/her refusal to participate in research would constitute undue influence on the decision of whether to consent.

78. For their consent to be valid, the persons in question must have been informed about the relevant facts regarding the intervention being contemplated. This information must include the purpose, nature and consequences of the intervention and the possible risks involved. Although the research use of biological materials which have been previously removed in the course of a clinical intervention are beyond the scope of this Protocol, it should be noted that if there is an intention to utilise biological materials or personal data obtained during a medical intervention for research purposes after the medical intervention, it is good practice for specific consent to be obtained for such research uses not related to the medical intervention.

79. This article requires consent to be informed, free, express, specific and documented. Express consent may be either verbal or written as long as it is documented. Best practice demands that written consent be obtained, except in exceptional circumstances.

80. Freedom of consent implies that consent may be withdrawn at any time and that the decision of the person concerned shall be respected once he or she has been fully informed of the consequences. This principle is laid out in sentence 2 of paragraph 1. Paragraph 2 adds that such a decision shall not lead to any form of discrimination against the person concerned, in particular regarding the right to medical care. The participant cannot be held liable for any consequences of withdrawal, particularly of a financial nature. The participant should not be required to give a reason for withdrawal. Any obligation arising out of the mere fact of withdrawal would be contrary to the right to withdraw consent. This principle does not mean that the withdrawal of a patient's consent must be acted on immediately if, for example, the abrupt discontinuation of a course of therapy could be hazardous to the patient. In such cases, the doctor or other healthcare professional has an obligation to explain to the participant the risks of discontinuing the study concerned, and to seek consent to continue in the study or for treatment as explained in paragraph 38 of the Explanatory Report to the Convention.

81. Paragraph 3 of this article requires arrangements to be put into place to verify whether a potential research participant has the capacity to give informed consent, if the capacity of the person is in doubt. Such persons may be those who have not been declared incapable of giving consent by a legal body, but whose capacity to give consent may be questionable due to an accident or due to a persistent or worsening condition, for instance. The aim of this paragraph is not to set out any particular arrangement for verification, but to require that such procedures exist. The arrangements would not necessarily be in the framework of the courts; they could be developed and implemented through professional standards. In such cases, the researcher is responsible for verifying that the participants from whom he obtains consent have the capacity to give the consent. Information on arrangements for such verification in the context of a specific research project should be submitted to the ethics committee reviewing the project.

CHAPTER V – Protection of persons not able to consent to research

Article 15 (Protection of persons not able to consent to research)

Paragraph 1

82. The Article sets out the requirements governing the participation in research of persons not able to consent. Paragraph 1, indent i establishes a principle with regard to research on a person who is not able to consent: that the research must be potentially beneficial to the health of the person concerned. The benefit must be real and follow from the potential results of the research, and the risk must not be disproportionate to the potential benefit.

83. Moreover, to allow such research, indent ii sets out the principle that there should be no alternative individual with full capacity. It is not sufficient that there should be no volunteers with the capacity to consent. Recourse to research on persons not able to consent must be, scientifically, the sole possibility. This will apply, for instance, to research aimed at improving the understanding of development in children or improving the understanding of diseases affecting these people specifically, such as infant diseases or certain psychiatric disorders such as dementia in adults. Such research can only be carried out, respectively, on children or the adults concerned.

84. Indent iii sets out the requirement that the persons have been informed of their rights and the safeguards prescribed by law for their protection, unless the person is not in a state to

receive the information. The indent uses the term "not in a state to receive the information" because there may be cases where a person cannot perceive or comprehend the information because of his/her condition. An example would be the case of someone in a coma.

85. Protection of the person not able to consent is also strengthened by the requirement that the necessary authorisation as provided for under indent iv of this article (and Article 6 of the Convention) be given specifically and in writing. Indent iv further states that previously expressed wishes or objections shall be taken into account. Advance directives are not referred to in the Article, but are recognised as a possible way of clarifying a person's wishes. As specified in Article 6, paragraph 5 of the Convention, such authorisation may be freely withdrawn at any time.

86. Indent v sets out the requirement that the research must not be carried out if the person concerned objects. In the case of infants or very young children, it is necessary to evaluate their attitude taking account of their age and maturity. The rule prohibiting the carrying out of the research against the wish of the person reflects concern, in research, for the autonomy and dignity of the person in all circumstances, even if the person is considered legally incapable of giving consent. Objections may be expressed by non-verbal means. The opinion of the caregiver, when there is one, should be taken into account in interpreting the wishes of those unable to express themselves. This provision is also a means of guaranteeing that the burden of the research is acceptable to the person at all times.

