

Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics

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3. Appendix 3 on biobanks has been cancelled, see section 4.7 on register research projects involving human biological material that has already been removed.
4. Guidelines on research with pre-implantation diagnostics have been cancelled, see section 4.9 on applications for trials with fertilised eggs, stem cells or stem cell lines.
5. Guidelines on the application of ionising radiation in biomedical trials.
6. Guidelines on remuneration and other payments of voluntary trial subjects.

The committee system of research ethics has prepared the document: "The rights of a trial subject in a biomedical research project"

The committee system of research ethics has preprinted declarations of consent.

1.0 Approval of biomedical research projects.

No biomedical research project shall be initiated until a research ethical evaluation has been made and approval has been granted by the regional committee, cf. section 9(1) of the Act on a Committee System on Biomedical Research Ethics and Processing of Biomedical Research Projects (hereinafter referred to as the "Committee Act" or simply "the Act"). This shall also apply to supplementary protocols. The Executive Order on Information and Consent at Inclusion of Trial Subjects in Biomedical Research Projects (hereinafter referred to as the Executive Order on Information) prescribes the detailed requirements regarding informed consent from trial subjects.

Within 90 days of the termination of the project, the chief investigator shall inform the committee accordingly. The project is considered completed once the last trial subject has completed treatment. If the project is prematurely terminated, the committee shall be informed accordingly within 15 days from the time when the decision to terminate the project was made, cf. section 22(4) of the Committee Act.

In case of clinical trials involving medicinal products, approval shall also be granted by the Danish Medicines Agency. Reference is made to the Danish Medicines Agency's Guideline on notification of clinical trials involving medicinal products for humans and Guidance on application for the authorisation for clinical investigations of medical devices on human subjects.

The Committee Act implements the directive on good clinical practice in connection with trials involving medicinal products (Directive 2001/20/EF) and a provision in the subsequent directive on the principles and detailed GCP requirements (Directive 2005/28/EF) as well as the European Council Convention on Human Rights and Biomedicine.

2.0 What is to be notified?

Any biomedical research project shall be notified to the regional committee on biomedical research ethics, cf. section 8 of the Committee Act. It is a precondition, however, that

research activity is carried out in Denmark, i.e. that the chief investigator works in this country.

2.1 Definition of a biomedical research project.

In section 7 of the Act, a biomedical research project is defined as a project that involves trials on

1. Live born human individuals
2. Human germ cells intended for use in fertilisation, human fertilised eggs, embryos and fetuses,
3. Tissue, cells and genetic material from humans, fetuses, etc., or
4. deceased individuals.

A biomedical research project shall mean an activity planned according to research methods which aim at producing new, valuable knowledge about human biological and psychological processes, either in relation to healthy persons or for the purpose of prevention, recognition, relief, treatment or cure of disease, symptoms and pain, including affecting bodily functions.

Biomedical research primarily comprises research within medical subjects, clinical and socio-medical-epidemiological research. In addition to research of somatic diseases, it also covers psychiatric and clinical-psychological diseases and conditions as well as odontological and pharmaceutical research.

2.2 Medicinal product trials.

2.2.1 Clinical trials involving medicinal products.

Clinical trials involving medicinal products include trials with the purpose of discovering or verifying the clinical, pharmacological or other pharmacodynamic effects on humans, including identification of any adverse reactions or study of pharmacokinetics in order to obtain knowledge of the safety or efficacy of medicinal products on humans, cf. section 7(1)(i) of the Committee Act. Clinical trials involving medicinal products shall be notified to the committee system and to the Danish Medicines Agency, cf. section 7(1)(i) of the Committee Act and section 88 of the Danish Medicines Act. See sections 4.3, 4.4 and 4.6 on requirements regarding application for trials involving medicinal products.

Make sure to apply for identical approval periods in the committee system and in the Danish Medicines Agency. The chief investigator is responsible for securing the required approval from these two agencies throughout the duration of the trial – possibly by applying for prolongation.

2.2.2 Non-intervention trials involving medicinal products.

Non-intervention trials involving medicinal products are studies where one or more medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorisation. The decision to prescribe the medicinal product is clearly separated from the decision to include the patient in a study. The actual treatment does not take place in accordance with a trial protocol but follows current practice. There are no additional diagnostic or monitoring procedures, and epidemiological methods shall be used for the analysis of collected data.

Non-intervention trials involving medicinal products shall not be notified to the committee system as the patient is not exposed to any special harm or risk, and the primary aim of prescribing the medicinal product is treatment.

Take care to apply for identical approval periods in the committee system and in the Danish Medicines Agency. The chief investigator is responsible for securing the required approval from these two agencies throughout the duration of the trial – possibly by applying for prolongation.

2.3 Clinical investigations of medical devices.

Clinical investigations of medical devices shall also be notified to the relevant committee. The committee shall make an evaluation to decide whether the clinical investigation is in conformity with the Committee Act. See sections 4.3, 4.4 and 4.6.1.

Medical devices are used for the diagnosis, prevention, monitoring, treatment or alleviation of illness in humans such as syringes, surgical instruments, hospital beds, pacemakers, hip prostheses or

condoms. Section 1(2) in Executive Order no. 1263 of 15 December 2008 for Medical devices is defining medical devices. The Danish Medicines Agency is competent authority.

All clinical investigations of medical devices must be notified to the committee system because clinical investigation is in itself a biomedical research project. Clinical investigations of medical devices on human subjects shall mean any clinical investigation involving people with the purpose of uncovering or verifying the safety and/or performance of medical devices, cf. Section 1,2 no 15 of the Order. The medical device to be tested may be a new medical device or a well known medical device which is already on the market in Denmark. See www.medicinskudstyr.dk.

Case handling and the ethical assessment does not differ from the handling of other cases by the committee system.

2.4 Scientific trials vs. treatment trials.

Sometimes there are doubts as to whether new treatments have to be notified or not. The decisive factor is whether the aim is to generate new knowledge in addition to treatment of the patient. If this is the case, the project shall be notified.

Notification to a committee on biomedical research ethics and the preparation of a protocol is not required if considerable clinical experience is available that convincingly demonstrates the effects, side effects and risks involved in the treatment. The doctor responsible therefore has to consider whether there is sufficient evidence to introduce the treatment. In case of any doubts, the trial shall be notified to the committee system on biomedical research ethics. This shall also apply if there is any doubt as to the results that form the basis for introduction of a new treatment.

An individual trial involving prevention, diagnostics or treatment may, however, be implemented without the duty to report if, in the assessment of the doctor, this is assumed to be the best solution for the patient in the actual situation and it is made at the doctor's responsibility based on stricter informed consent from the patient. This could be situations where other treatments have been exhausted or have to be excluded for particular reasons, and treatment is implemented as a last resort. The decisive factor is whether the aim is to treat the patient and not to generate new knowledge.