Paragraph 2

87. Paragraph 2 provides exceptionally, under the protective conditions prescribed by domestic law, for the possibility of waiving the direct benefit rule on certain very strict conditions. Were such research to be banned altogether, progress in the battles to maintain and improve health and to combat diseases only afflicting children, mentally disabled persons or persons suffering from senile dementia would become impossible. It is the aim of such research to benefit persons in those groups through a better understanding of the factors which will help to maintain and improve health and well being or through a better understanding of disease processes.

88. As well as the general conditions applicable to research on persons not able to consent, a certain number of supplementary conditions must be fulfilled. In this way the Protocol and Convention enable persons in these categories to enjoy the benefits of science in the fight against disease, while guaranteeing the individual protection of the person who undergoes the research. The required conditions imply that:

- in order to obtain the necessary results for the patient group concerned, there is neither an alternative method of comparable effectiveness to research on humans, nor the possibility of research of comparable effectiveness on individuals capable of giving informed consent;
- the research has the aim of contributing to the ultimate attainment of results capable of conferring a 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, through significant improvements in the scientific understanding of the individual's condition, disease or disorder;
- the research entails only minimal risk and minimal burden for the individual concerned (addressed by Article 17 – Interventions with minimal risk and minimal burden);
- the research project not only has scientific merit but is also ethically and legally acceptable and has been given prior approval by the competent bodies;
- the person's representative or an authority or a person or body provided for by law has given authorisation (adequate representation of the interests of the patient);
- the person concerned does not object (the wish of the person concerned prevails and is always decisive);
- authorisation for this research may be withdrawn at any phase of the research.

89. One of the two supplementary conditions is that this research should have the aim of

contributing, through significant improvement in the scientific understanding of a person's health condition, disease or disorder, to the ultimate attainment of results capable of conferring benefit to the health of the person undergoing research or the health of persons in the same category. This means, for example, that a minor may participate in research on a condition from which he or she suffers even if the minor would not benefit by the results of the research, provided that the research might be of benefit to other children suffering from the same condition. In the case of healthy minors undergoing research it is obvious that the result of the research might be of benefit only to other children; however such research may well be of ultimate benefit to healthy children taking part in this research. While this article allows research on minors for the benefit of other minors, it would be ethically inappropriate to undertake research on minors who may also be vulnerable for other reasons, if the research could be conducted on those without such additional vulnerabilities.

90. The research on "the individual's condition" might include, with regard to research on children, not only diseases or abnormalities peculiar to childhood or certain aspects of common diseases that are specific to childhood, but also the normal development of the child where knowledge is necessary for the understanding of these diseases or abnormalities.

91. While Article 6 restricts research in general by establishing a criterion of risk/benefit proportionality, this article lays down a more stringent requirement for research without direct benefit to persons incapable of giving consent, namely only minimal risk and minimal burden for the individual concerned. Minimal risk and minimal burden are addressed further in Article 17 of this Protocol.

92. Diagnostic and therapeutic progress for the benefit of sick children depends to a large extent on new knowledge and insight regarding the normal biology of the human organism and calls for research on the age-related functions and development of normal children before it can be applied in the treatment of sick children. Moreover, research on children concerns not only the diagnosis and treatment of serious pathological conditions but also the maintenance and improvement of the state of health of children who are not ill, or who are only slightly ill. In this connection mention should be made of prophylaxis through vaccination or immunisation, dietary measures or preventive treatments whose effectiveness, especially in terms of costs and possible risks, urgently requires evaluation by means of scientifically controlled studies. Any restriction based on the requirement of "potential direct benefit" for the person undergoing the test would make such studies impossible in the future.

93. As examples, the following fields of research can be mentioned, provided all conditions outlined above are met (including the condition that it is impossible to obtain the same results through research carried out on capable persons and the condition of minimal risk and minimal burden):

- in respect of children: replacing X-ray examinations or invasive diagnostic measures for children by ultrasonic scanning; removal of blood samples from newborn infants without respiratory problems in order to establish the necessary oxygen content for premature infants; discovering the causes and improving treatment of leukaemia in children (for example by taking a blood sample), research on diet and nutrition, immunisation studies;
- in respect of adults not able to consent: research on patients in intensive care, with Alzheimer's disease and other types of dementia or in a coma to improve the understanding of the causes of coma, Alzheimer's disease and other types of dementia or the treatment in intensive care.

The above-mentioned examples of medical research cannot be described as routine treatment. They are in principle without direct therapeutic benefit for the patient. However, they may be ethically acceptable if the above highly protective conditions are fulfilled.

Paragraph 3

94. The third paragraph requires that 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.

Article 16 (Information prior to authorisation)

95. This article sets out the requirements for the information that must be submitted prior to

authorisation being given for participation in research. The information shall be provided to the individual concerned, unless the person is not in a state to receive the information. This information should also be provided to a caregiver or member of the family, when appropriate. In all cases, this is the same information that must be given to those able to consent in Article 13.

Article 17 (Research with minimal risk and minimal burden)

96. The Article defines minimal risk and minimal burden, which is a precondition of Article 15, paragraph 2, for research on persons unable to consent that is not potentially of direct benefit to their health. It is only in respecting this and the other preconditions of Article 15 that such research may be carried out. To act otherwise would be to exploit these persons contrary to their dignity. For example, taking a single blood sample from a child would generally only present a minimal risk, and might therefore be regarded as acceptable. However, it must be noted that minimal risk and minimal burden depend on the current state of knowledge and availability of procedures, and less invasive procedures should be utilised once they become available. Professional bodies, including professional associations in fields such as internal medicine or surgery, may provide guidance on the current state of knowledge in their fields. The risk for such participants cannot be increased beyond minimal even if the research promises a higher level of benefit.

97. The first paragraph defines research bearing minimal risk as that which, in terms of the nature and scale of the intervention(s), would result in an individual case at the most in a very slightly detrimental and temporary impact on the health of the person concerned.

98. The second paragraph defines minimal burden as that for which the expected discomfort, which might be associated with the research, will be at most temporary and very slight for the individual.

99. Furthermore, it states that, where appropriate, a person enjoying the special confidence of the person concerned shall assess the burden. A person enjoying the special confidence of the person could be a family member, a caregiver, partner or close friend.

100. Examples of research with minimal risk and minimal burden may include:

- obtaining bodily fluids without invasive intervention, e.g. taking saliva or urine samples or cheek swab,
- at the time when tissues samples are being taken, for example during a surgical operation, taking small additional tissue samples,
- taking a blood sample from a peripheral vein or taking a sample of capillary blood,
- minor extensions to non-invasive diagnostic measures using technical equipment, such as sonographic examinations, taking an electrocardiogram following rest, one X-ray exposure, carrying out one computer tomographic exposure or one exposure using magnetic resonance imaging without a contrast medium.

However, for certain participants, even these procedures might entail risk or burden which cannot be considered minimal. Assessment on an individual basis must therefore be carried out.

CHAPTER VI – Specific situations

Article 18 (Research during pregnancy or breastfeeding)

101. This article covers the woman, foetus, and the embryo *in vivo* during pregnancy. Further, in its paragraph 2, it covers women breastfeeding during research. The Article does not presuppose that States must permit research with no potential benefit for the woman, the embryo, the foetus, or the child after birth.

102. Paragraph 1 of this article requires that if the results of the research do not have potential direct benefit for the health of the woman, embryo, foetus, or child after birth, there must be no more than minimal risk and minimal burden. The rule is applicable to all those for whom the research may result in risk or burden. Consequently, particular care shall be taken to ensure that the research only entails minimal risk for the woman, the embryo, the foetus, or the child

after birth. Minimal risk and minimal burden are addressed in Article 17 and in paragraphs 96 to 100 of this Explanatory Report.

103. Indent i requires that the research be aimed at benefiting other women in relation to reproduction, or other embryos, fetuses or children. The wording "in relation to reproduction" should be understood broadly; for example it would include research relevant to the health of women following pregnancy, or research relevant to women's choice on whether or not to become pregnant. Indent ii requires that research of comparable effectiveness cannot be carried out on women who are not pregnant. Recourse to research on pregnant women, embryos or fetuses must be, scientifically, the sole possibility if it does not produce a significant direct benefit for the participant or her embryo, foetus or child. This provision should not be considered discrimination against the pregnant woman, but protection of her health and that of her embryo, foetus or child. The notion of discrimination has been interpreted consistently by the European Court of Human Rights in its case law regarding Article 14 of the Convention on Human Rights. In particular, this case law has made it clear that not every distinction or difference of treatment amounts to discrimination. As the Court has stated, for example, in the judgement in the case of *Abdulaziz, Cabales and Balkandali v. the United Kingdom*: "a difference of treatment is discriminatory if it 'has no objective and reasonable justification', that is, if it does not pursue a 'legitimate aim' or if there is not a 'reasonable relationship of proportionality between the means employed and the aim sought to be realised' (judgement of 28 May 1985, Series A, no. 94, paragraph 72).