The Guidelines of 2 July 1999 issued by the National Board of Health on the introduction of new treatments in the health service include further examples of when the utilisation of new methods of clinical treatment require formal handling of the trial and therefore need to be notified to the committee system on biomedical research ethics.

2.5 Quality control.

Quality development projects or quality control shall not be notified to the committee system. Typically, this refers to an activity included in the operation of the health service, for instance concerning treatment results for a given group of patients achieved by a hospital ward. This may concern comparison of standard treatment with treatment instructions in force, evaluation of cost and effect of various treatment principles. Often this will concern retrospective studies or prospective studies involving observation without intervening in treatment etc. This also applies to the product development of an enterprise. Here, the aim is not to acquire new valuable knowledge, but to test the clinical function of a hospital ward or the effects of a product.

2.6 Research affecting biological material.

A biomedical research project which involves trials on human biological material such as blood, cells, tissue and body fluids, but also hair, saliva, specimens of urine, must be notified to the Committee on Biomedical Research Ethics whether the material is identifiable with a person or it is "anonymous". Data are identifiable with individual subjects if it is possible to identify such subjects either by name or by code. If just one subject has the "key", the material is identifiable with a subject and is not "anonymous".

A biobank is a structured collection of human biological material which is accessible under certain criteria, and where information contained in the biological material can be traced back to individuals. The setting up of a biobank shall be notified to the Danish Data Protection Agency.

Where biological material is included as an **integrated** part of a concrete biomedical research project, this implies a **research biobank**. Whether the biological material is removed and stored in

the project or it is requested from an existing biobank, the material constitutes a research biobank, cf. Circular of 13 June 2005 from the Ministry of the Interior and Health.

Concerning research on the application of fertilised eggs, stem cells and stem cell lines reference is made to Section 2.9.

Concerning research on deceased persons, see Section 4.5.

2.6.1 Removal of biological material for a concrete research project – setting up a research biobank.

Where, in a concrete biomedical research project, biomedical material is removed and stored for use in connection with the concrete biomedical research project, this implies the setting up of a research biobank. This must appear from the protocol to the Committee on Biomedical Research Ethics.

Where, in the research project, for instance merely blood samples are taken which are immediately sent for analysis and subsequently destroyed, this typically does not imply actual *storage*, and therefore this does not imply the setting up of a research biobank.

If, however, a researcher collects biological material for the purpose of analysis, for instance abroad, and the samples are therefore stored for a significant duration, this will in fact imply a research biobank.

A research biobank is only implied if the material is included as an integrated part of the research project. If, in connection with a project, biological material is removed for **future research**, this shall not appear from the protocol or the information to participants to the Committee on Biomedical Research Ethics. Such biobanks with a future research objective shall be notified exclusively to the Danish Data Protection Agency, cf. Circular of 13 June 2005 from the Ministry of the Interior and Health

See Sections 4.1. - 4.4. and 4.6 on the requirements of notification of concrete research projects during which biological material is removed.

Concerning notification to the Danish Data Protection Agency, please see the Agency's relevant guidelines: Private Research and Statistics Projects, Biobanks are manual registers and Research Biobanks.

2.6.2 Register research projects that incorporate biological material – setting up a research biobank.

Register research projects that include human biological material shall be notified to a committee on biomedical research ethics, cf. Section 8(3) of the Committee Act. A research project involving imported biological material shall also be notified. The crucial issue is that the research activity takes place in Denmark.

If for instance a chief investigator wants to investigate biological material **from abroad** (e.g from a clinical biobank) in order to establish new knowledge about a given type of disease etc., the regional research ethics committee must be notified of this, cf. Section 4-7-1 below.

If, however, a Danish researcher or a laboratory undertakes analysis of biological material from abroad on behalf of a researcher or a company that is established abroad, notification is **not** required if only laboratory services etc. are concerned and the results obtained are communicated back to the researcher or the company abroad.

Concerning notification to the Danish Data Protection Agency, please see the Agency's relevant guidelines: Private Research and Statistics Projects, Biobanks are manual registers and Research Biobanks.

"Register" ('filing system') shall mean any structured set of personal data which are accessible according to specific criteria, whether centralised, decentralised or dispersed on a functional or geographical basis, cf. S.3(3) of the Act on Processing of Personal Data.

A biobank is also a register, ref. the relevant guideline of the Danish Data Protection Agency: Biobanks are manual registers. Please note that register research contains "personal data", i.e. data identifiable with individual subjects. Data are identifiable with individual subjects if it is possible to identify such subjects either by name or by code. If just one subject has the "key", the material is traceable to a subject and is not "anonymous".

Consequently, where material from existing biobanks is used, this implies register research projects which include human biological material. This may include research in:

- Biobanks previously established for research purposes
- Clinical biobanks – also known as treatment biobanks The clinical biobanks are biobanks that are set up in connection with a person's contact with the health service for clinical purposes, for instance prevention, diagnostics, treatment or care, etc.
- Other forms of biobanks.

If the material originates from a clinical biobank, the researcher shall contact the biobank supervisor to enquire whether the patient has notified the Register on Application of Tissue that the material shall be used only for treatment and **not** for research. Such a decision by the patient shall apply, even if permission to the trial has been granted from the committee system, cf. S. 29 (1) of the Health Act. The provision applies to material removed after 1 September 2004.

However, trials on cell lines (laboratory cultures) or the like (e.g. cell cultures) that originate from trials involving collection of cells or tissue that have obtained the necessary authorisation are **not** to be notified to the committee system, cf. S. 8(4) of the Committee Act. Cell lines occur when a primary cell culture taken directly from the organism is sub-cultured. The Act presumes that collected tissue can result in a large number of research projects in the same cell line. The words "cell lines or the like" shall have an elastic definition until such time when the Ministry of Health and Prevention may introduce a detailed definition. The necessary authorisation is also intended to include imported cell lines or laboratory cultures originating from other countries which in the country of origin have obtained the necessary authorisation for use in trials in the country of origin. These may include the EU states, other European countries and countries such as the USA and Canada and other countries that have a research ethics committee system or similar legal guarantees.

See Section 4.7 on the requirements of notification of concrete register research projects which include biological material.

2.6.3 Research in anonymous biological material.

Research in anonymous biological material shall also be notified to the biomedical research ethics committee. This concerns material which is not identifiable with individual subjects. Data are identifiable with individual subjects if it is possible to identify such subjects either by name or by code. If just one subject has the "key", the material is traceable to a subject and is not "anonymous". See above concerning personally identifiable material.

A research biobank is **not** set up where the material is anonymous.

See Section 4.8 on research projects involving anonymous biological material.