104. Paragraph 2 of the Article requires that when research is undertaken on a breastfeeding woman, particular care should be taken to avoid any adverse impact on the health of the child.

Article 19 (Research on persons in emergency clinical situations)

105. The Article addresses research that can only be undertaken in emergency situations and which is intended to improve emergency response or care. A recognised emergency situation is one that is unforeseen and which requires prompt action. Present medical treatment for some conditions giving rise to a clinical emergency situation, for example severe head injury, is still limited, and the risk of death is high. If the person does survive, they may develop serious disability. It is therefore important that research is undertaken both into new treatments for these conditions, and in some cases into the underlying mechanisms that lead to the damage. However, any treatment or research intervention may need to be started rapidly if there is to be any chance of it being effective. Without research, the outcome for patients in a clinical emergency situation, particularly situations in which the risk of death or serious disability is high, is unlikely to improve. There are many examples of research that may be of potential direct benefit to the person that may be covered by this article. They may include new drug treatments, or they may concern the use of devices, such as defibrillators used to restart the heart after a cardiac arrest.

106. Research in which the results do not have the potential to be of direct benefit to the person concerned includes discovering more, for example, about the mechanisms of head injury. Of course, the person will also be receiving standard medical treatment at the same time; but if the research itself, for example performing computed tomography scans, is not of direct benefit to the person concerned it must be of minimal risk and minimal burden. It is for the law of the Parties to determine whether, and under which conditions, this research can take place. Paragraph 1, indent i states that this article is applicable if the person in question is "not in a state to give consent." This takes account of the fact that in some legal systems a distinction may be made between those who are, legally, unable to consent and those who may be de facto unable to consent, but for whom the relevant legal process to declare them unable to consent has not been completed. This article addresses the emergency situation of those who are factually unable to consent as well as those minors or adults who may, according to law, be considered unable to consent. In this respect, paragraph 3 of Article 14 is also relevant because there may be persons who have been involved in an emergency, a car accident for instance, but who are not unconscious. However, because of the shock of the emergency situation, any consent obtained from them would not be acceptable.

107. The reference to "additional" conditions signifies that these conditions are supplementary to the protective conditions of the Protocol otherwise applicable. It was felt that, in addition to the general conditions applicable to other types of research, persons finding themselves in emergency situations should benefit from specific protection. The law must include the conditions that research of comparable effectiveness cannot be carried out on persons in

non-emergency situations and that the research project has been approved specifically for emergency situations. Research without the potential to produce results of direct benefit shall entail only minimal risk and minimal burden. Any relevant previously expressed objections of the person known to the researcher shall be respected. It must be remembered that emergency research must commence very rapidly and a researcher cannot undertake a search of archives, for instance, to establish whether someone has registered an objection. "Known to the researcher" in this context would mean that the potential participant has a card on his person registering such an objection or someone accompanying the potential participant informs the researcher.

108. Paragraph 3 requires that the patient be informed as soon as it becomes possible of his/her participation in the research. Additionally, if and when the research participant recovers full understanding while still undergoing research, the participant must be asked for consent to continue. If the research participant does not recover full understanding but there is enough time available to obtain the relevant authorisation, such authorisation must be obtained for participation to continue. If the person dies before authorisation or consent is obtained, it is best practice to inform relatives of the research participation.

Article 20 (Research on persons deprived of liberty)

109. The Article sets out the additional conditions pertaining to research on persons deprived of their liberty in which the results do not have the potential to produce direct benefit to their health. Those who are deprived of their liberty are in a position of constant dependence on those who provide them with food, health care and the other amenities of life.

110. Persons may be deprived of their liberty for a variety of reasons, for example within the context of the criminal justice system as a consequence of an offence or under mental health legislation. The term "deprived of liberty" comes from Article 5 of the European Convention on Human Rights. In this article, it states that, " No one shall be deprived of his liberty save in the following cases and in accordance with a procedure prescribed by law:

- a. the lawful detention of a person after conviction by a competent court;
- b. the lawful arrest or detention of a person for non-compliance with the lawful order of a court or in order to secure the fulfilment of any obligation prescribed by law;
- c. the lawful arrest or detention of a person effected for the purpose of bringing him before the competent legal authority on reasonable suspicion of having committed an offence or when it is reasonably considered necessary to prevent his committing an offence or fleeing after having done so;
- d. the detention of a minor by lawful order for the purpose of educational supervision or his lawful detention for the purpose of bringing him before the competent legal authority;
- e. the lawful detention of persons for the prevention of the spreading of infectious diseases, of persons of unsound mind, alcoholics or drug addicts or vagrants;
- f. the lawful arrest or detention of a person to prevent his effecting an unauthorised entry into the country or of a person against whom action is being taken with a view to deportation or extradition."

111. Accordingly, deprivation of liberty applies not only to those detained for security reasons but also to those confined for health reasons. The provisions of Article 20 would apply to all persons deprived of liberty irrespective of the lawfulness of their detention. These provisions set out the following conditions.

112. Indent i specifies that it must not be possible for research of comparable effectiveness to be carried out without the participation of persons deprived of liberty. Indent ii specifies that the research must have the aim of contributing to the ultimate attainment of results capable of conferring benefit to persons deprived of liberty. It was agreed that this article should not be interpreted as impeding the possibility, for a Party, to allow participation in research concerning specific situations, such as family genetic studies, if that research could not be carried out without the participation of that specific person, coincidentally deprived of liberty, because of his or her health condition or genetic characteristics. It was considered that, because of its rarity, this exception, noted in the Explanatory Report, did not need to be reflected in the text

of the Protocol itself.

113. Indent iii specifies that the research must entail only minimal risk and minimal burden. Any consideration of additional potential benefits of the research shall not be used to justify an increased level of risk or burden above the level of minimal risk and minimal burden.

114. The provisions of Article 20 are additional to the protective conditions of the Protocol otherwise applicable. Particular care must be taken to ensure that the requirements of Article 23 (Non-interference with necessary clinical interventions) addressing the use of placebos in research are fulfilled when persons deprived of liberty are to participate in the research. Good practice requires that particular attention be paid to the fulfilment of the requirement of Article 12 (Undue influence) in regard to persons deprived of their liberty.

CHAPTER VII – Safety and Supervision

Article 21 (Minimisation of risk and burden)

115. The Article requires that all reasonable measures be taken to ensure safety and to minimise risk and burden for research participants. These must include appropriate arrangements for monitoring the health of participants and promptly recording and assessing adverse events. Article 8 (Scientific quality) also applies here. Best practice recommends, especially in research involving particular risk, the establishment of a safety monitoring board to follow the conduct of a trial. In the course of formulating an opinion on the proposed research project, the ethics committee shall consider the arrangements for monitoring adverse events, including the intention to establish (or not) a safety monitoring board.

116. The second paragraph sets out the requirement that research involving interventions on persons shall be carried out under the supervision of a clinical professional who possesses the necessary qualifications and experience. While acknowledging that students and non-health care professionals may be members of a biomedical research team, the Article requires for the protection of the research participants that any research involving interventions on persons be under the supervision of such a professional. Such supervision would not be constant in most cases, but the participants must always have access to the professional. The professional should be prepared to respond to their health concerns.

Article 22 (Assessment of health status)

117. The Article requires that researchers take all necessary steps to assess the state of health of potential research participants if the research involves interventions on persons, to ensure that those at increased risk in relation to a specific project be excluded. The necessary steps may include a clinical examination but this might not always be necessary. For instance, when patients are invited to take part in research by departments caring for them, a formal clinical examination could serve merely as a formality and provide no new information. In other cases when the research involves only an interaction such as an interview, a full clinical examination could also be excessive and not serve to protect the individual in the context of the research.

118. Paragraph 2 requires when research is undertaken on persons in the reproductive stage of their lives that particular consideration be given to the possible adverse impact on a current or future pregnancy and the health of the embryo, foetus or child. However, this protection should not lead to the automatic exclusion of women, or men, in the reproductive stage of their lives from research projects that could be of benefit to them or to others in their position. The necessary conditions for research involving pregnant or breastfeeding women in which the results do not have the potential to produce direct benefit to the woman's health or that of the embryo, foetus or child are found in Article 18 on research during pregnancy or breastfeeding.

Article 23 (Non-interference with necessary clinical interventions)

119. Paragraph 1 of this article lays down the principle that research on human beings shall not delay nor deprive them of medically necessary preventive, diagnostic or therapeutic procedures. "Delay" in this article should be understood as any delay that would be detrimental to the medical care of a patient. The treatment of a patient should not be altered in a detrimental manner in order to facilitate research.

120. Paragraph 2 requires that in research associated with prevention, diagnosis or treatment, participants assigned to control groups be assured of a proven method of prevention, diagnosis, or treatment. It is expected that a proven method of treatment that is available in the country

or region concerned be utilised. "Region" may signify several neighbouring countries or an even wider area, to take into account multicentre studies that may cross national boundaries and to recognise the fact that Europeans may often utilise healthcare available in a neighbouring country.