2.7 Register research projects that do not incorporate biological material.

As mentioned above under Section 2.6.2 a register shall mean any structured set of personal data which are accessible according to specific criteria, whether centralised, decentralised or dispersed on a functional or geographical basis, cf. S.3(3) of the Act on Processing of Personal Data.

A register research project where **only** information in the form of sign-based symbols, including figures, letters, etc. is applied shall **not** be notified to research ethics committees. This may include the collection of information from patients' records. If information from patients' records is to be used – in register research projects without the use of biological material – an application for such

approval shall be submitted to the National Board of Health, cf. S. 46 (2) of the Health Act, see the National Board of Health Guidelines: Guidelines concerning approval of disclosure of information from patients' records etc. to be used for concrete research projects.

2.8 Questionnaire-based projects and interview examinations.

As a starting point, questionnaire-based examinations shall be treated like the so-called register research projects, i.e. that they have to be notified only if the project will include examination of human biological material or examination of individuals, cf. S. 8(3) of the Committee Act.

Interview examinations are comparable to questionnaire-based examinations.

2.9 Trials concerning fertilised eggs, stem cells or stem cell lines.

Biomedical trials concerning the application of fertilised eggs, stem cells and stem cell lines the aim of which is to obtain new knowledge that may improve the possibilities for treatment, diagnostics, and research shall be notified to the committee system, cf. S. 8 of the Committee Act.

Under S.25 of the Act on In-Vitro Fertilisation, trials may be made only on fertilised human eggs and on human germ cells intended to be used in fertilisation, if they are for the purpose of:

- 1) Improving in-vitro fertilisation or similar techniques to induce a pregnancy, or
- 2) Improving techniques for genetic examination of a fertilised egg for the purpose of establishing whether a serious hereditary disease or significant chromosome abnormality is present (pre-implantation diagnostics), or
- 3) If the trials are aimed at acquiring new knowledge which may be used for treatment of diseases in humans.

Thus, projects involving embryonic stem cells shall be notified. This also applies to projects aimed at creating stem cell lines on the basis of embryonic stem cells, regardless of the stage in which the stem cell line is found.

See Section 4.9 below on the requirements of an application for trials with fertilised eggs, stem cells or stem cell lines.

3.0 Notification.

The chief investigator shall notify the research project to the regional committee for the area in which the chief investigator is operating. A chief investigator shall mean an individual following a profession acknowledged for performance of research who is responsible for the practical implementation of the trial in a certain trial location. A profession acknowledged for performance of research shall mean employment as a researcher or a PhD-student or involvement in actual research work.

A multi-centre clinical trial shall mean any trial carried out in accordance with one and the same trial protocol, but in different locations in Denmark with different trial investigators and with one investigator as a co-ordinator.

A multi-centre trial shall be notified by the co-ordinating chief investigator to the regional committee for the area in which the coordinating chief investigator is operating.

In case of research initiated or financed by an enterprise, for instance clinical trials with medical products, the enterprise may on behalf of the chief investigator be in charge of the practical issues around the notification, such as submission of the notification.

4.0 Form and content.

Biomedical research projects shall be notified electronically via www.drkv.dk/anmeldelse/. A notification form is completed electronically, sent electronically and subsequently printed.

The printed notification form shall be signed and sent together with the other project material to the regional committee who will process the application. A guide on completion is available on the site.

The Committee Act mentions the concept of "a duly formulated application". A duly formulated application includes the following material:

1. An electronically completed notification form.

The following documents shall be enclosed with the notification form:

- Documentation of the identity of the notifier, e.g. a copy of the individual's health security card, authorisation or a passport for foreign citizens. If you have an electronic signature, this is sufficient identification.
- A statement that the chief investigator has a profession acknowledged for performance of research or that he is involved in actual research work.

In case of trials involving medical products and clinical investigations of medical devices, these documents shall also be submitted:

- 1) A copy of a completed application for the Danish Medicines Agency (front page)
- 2) Documentation of the notifier's medical or dental training (certificate of graduation or authorisation)
- 3) CV indicating the notifier's clinical experience
- 4) Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- 5) Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/fee for the chief investigator, the chief investigator's access to data and on publication of trial results

2. Trial protocol.

A trial protocol is a document describing the objective, design, methodology, planning, statistical considerations, research-ethical considerations, finances, publication and information for participants in connection with a biomedical research project, etc.

The following documents shall be enclosed with the trial protocol:

- Lay person summary
- Written information for participants
- Description of procedures for communicating oral information to participants
- Declaration of consent
- Advertising material for recruitment of participants
- Questionnaires
- Other material specified in detail in the following sections

The material must be written in Danish. In case of multi-centre trials, where a British protocol has been approved abroad, a protocol in Danish shall be submitted to the committee. The protocol in Danish does not necessarily have to be a full and complete translation of the protocol in English, but this will be an independent Danish protocol which has to observe the requirements of the guidelines, cf. Section 4. The Danish protocol shall apply to the Danish trial locations. As an exemption statistics can in multi-centre trials however be accepted in English.

4.1 Trials involving legally competent subjects.

Section 4.1 describes the requirements regarding application for a biomedical research project involving legally competent trial subjects, i.e. persons who are at least 18 years of age and legally competent.

Regarding trials with medical products and clinical investigations of medical devices involving legally competent subjects, see section 4.3.

4.1.1 Trial protocol.

The trial protocol shall contain descriptions of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the research standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent.

d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.

e. **Trial subjects, including criteria for inclusion and exclusion.** Inclusion and exclusion criteria shall be stated. The gender and age of the trial subjects shall be stated, including whether the subjects included are patients and/or healthy trial subjects. If pregnant or breast-feeding subjects are included, this shall be stated. If possible, a statistical reason for the planned number of trial subjects shall be given.

Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

If the trial involves trial subjects who, because of placement in an institution, incarceration pursuant to the Psychiatry Act or due to circumstances of employment, are particularly exposed to pressure regarding participation in the research project, this shall be stated. In connection with employment, the employee is in a state of loyalty and dependence of the employer. Where the chief investigator or the sponsor is the employer, this may influence the decision of the employee. In such cases stricter requirements regarding information and consent may apply. Consequently, the committee may decide that the trial subject's consent should be given to a person who has been approved by the committee. The committee may also decide that the information should state that the project is monitored by an independent professional.

It should also be stated in the protocol if persons are included who due to physical handicaps are unable to sign a declaration of consent. In such cases the trial subject may authorise another person to sign the declaration of consent on his or her behalf.

f. **Side effects, risks and inconveniences** for the trial subjects. A description of predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. See item m concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore, the trial protocol shall describe any safety measures.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials shall be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

g. **Respect for the physical and mental integrity of the trial subjects and their right of privacy.** Statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in another EU country). If the Danish Act on personal data does not apply, it must be stated in the information material for participants what national laws on data protection apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information on the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** The protocol shall state:
1. Who initiated the biomedical research project,
 2. Names of commercial as well as non-commercial sponsors,
 3. Amounts granted from each sponsor and the way in which the financial support is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
 4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.
- i. **Remuneration or reimbursement of expenses** for trial subjects. Any remuneration (including reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
- j. **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the web address in question should be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
- k. **Availability of information** for trial subjects. Indication shall be provided as to how the trial subject is guaranteed access to further information on the project, such as reference to a health professional who may act as a contact person.
- l. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- m. **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues raised by the biomedical research project, including an argumentation that the project is sound in terms of biomedical research ethics.