121. The third paragraph permits the use of placebo only where there is no method of proven effectiveness or where withdrawal or withholding of such methods does not present unacceptable risk or burden to the participant. Whether risk or burden is acceptable or not is to be assessed by the ethics committee and competent body, who should pay particular attention to such projects and assess each specific project individually. If placebo is used in research on persons not able to consent to research, Article 15 also applies.

Article 24 (New developments)

122. The Article foresees that scientific developments or events arising in the course of the research may justify the re-examination of the research project. Such scientific developments or events could be, for example, publication of results by other researchers that raise questions concerning the relevance of the research project, or unforeseen complications affecting one or more participants.

123. The Article requires Parties to this Protocol to take measures to ensure that the research project is re-examined if this is justified in the light of scientific developments or events arising in the course of the research. In that regard, national law may provide guidance on the nature of the developments or events that would justify a re-examination. The Article does not set out which person or body shall carry out the re-examination, leaving this to national law or practice. However, if scientific developments or events justify such a re-examination, this may be done by the competent body or ethics committee and where relevant the data and safety monitoring board. Parties may provide further guidance about the nature of the developments or events that should lead to a re-examination, and should clarify the person or body responsible for conducting the re-examination. It is also the duty of the researcher to review the research project him/herself if developments or events seem to undermine its ethical acceptability even if the official bodies have not yet commenced a re-examination.

124. The purpose of the re-examination is to establish whether, in the light of the developments or events, the research needs to be discontinued or if changes to the research project are necessary. Further, its purpose is to establish whether research participants, or if applicable their representatives, need to be informed of the developments or events. Finally, it shall establish whether additional consent or authorisation for participation is required. The consent form presented to future participants may need to be modified in the event of changes to the research project. An example of when it would be appropriate to seek a renewed consent or authorisation for participation would be if the implications for the participants have changed.

125. The third paragraph of the article requires participants, or if applicable their representatives, be made aware of any new information relevant to the person's participation in research. This is in addition to the duty of the researchers to inform the potential participants of foreseeable risks before they consent to participation in the research project.

126. The fourth paragraph of this article addresses permissible premature termination of research. The Article seeks to prevent inappropriate premature termination of the research, for example to prevent an adverse commercial outcome if a statistically significant negative result was reached which would, according to Article 28, need to be made public. Such actions could lead to the research being repeated by other researchers, needlessly involving human participants and possibly exposing them to risk. The ethics committee must be informed of the reasons for such premature termination and may require that such a termination be justified, but it is not responsible for the termination itself.

127. An example of an acceptable reason for termination of a research project is when it becomes statistically clear that the research treatment is significantly worse than standard treatment, and hence it would be ethically unacceptable to continue the research project. Another example would be the publication of results by other researchers from studies that may either negate the original justification for the study (although it must be remembered that verification is an essential element of the process of validation in science) or that raises questions about the safety of the research in question.

CHAPTER VIII – Confidentiality and right to information

Article 25 (Confidentiality)

128. Article 25 sets out the principle of confidentiality. The first paragraph establishes the right to privacy of information in the field of biomedical research, thereby reaffirming the principle introduced in Article 8 of the European Convention on Human Rights and reiterated in the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data. It should be pointed out that, under Article 6 of the latter Convention, personal data concerning health constitute a special category of data and are as such subject to special rules. This principle was also reiterated in Article 10 of the Convention on Human Rights and Biomedicine.

129. The second paragraph states that the law shall protect against inappropriate disclosure of information related to a research project that has been submitted in compliance with the Protocol. Failure to provide such protection could lead researchers to submit information to ethics committees lacking in detail, making it more difficult for the proper evaluation of the research project. Therefore, as the primary goal of this Protocol is to protect research participants, such protection against inappropriate disclosure to competitors or rivals serves also to enable the ethics committees to better protect human beings in research.

Article 26 (Right to information)

130. This article states that research participants shall be entitled to know any information collected on their health in conformity with Article 10 of the Convention. It adds that all other personal information collected for a research project will be accessible to them in conformity with law on the protection of individuals with regard to processing of personal data.

Article 27 (Duty of care)

131. This article sets out the requirement that information arising from research of relevance to the current or future health or quality of life of participants must be made accessible to those persons. This information could be the conclusions of the research or incidental information collected during the research. In principle, the researcher must evaluate whether such information is of relevance to the current or future health or quality of life of research participants. The researcher may seek the advice of the ethics committee as to the potential relevance of the information in question to research participants. This requirement also applies to anonymised data if it has been coded in such a manner that it can be relinked to the personal identifiers of the participants. The term "offered" was used in order to acknowledge that individuals have the right not to receive such conclusions if they so wish. Best practice requires that the wish of the participant to know or not to know should be established prior to commencement of the research.

132. The second sentence requires, for the protection of these persons, that this information be made accessible within a framework of healthcare or counselling. This is because proper counselling or other healthcare assistance may be necessary to explain the nature of the results and the options available to react to the participant.

133. The third sentence sets out the requirement for due care for the protection of confidentiality and respect for the right not to know in the communication of the conclusions. Patients may have their own reasons for not wishing to know about certain aspects of their health. Participants may only wish to exercise their right to know under certain circumstances and such wishes must also be observed.

134. In some circumstances, the right to know or not to know may be restricted in the patient's own interest or else on the basis of Article 26.1 of the Convention, for example, in order to protect the rights of a third party or one of the specified public interests. Additionally, the last paragraph of Article 10 of the Convention sets out that in exceptional cases domestic law may place restrictions on the right to know or not to know in the interests of the patient's health.

Article 28 (Availability of results)

135. Accountability is implicit in the relationship between the researcher and the participant. For this reason, this article requires that the conclusions of the research be made available on request to research participants in a form comprehensible to them.

136. The Article requires researchers to submit a summary or report of the research to the ethics committee or competent body, and to make public the results of their research even if

the outcome is negative. Such results must be published or made otherwise available in a manner accessible to other researchers. The aim of the Article is to prevent the needless repetition of research using persons due to the non-publication of previous results, and to prevent the suppression of negative or positive results for commercial or other non-scientific reasons. It is stated that this be done "in reasonable time" so as to not prejudice a patent application or scientific publication. This obligation to publish cannot be restricted by contractual obligations. However, under the terms of Article 26 paragraph 1 of the Convention, the obligation to publish research results would be waived if publication would potentially compromise, for example, public health or safety or the rights and freedoms of others. An example of such research could be that concerning counter-measures to the use of biological weapons, the publication of which could compromise public safety.

CHAPTER IX – Research in States not party to this Protocol

Article 29 (Research in States not party to this Protocol)

137. At present, considerable numbers of research projects are conducted on a multinational basis. Teams of researchers based in different States may participate in a single project. Further, internationally-based organisations may be able to choose the country in which a particular research project that they are conducting or funding is carried out. This has led to concerns being expressed about the possibility of fundamentally different standards of protection for participants being applied in different countries. In particular, concern has been expressed about the possibility of research that might be widely viewed as ethically unacceptable being carried out in another State where systems for the protection of research participants are less well established.

138. The Article sets out the conditions for sponsors and researchers within the territory of a Party to this Protocol who plan to undertake or direct a research project in a State not party to this Protocol. In addition to complying with all the conditions applicable in the State in the territory of which the research is to be undertaken, the principles on which the provisions of this Protocol are based must be complied with. The term "principles" implies that while it may be impracticable to implement all the detailed provisions contained in this Protocol when a research project is carried out in a State that is not party to the Protocol, it is nevertheless mandatory to observe the principles that those provisions develop. For example, there may not be a body capable of undertaking appropriate independent scientific and ethical evaluation of research in the country, but the principle of the research project being submitted to an independent body for review must be observed. Examples of these principles are informed consent, the protection of those unable to consent, confidentiality, the balance between risks and benefits, and ethical review of research projects. This does not imply that a body in the State Party to the Protocol has the authority to approve research in the non-Party State if that State does not approve the research, or to override its regulations. However, researchers from the Party State may be required to observe additional conditions, in accordance with the principles on which the provisions of this Protocol are based, to those applicable in non-Party States. The Article is not intended to discourage otherwise ethical research in less developed countries that might utilise less expensive treatment than that routinely utilised in wealthier countries.

139. The wording "sponsors and researchers within the jurisdiction of a Party to this Protocol" signifies those who fall under the authority of the State concerned. In practice, in conformity with the law of that State, such cases could be those of sponsors having their head office on its territory, or of those established on its territory for the exercise of activities insofar as they plan to undertake or direct the conduct of the research in question; further, such cases could be, in conformity with the law of the Party concerned, of researchers residing on the territory of the Party, or who are established there professionally, or who are its nationals, insofar as they are involved in directing the conduct of the research in question.