The statement shall incorporate a thorough risk/benefit assessment of the trial. The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall display care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act consideration for the safety, rights and welfare of the trial subject shall take precedence

over any scientific or social interests. In any event, the regard for the trial subject's integrity and autonomy shall form the basis for the considerations in the section.

When placebo (or no treatment) is used it shall be explained that either there is no effective treatment or that the use of placebo is necessary/acceptable for methodological reasons and that trial subjects will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk.

4.1.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information on external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.1.3 Information for participants

The trial subject has the right to obtain information on the biomedical research project in which he or she considers to participate, cf. section 16 of the Committee Act and section 7 of the Executive Order on Information.

4.1.3.1 Guidelines for oral information for participants

The guidelines for communicating oral information to participants, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator shall be responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact to the trial subject made?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How to make sure that the trial subject is given the option to have an observer present at the information interview?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?

- When to ask for consent?
A clear correlation between information and consent is required, i.e. the trial subject should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- An appointment for the interview shall be made.
- Attention must be drawn to the fact that it is possible to have an observer present at the interview.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.
- The researcher shall consider the trial subjects' right to decline knowledge of information about his or her own state of health.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the trial subjects have sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerably adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the trial subject is believed to be unaware, but which is of importance to the trial subject's decision, e.g. that remuneration for participants is a taxable income.

After the information interview:

- The trial person shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The trial subject who is still actively involved in the trial shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The trial subject shall be informed, if during the implementation of the research project, significant information becomes available on the trial subject's state of health, unless the trial subject has expressly stated that he or she does not want this, cf. section 13 of the Executive Order.
- If it is feasible and the trial subject so wishes, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the trial subject of the results achieved and of any consequences for the individual subject.

4.1.3.2 Written information for participants

The trial protocol shall also include written information for participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, the trial subject may require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial at the beginning of the information.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 5) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 6) The possible benefits of the research project. A distinction must be drawn between benefits for the individual trial subject, for others and for scientific progress.
- 7) Circumstances which may result in the involuntary exclusion of the trial subject from the research project, as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance pregnancy is a criterion for exclusion and the subject becomes pregnant during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.
- 8) Information about the standard treatment and about alternative treatment methods in situations where the project aims at results in terms of science as well as treatment.
- 9) Possible remuneration for the trial subject, including information on taxation of the amount.
- 10) Who initiated the biomedical research project.
- 11) Names of commercial as well as non-commercial sponsors.

- 12) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 13) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 14) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 15) Where the trial subject may obtain further information on the research project (e.g. from the contact person), and
- 16) A recommendation to read the attached appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects.

The above concerns requirements regarding the application. Further reference is made to Appendix 1, Drawing up useful information for participants.

4.1.4 Declaration of consent

No biomedical research projects shall be initiated or continued without the informed consent of the legally competent trial subject, cf. section 16 of the Committee Act and section 4 of the Executive Order on Information.

In a biomedical research project, an informed consent is a decision to participate in a research project which has been made upon due information on the nature, significance, implications and risks of the project and receipt of suitable documentation. The decision is made voluntarily by a person who is capable of giving his or her consent, cf. section 7(1)(viii) of the Committee Act. The consent shall be in writing, dated and signed or provided using an electronic signature.

The trial protocol shall be accompanied by a copy of the declaration of consent.

The trial protocol should be accompanied by one of the ready-printed declarations (S1-S4) of the committee system concerning "Informed consent to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall request the person concerned for his/her consent to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and as soon as possible after receipt of the written and oral information. The consent shall be given to the chief investigator or a person authorised to provide the oral information. This person shall have direct connection with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that the written information has been given to the trial subject and that communication of the oral information has taken place, cf. section 4(4) of the Executive Order.

Original declarations of consent shall be stored by the chief investigator, and the trial subject is entitled to have a copy of the declaration of consent.

Where, because of placement in an institution, incarceration that is not covered under the psychiatry act or under circumstances of employment or in similar circumstances, the trial subject is particularly exposed to pressure regarding participation in a biomedical research project, but where

the subject is otherwise capable of making decisions, the committee may upon a concrete assessment decide that the consent of the trial subject to participate in the research project shall be given to a person authorised by the committee. The committee may also decide that in such cases the information shall be supplemented by a statement that the implementation of the research project shall be observed by an independent professional, cf. section 15 of the Executive Order.

4.2 Trials with legally incompetent trial subjects

Section 4.2 describes the requirements regarding a duly formulated application for biomedical research projects involving trial subjects who because of age or reduced physical or mental abilities due to depression, age, mental deficiencies or similar conditions are incapable of giving informed consent to participation in a trial.

Regarding trials with medical products and clinical investigations of medical devices, see sections 4.4 and 4.6.

4.2.1 Trials with children and young people under the age of 18

This section describes requirements regarding an application involving children and young people under the age of 18. The assumption in the text is that the custodial parent gives surrogate consent. If someone other than the custodial parent gives consent on behalf of the minor, this person assumes the rights described for the custodial parent.

Regarding trials with medical products and clinical investigations of medical devices involving minors, see section 4.4.1.

4.2.1.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the research standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?

- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent.

- d. Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.
- e. Trial subjects, including criteria for inclusion and exclusion.** Inclusion and exclusion criteria shall be stated. The gender and age of the child or the youth shall be given, including whether the subjects included are patients and/or healthy trial subjects. The least vulnerable children should be preferred. That means older children should be preferred before younger children. If pregnant or breast-feeding minors are included, this shall be stated. If possible, a statistical reason for the planned number of trial subjects shall be stated.

Children or young people subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

At the evaluation of research projects involving minors, the committee shall, prior to the approval, ensure that the project cannot with similar benefit be conducted by including legally competent trial subjects, that the surrogate consent is in accordance with the interest of the child or the youth, and that the criteria of section 13 of the Committee Act have been observed.

That section of the protocol shall therefore include a special argumentation for including persons who cannot give informed consent. According to section 13 of the Act, the trial can be approved if:

A

The project is essential to verify data collected through trials on individuals who are capable of giving their informed consent or through other trial methods, and the project concerns the clinical condition of the child or the youth, and the project provides direct benefit to the patient group.

or if

B

The project cannot be implemented with the same benefit by including legally competent trial subjects and the project is expected to be of direct benefit to the child or the youth.

or if

C

The project can be carried out only by the inclusion of individuals in the particular age group with the disease or condition concerned, and the project is expected to

be of considerable benefit to the group of patients of the same age, with the same disease or condition as the trial subject, and the project entails minimal risk and discomfort for the child or the youth.