140. It is up to each Party to take appropriate measures with a view to assuring that the research project respect the principles on which the provisions of this Protocol are based. These measures could consist of adoption of norms setting out the obligation, for the relevant sponsors and researchers, of respecting these principles. In the case where the research must be undertaken in States not having well established systems of protection, the provisions could foresee the obligation to submit the research project to an ethics committee of the Party concerned.

CHAPTER X – Infringement of the provisions of the Protocol

Article 30 (Infringement of the rights or principles)

141. This article requires the Parties to make available a judicial procedure to prevent or put a stop to an infringement of the principles set forth in the Protocol. It therefore covers not only infringements that have already begun and are ongoing but also the threat of an infringement.

142. The judicial protection requested must be appropriate and proportionate to the infringement or the threats of infringement of the principles. Such is the case, for example, with proceedings initiated by a public prosecutor in cases of infringements affecting several persons unable to defend themselves, in order to put an end to the violation of their rights.

143. Under the Protocol, the appropriate protective mechanisms must be capable of operating rapidly as it has to allow an infringement to be prevented or halted at short notice. This requirement can be explained by the fact that, in many cases, the very integrity of an individual has to be protected and an infringement of this right might have irreversible consequences.

144. The judicial protection provided by the Protocol applies only to unlawful infringements or to threats thereof. The reason for this qualifying adjective is that the Convention, in Article 26.1, permits restrictions to the free exercise of the rights it recognises.

Article 31 (Compensation for damage)

145. This article sets forth the principle that persons who have suffered damage resulting from their participation in research shall be fairly compensated according to the conditions and procedures prescribed by law. The wording "damage" takes in to account the different contexts in which research is undertaken, ranging from studies on healthy volunteers to research on people suffering a very serious terminal illness. Whether or not compensation was fair would need to take in to account these different contexts, and may need to involve an assessment of the extent to which a given effect can be attributed to the research or may reflect a progression of the patient's existing health condition. On the subject of fair compensation, reference can be made to Article 41 of the European Convention on Human Rights, which allows the Court to afford just satisfaction to the injured party.

146. Compensation conditions and procedures are prescribed by national law. In many cases, this establishes a system of individual liability based either on fault or on the notion of risk. In other cases, the law may provide for a collective system of compensation irrespective of individual liability.

Article 32 (Sanctions)

147. Since the aim of the sanctions provided for in Article 32 is to guarantee compliance with the provisions of the Protocol, they must be in keeping with certain criteria, particularly those of necessity and proportionality. As a result, in order to measure the expediency and determine the nature and scope of the sanction, the domestic law must pay special attention to the content and importance of the provision to be complied with, the seriousness of the offence and the extent of its possible repercussions for the individual and society.

CHAPTER XI – Relation between this Protocol and other provisions and re-examination of the Protocol

Article 33 (Relation between this Protocol and the Convention)

148. As a legal instrument, the Protocol supplements the Convention. Once in force, the Protocol is subsumed into the Convention for those Parties having ratified the Protocol. The provisions of the Convention are therefore to be applied to the Protocol.

149. Thus, Article 36 of the Convention, which sets out the conditions under which a State may make a reservation in respect of any particular provision of the Convention, will also apply to the Protocol. Using this provision States may, under the conditions set out in Article 36 of the Convention, make a reservation in respect of any particular provision of this Protocol.

Article 34 (Wider protection)

150. In pursuance of this article, the Parties may apply rules of a more protective nature than those contained in the Protocol. In other words, the text lays down common standards with which States must comply, while allowing them to provide greater protection of the human

being and of human rights with regard to biomedical research.

151. A conflict may arise between the various rights established by the Protocol, for example between a scientist's right of freedom of research and the rights of a person submitting to the research. However, the expression "wider protection" must be interpreted in the light of the purpose of the Protocol, as defined in Article 1, namely the protection of the human being with regard to any research in the field of biomedicine involving interventions on human beings. In the example quoted, any additional statutory protection can only mean greater protection for a person participating in research.

Article 35 (Re-examination of the Protocol)

152. This article provides that the Protocol shall be re-examined no later than five years from its entry into force and thereafter at such intervals as the designated Committee may determine. Article 32 of the Convention identifies this Committee as the Steering Committee on Bioethics (CDBI), or any other Committee so designated by the Committee of Ministers.

CHAPTER XII – Final clauses

Article 36 (Signature and ratification)

153. Under the provisions of Article 31 of the Convention, only States that have signed or ratified the Convention may sign this Protocol. Ratification of the Protocol is subject to prior or simultaneous ratification of the Convention. A State which has signed or ratified the Convention is not obliged to sign the Protocol or, if applicable, to ratify it.