The trial protocol shall state which of the categories A, B, or C justifies implementation of the project.

- f. **Side effects, risks and inconveniences** for the child or the youth. The description shall cover predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. Cf. item m below concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the child or the youth. Therefore, the trial protocol shall describe any safety measures.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials must be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Attention is drawn to the fact that the child or the youth shall receive oral information of the research project, its risks and benefits from a person with knowledge of the project area and also with the educational qualifications to be able to communicate the contents to the age group comprised by the project, cf. section 20 of the Executive Order on Information. It is not a requirement that this person has educational training. The section in the trial protocol shall describe how this requirement will be taken into consideration.

On information to the age group from 15-17, see section 4.2.3. Written information for this target group shall be attached to the trial protocol, cf. Appendix 2, Guidelines for information to the age group from 15-17.

- g. **Respect for the physical and mental integrity of the child or the youth** and their right of privacy. Statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information about the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** The protocol shall state:
1. Who initiated the biomedical research project,
 2. Names of commercial as well as non-commercial sponsors,
 3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or

as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,

4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.
- i. **Compensation** for participation in a biomedical research project. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
 - j. **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the web address shall be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
 - k. **Availability of information** for the minor or the parents. How the trial subject or the parents are guaranteed access to further information on the project shall be stated, e.g. reference to a health professional who may be a contact person.
 - l. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a scientific journal, it shall be published in another way (possibly on www.clinicalstudyresult.org). Information on how publication will be made shall be stated.
 - m. **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues raised by the biomedical research project, including argumentation that the project is sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial and enable the committee to make a stricter risk/benefit assessment considering the inclusion of trial subjects who cannot give informed consent.

The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall display care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. Regard for the trial subject's integrity and autonomy, where the latter may be expressed, shall form the basis for the considerations in the section.

When placebo (or no treatment) is used it shall be explained that either there is no effective treatment or that the use of placebo is necessary/acceptable for

methodological reasons and that the child or the youth will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk

4.2.1.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol regarding purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information about external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.2.1.3 Information for the custodial parents

Surrogate consent shall be obtained from both custodial parents when a child or a youth under the age of 18 participates in a biomedical research project. Therefore, the custodial parent shall be informed of the research project pursuant to section 17 of the Committee Act and section 16 of the Executive Order on Information.

The general rule is that surrogate consent shall be given on the basis of satisfactory information of the nature, importance, scope and risks of the project as well as suitable documentation.

The child or the youth shall also receive **oral** information on the research project. The information shall be provided by a person who has knowledge of the area that the research project concerns and the educational qualifications to communicate the contents to the age group comprised by the project. However, it need not be a person with educational training.

The child or the youth shall be informed of and involved in the interviews with the parents on the biomedical research project to the extent that the child or the youth understands the trial situation. However, this does not apply if it may harm the trial subject.

The comments of the child or the youth shall, if these comments are relevant, be taken seriously, cf. section 17 of the Executive Order on Information.

If the **15-17-year-old** trial subject so wishes and the information may clarify the trial and the risks and benefits to the young person, he or she shall also receive **written** information about the project. Both the oral and the written information shall be adjusted to the age of the youth. The information shall be based on the parent information and be attached to the trial protocol, cf. Appendix 2, Participant information for the age group from 15-17.

In some cases the 15-17-year-old subjects may give informed consent. Then, the custodial parent shall have the same information about the research projects as the 15-17-year-old and be involved in the decision of the youth. This ensures that the parents are informed and able to support the youth in his or her decision. See section 4.2.1.4 on the possibility of young people giving consent to participation in certain trials.

4.2.1.3.1 Guidelines for oral information

The guidelines for submitting oral information to custodial parents, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The

guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact to the parents made?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How much time for reflection shall be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the trial subject should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.

Information interview with the parents:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the parents have sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerably adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the parents are believed to be unaware, but which are important for their decision, e.g. that remuneration is a taxable income.

After the information interview:

- The parents shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The parents shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The parents shall be informed if, during the implementation of the research project, significant information becomes available on the state of health of the child or the youth.
- If it is feasible, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the parents of the results achieved and of any consequences for the child or the youth.

4.2.1.3.2 Written information

The trial protocol shall also include written information for the custodial parents, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written **parent information** shall include the following:

1. The title of the project. If an abbreviated title is used on the information and not the title stated on the notification form, the original title shall be stated as well.
2. Request regarding participation in a scientific trial at the beginning of the information.
3. Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
4. Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
5. If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

6. The possible benefits of the research project. A distinction must be made between benefits for the individual child or youth, for others and for scientific progress.
7. Circumstances which may result in the involuntary exclusion of their son or daughter from the research project, as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An

example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.

8. Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.
9. Possible remuneration for the child or the youth, including information on taxation of the amount.
10. Who initiated the biomedical research project.
11. Names of commercial as well as non-commercial sponsors.
12. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
13. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
14. Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
15. Where the parents may obtain further information on the research project (e.g. from the contact person), and
16. A recommendation to read the attached appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects, cf. section 11 of the Executive Order.

The above concerns requirements regarding the actual application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.2.1.4 Consent from the custodial parents

The committee may only grant authorisation to initiate and continue a biomedical research project that involves children and youths under the age of 18 if consent from the custodial parents is obtained, cf. section 17 of the Committee Act and section 16 of the Executive Order.

Children or young people subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry cannot participate in biomedical trials, cf. section 23(1) of the Act.

The consent shall be in writing, dated and signed or submitted using an electronic signature. Please note that a precondition for inclusion of **minors** in trials is consent from both custodial parents. Therefore, both parents have to sign. However, this does not apply if one parent has authorised the other in writing to make a decision regarding the child's participation in a biomedical trial. Such an authorisation must clearly state the purpose (e.g. the child's participation in a trial at "the oncology department") and for how long time the authorisation is valid. There are no legal requirements for an authorisation. The signatures of two deponents may be required if there is a need to certify that the signature is genuine and that the signer is legally competent.

In case of non-intervention trials, e.g. swabs, consent from one custodial parent is sufficient.

The consent shall be an expression of the interest of the child or the youth, i.e. expected will. Regardless of a surrogate consent, the trial cannot be completed if the trial subject objects to it, cf. section 17(2) of the Executive Order. An objection is also any resistance that the trial subject does not formulate orally, but is indicated by the person's attitude, body language or resistance against physical interference.

If the minor comes of age during the course of the research project, informed consent shall be obtained from the trial subject before the project may continue, cf. section 19 of the Executive Order.

The trial protocol shall be accompanied by a copy of the declaration of consent.

The trial protocol should be accompanied by one of the ready-printed declarations (S5-S6) of the committee system concerning "Consent from the holder of custody for the child to participate in a biomedical research project". If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall ask for consent for the child/ the young person is involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and as soon as possible after the written and oral information. The consent shall be given to the chief investigator or a person authorised by him/her to provide the oral information. This person shall have direct connection with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that the written information has been submitted to the custodial parent. He or she is also entitled to receive a copy of the declaration of consent. Original declarations of consent shall be stored by the chief investigator, and the chief investigator is responsible for providing a copy of the declaration of consent to the trial subject or the custodial parent.

Under section 19 of the Committee Act, the committees may grant exemption from parents' consent when the trial subject has reached the age of 15. In this case the **15-year-old** shall give his or her own consent. Section 21 of the Executive Order states that this applies to cases where the research project does not or only to a limited extent involves intervention, and where the research project is deemed to present no harm or risk to the trial subject. This includes, for instance, swabs, blood tests, etc. If the 15-17-year-old gives his/her own informed consent, the pre-printed declaration of consent for legally competent trial subjects (S1 or S3) shall be used.

The consent shall be given to the chief investigator or a person authorised by him/her who is connected to the project. Original declarations of consent shall be stored by the chief investigator.

4.2.2 Trials with legally incompetent adults

This section is about the application requirements where legally incompetent adult trial subjects are involved. In these trials the guardian or the next-of-kin and the general practitioner alternatively the medical officer of health give surrogate consent.

Regarding trials with medical products and clinical investigations of medical devices, see section 4.4.2.

4.2.2.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the scientific standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent.

- d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.
- e. **Trial subjects, including criteria for inclusion and exclusion**. The inclusion and exclusion criteria shall be stated. The gender and age of the trial subjects shall be given, including whether the subjects included are patients and/or healthy trial subjects. If possible, a statistical reason for the planned number of trial subjects shall be given.

Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

At the evaluation of research projects initiated on the basis of surrogate consent, the committee shall, prior to the approval, ensure that the project cannot with similar benefit be conducted by including legally competent trial subjects. The committee shall also ensure that the surrogate consent is in accordance with the interest of the trial subject and that the criteria of section 13 of the Committee Act have been observed.

That section of the protocol shall therefore include a special argumentation for including persons who cannot give informed consent. According to section 13 of the Act, the trial can be approved if:

A

The project is essential to verify data collected through trials on individuals who are capable of giving their informed consent or through other trial methods, and the project concerns the clinical condition of the trial subject, and the project provides direct benefit to the patient group.

or if

B

The project cannot be implemented with the same benefit by including legally competent trial subjects and the project is expected to be of direct benefit to the trial subject.

or if

C

The project can be carried out only by the inclusion of individuals in the particular age group and with the disease or condition concerned, and the project is expected to be of considerable benefit to the group of patients of the same age group with the same disease or condition as the trial subject, and the project entails minimal risk and discomfort for the trial subject.

The trial protocol shall state which of the categories A, B, or C justifies implementation of the project.

- f. **Side effects, risks and inconveniences** for the trial subjects. The description shall cover predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. See item m concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore, any safety measures shall be stated in the trial protocol.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials shall be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

- g. **Respect for the physical and mental integrity of the trial subjects** and their right of privacy. A statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information about the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** The trial protocol shall include:
1. Who initiated the biomedical research project,
 2. Names of commercial as well as non-commercial sponsors,
 3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
 4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.
- i. **Compensation** for participation in a biomedical research project. Any remuneration (including reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
Compensation for participation in a biomedical research shall be described. See Appendix 6, Guidelines on remuneration of trial subjects.
- j. **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the web address shall be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
- k. **Availability of information** for trial subjects. Indication shall be provided as to how the trial subject or his/her representative is guaranteed access to further information on the project, such as reference to a health professional who may act as a contact person.
- l. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible, in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- m. **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues created by the biomedical research project, including an argumentation for the project being sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial to enable the committee to make a stricter risk/benefit assessment considering inclusion of trial subjects who are unable to give informed consent.

The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall display care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. In any event, the regard for the trial subject's integrity and autonomy shall form the basis for the considerations in the section.

When placebo (or no treatment) is used, it shall be explained that either there is no effective treatment, or that the use of placebo is necessary/acceptable for methodological reasons and that the trial subjects will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained, and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk.

4.2.2.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information on external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.2.2.3 Information in case of surrogate consent for legally incompetent adults

Surrogate consent is required when trial subjects are included who are unable to give informed consent to participate in the biomedical research project, cf. section 17 in the Committee Act and section 16 in the Executive Order on Information. This means that the person giving the surrogate consent shall be informed of the research project.

The general rule is that surrogate consent shall be given on the basis of satisfactory information about the nature, importance, scope and risks of the project as well as suitable documentation.

The legally incompetent adult trial subject shall be informed of and involved in the discussions about the biomedical research project to the extent that the person understands the trial situation, unless this may be harmful to the trial subject. The comments of the trial person shall, if they are relevant, be taken seriously, cf. section 17 in the Executive Order on Information.

If the trial subject obtains or regains his or her legal capacity during the research project, informed consent shall be obtained from the trial subject before the research project can continue, cf. section 19 of the Executive Order.

4.2.2.3.1 Guidelines for oral information

Guidelines for oral information, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact made to the person giving surrogate consent?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the person giving the consent should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the person giving surrogate consent has sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerately and adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the person giving surrogate consent is believed to be unaware, but which are important for the decision of the trial subject, e.g. that remuneration for the participants is a taxable income.

After the information interview:

- The person giving surrogate consent shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.

- The person giving surrogate consent shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The person giving surrogate consent shall be informed if, during the implementation of the research project, important information becomes available on the state of health of the trial subject.
- If it is feasible, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the person giving surrogate consent of the results achieved and of any consequences for the individual.

4.2.2.3.2 Written information

The trial protocol shall also include written information for the participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information for participants and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial at the beginning of the information for participants.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 5) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 6) The possible benefits of the research project. A distinction shall be made between benefits for the individual trial subject, for others and for scientific progress.
- 7) Circumstances which may result in the involuntary exclusion of the trial subject from the research project as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An

example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.

- 8) Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.
- 9) Possible remuneration for the trial subject, including information on taxation of the amount.
- 10) Who initiated the biomedical research project.
- 11) Names of commercial as well as non-commercial sponsors.
- 12) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 13) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 14) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 15) Where the trial subject may obtain further information on the research project (e.g. from the contact person), and
- 16) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects.

The above concerns requirements regarding the application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.2.2.4 Surrogate consent for legally incompetent adults

If a biomedical research project involves trial subjects who are unable to give informed consent to participation in the trial due to reduced physical or mental abilities caused by depression, age, mental deficiencies or the like, the committee may give permission to participation in the project if surrogate consent is obtained, cf. section 17 of the Committee Act and section 16 of the Executive Order on Information.

Persons subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

In trials with legally incompetent adults who are not under guardianship, **the next-of-kin and the general practitioner alternatively the medical officer of health** shall give surrogate consent.

A concrete assessment shall decide who is the next-of-kin. This person may be the trial subject's cohabiting spouse or cohabitor, relatives in direct line and siblings. Often foster children will be considered as next-of-kin. Depending on the circumstances, and especially where there is no spouse, cohabitor or children, those relatives to whom the trial subject is very close or closely related by marriage may also be considered as next-of-kin. Emphasis is placed on family circumstances and on the closeness of the relationship. The person giving surrogate consent must

have the trust of the trial subject and know the subject well. Therefore, a close friend may sometimes give surrogate consent.

Surrogate consent from **the general practitioner** shall be given on the basis of the doctor's knowledge of the trial subject or on the doctor's ability to familiarize himself with the trial subject or with the state of health of the trial subject combined with the doctor's assessment of the content of the biomedical research project, cf. section 22(2) of the Executive Order..

In the absence of the trial subject's general practitioner (e.g. vacation, sickness etc) or if the trial subject does not have a permanent general practitioner, the surrogate consent shall be obtained from the next-of-kin and the medical officer of health, cf. section 22(3). It is not possible generally to replace surrogate consent from the general practitioner with surrogate consent from the medical officer.

Consent from the general practitioner or the medical officer shall be obtained in order to ensure additional safeguarding of the legally incompetent adult, and surrogate consent must express the best interest of the trial subject.

The general practitioner or the medical officer of health shall by way of his employment or professional function in relation to the legally incompetent adult ensure that the consent to the legally incompetent adult's participation in the research project concerned be administered in a manner so as not to harm the trial subject. This may be done on the basis of either the doctor's knowledge of the trial subject or on the doctor's possibility to familiarize himself with the situation of the trial subject.

The assessment of whether surrogate consent to participation in a biomedical research project can be given shall be based on a medical assessment of the patient's condition and the complexity and possible consequences of the research project. It is to be expected, therefore, that when consent is given, the doctor has some knowledge of the content of the research project, and that the doctor on the basis of his or her medical knowledge considers that participation in the research project by the legally incompetent adult is justified.

It depends on a concrete assessment of the complexity of the research project what information is needed for the general practitioner or the medical officer to be able to give surrogate consent. In general it would be sufficient that the layman's summary and participant information is sent to the general practitioner or the medical officer. At the same time the chief investigator must ensure that the general practitioner or the medical officer is sufficiently informed of the framework of the surrogate consent, cf. guidance above.

When information is sent to the general practitioner or the medical officer, the chief investigator should, furthermore, ensure that clear contact information is provided so that the doctor can obtain further information about the project if this is needed in the concrete situation.

A **guardian** may give consent if the research project involves a person under personal guardianship. A condition for this is that the guardianship also covers the authority to give consent concerning participation in biomedical trials.

Adults who are legally incompetent, for example due to mental deficiencies, serious dementia or retardation of development or any other form of seriously impaired health, may participate by surrogate consent in accordance with the provisions in section 17(1) of the Executive Order.

The surrogate consent shall be an expression of the interest of the trial subject, and the committee can only give approval if the trial subject is willing to listen to the information that is adjusted to the person's ability to understand. Irrespective of a surrogate consent, the trial cannot be implemented if the trial subject objects, cf. section 17(2) of the Executive Order. An objection also means any resistance that the trial subject does not formulate orally, but is expressed by the attitude, body language of the person or any resistance against physical interference.

If the trial subject obtains or regains legal capacity during the term of the research project, informed consent shall be obtained from the trial subject, cf. section 19 of the Executive Order on Information, before the research project can continue.

The consent shall be in writing, dated and signed or submitted using an electronic signature. A copy of the declaration of consent shall be attached to the trial protocol.

The trial protocol should be accompanied by one of the ready-printed declarations (S7-S8) of the committee system concerning " Surrogate consent to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall ask for consent for the person to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and soonest after communication of the written and oral information. Consent shall be given to the chief investigator or a person authorised to communicate oral information. This person shall be directly associated with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that written information has been submitted to the person giving surrogate consent. He or she is also entitled to receive a copy of the declaration of consent. Original declarations of consent shall be stored by the chief investigator who is obliged to distribute a copy of the declaration of consent to the trial subject or the person giving surrogate consent.

The consent shall be given to the chief investigator or to a person authorised by him/her who is affiliated with the project. Original declarations of consent shall be stored by the chief investigator.

4.3 Trials with medical products and clinical investigations of medical devices involving legally competent trial subjects.

Section 4.3 describes the requirements regarding a duly formulated application for clinical trials with medical products and clinical investigations of medical devices. The trial subjects are legally competent, i.e. people who are at least 18 years of age and legally competent.

In trials with medical products and clinical investigations of medical devices there are supplementary requirements to the application as mentioned in section 4.0. These supplementary requirements are:

- A copy of a completed application for the Danish Medicines Agency (front page)
- Documentation of the notifier's medical or dental training. (certificate of graduation or authorisation)
- CV indicating the notifier's clinical experience
- Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of trial results.

In terms of finances, supplementary requirements regarding contents apply which are described in detail in section 4.4.1 h.

4.3.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography.. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the

research standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

Trials with medical products initiated by researchers shall also state who is the monitor on the trial.

- c. **Setting up a research biobank.** Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note: Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent

- d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.
- e. **Trial subjects, including criteria for inclusion and exclusion.** The inclusion and exclusion criteria shall be stated. The gender and age of the trial subjects shall be given, including whether the subjects included are patients and/or healthy trial subjects. If pregnant or breast-feeding subjects are included, this shall be stated. A statistical reason for the planned number of trial subjects shall be given.

Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

If the trial involves trial subjects who, because of placement in an institution, incarceration pursuant to the Psychiatry Act or due to circumstances of employment, are particularly exposed to pressure regarding participation in the research project, this shall be stated. In connection with employment, the employee is in a state of loyalty and dependence of the employer. Where the chief investigator or the sponsor is the employer, this may influence the decision of the employee. In such cases stricter requirements regarding information and consent may apply. Consequently, the committee may decide that the trial subject's consent should be given to a person who has been approved by the committee. The committee may

also decide that the information should state that the project is monitored by an independent professional.

It shall also be stated in the protocol if persons are included who due to physical handicaps are unable to sign a declaration of consent. In such cases the trial subject may authorise another person to sign the declaration of consent on his or her behalf.

- f. **Side effects, risks and inconveniences** for the trial subjects. The description shall cover predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. See item n below concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore the trial protocol shall describe any safety measures.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials shall be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

- g. **Respect for the physical and mental integrity of the trial subjects and for their right of privacy.** Statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information of the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** In case the chief investigator receives payment for the implementation of the trial, the size of such payment and the detailed rules for the payment shall be stated.

Moreover, the protocol shall state:

1. Who initiated the biomedical research project,
2. Names of commercial as well as non-commercial sponsors,
3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that

it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,

4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.

It shall be stated how any excess financial support should be used.

- i. **Relevant clauses in the contract between sponsor and the location of trial**, i.e. the physical or legal person responsible for the initiation, management or financing of the research project and the location of the trial/the chief investigator shall be emphasized in the contract which is to be presented to the committee. These are clauses on financial support for the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of the results which shall be translated into Danish when they are mentioned in the protocol or attached to the protocol, cf. CVK's webpage www.cvk.sum.dk.
- j. **Remuneration or reimbursement of expenses** for trial subjects. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
- k. **Recruitment of participants**. A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the address of the website shall be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
- l. **Availability of information** for trial subjects. Indication shall be provided as to how the trial subject is guaranteed access to further information on the project, such as reference to a health professional who may act as a contact person.
- m. **Publication of trial results**. The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, publication must be made in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- n. **Statement of biomedical research ethics**. The protocol shall include a statement concerning the ethical issues raised by the biomedical research project, including an argumentation that the project is sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial. The risk assessment shall comprise an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall display care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. Pursuant to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. In any event, regard for the trial subject's integrity and autonomy, where the latter may be expressed, shall form the basis for the considerations in the section.

When placebo (or no treatment) is used, it shall be explained that either there is no effective treatment or that the use of placebo is necessary/acceptable for methodological reasons, and that the trial subjects will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained, and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk.

4.3.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis of the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information on external financial support from private enterprises and foundations and a research-ethical account without using technical/professional terms.

4.3.3. Information for participants

The trial subject shall be entitled to receive information about the biomedical research project that he or she is considering to participate in, cf. section 16 of the Committee Act and section 17 of the Executive Order on Information.

4.3.3.1 Guidelines for oral information for participants

Guidelines for communication of oral information to participants, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact to the trial subject made?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How to make sure that the trial subject is given the option to have an observer present at the information interview?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?

A clear correlation between information and consent is required, i.e. the trial subject should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Attention must be drawn to the fact that it is possible to have an observer present at the interview.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.
- The researcher shall consider the trial subjects' right to decline knowledge of information about his or her own state of health.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the trial subjects have sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerably adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the trial subject is believed to be unaware, but which are important to the trial subject's decision, e.g. that remuneration for participants is a taxable income.

After the information interview:

- The trial person shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The trial subject who is still actively involved in the trial shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The trial subject shall be informed if, during the implementation of the research project, significant information becomes available on the trial subject's state of health, unless the trial subject has expressly stated that he or she does not want this, cf. section 13 of the Executive Order.
- If it is feasible and the trial subject so wishes, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the trial subject of the results achieved and of any consequences for the individual subject.

4.3.3.2 Written information for participants

The trial protocol shall also include written information for participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, the trial subject may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial at the beginning of the information.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Application of approved and non-approved medical products, the names of these products as well as dosage and use of randomisation, blind preparations, periods without treatment, including any known interaction with other medical products.
- 5) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 6) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 7) The possible benefits of the research project. A distinction shall be made between benefits for the individual trial subject, for others and for scientific progress.
- 8) Circumstances which may result in the involuntary exclusion of the subject concerned from the research project as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance pregnancy is a criterion for exclusion and the subject becomes pregnant during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.
- 9) Information about alternative treatment methods in situations where the project aims at results in terms of science as well as treatment.

- 10) Possible remuneration for the trial subject, including information on taxation of the amount.
- 11) Who initiated the biomedical research project.
- 12) Names of commercial as well as non-commercial sponsors.
- 13) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 14) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 15) If an authorisation is used to get access to a patient record, the content of such an authorisation must be further described. It is recommended that it is made clear what the information from the patient record is to be used for (e.g. monitoring, audit, inspection etc), to whom the authorisation is addressed (.e.g. sponsor, which employees of the sponsor, monitor etc), and for how long time the authorisation is valid, cf.CVK's webpage: www.cvk.sum.dk.
- 16) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 17) Where the trial subject may obtain further information on the research project (e.g. from the contact person), and
- 18) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects.

The above concerns requirements regarding the application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.3.4 Declaration of consent

No biomedical research projects shall be initiated or continued without the informed consent of the legally competent trial subject, cf. section 16 of the Committee Act and section 4 of the Executive Order on Information.

In a biomedical research project, an informed consent is a decision to participate in a research project which has been made upon satisfactory information on the nature, significance, implications and risks of the project and receipt of suitable documentation. The decision is made voluntarily by a person who is capable of giving his or her consent, cf. section 7(1)(viii) of the Committee Act. The consent shall be in writing, dated and signed or provided using an electronic signature.

The trial protocol shall be accompanied by a copy of the declaration of consent.

The trial protocol should be accompanied by one of the ready-printed declarations (S1-S4) of the committee system concerning "Informed consent to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If an authorisation is used to get access to the patient record, the authorisation must be included as an independent document (and may not form part of the declaration of consent). If, in connection with the research

project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall request the person concerned for his/her consent to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and as soon as possible after receipt of the written and oral information. The consent shall be given to the chief investigator or a person authorised to provide the oral information. This person shall have direct connection with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that the written information has been given to the trial subject and that communication of the oral information has taken place, cf. section 4(4) of the Executive Order.

Original declarations of consent shall be stored by the chief investigator, and the trial subject is entitled to have a copy of the declaration of consent.

Where, because of placement in an institution, incarceration that is not covered under the psychiatry act or under circumstances of employment or in similar circumstances, the trial subject is particularly exposed to pressure regarding participation in a biomedical research project, but where the subject is otherwise capable of making decisions, the committee may upon a concrete assessment decide that the consent of the trial subject to participate in the research project shall be given to a person authorised by the committee. The committee may also decide that in such cases the information shall be supplemented by a statement that the course of the research project shall be observed by an independent professional, cf. section 15 of the Executive Order.

4.4 Medical product trials and clinical investigation of medical devices involving legally incompetent subjects

Section 4.4 describes the requirements of a duly formulated application for biomedical research projects involving trial subjects who because of age or reduced physical or mental abilities due to depression, age, mental deficiencies or similar conditions are incapable of giving informed consent to participation in trials.

Regarding trials with medical products and clinical investigations of medical devices in emergency situations, see section 4.6.

4.4.1 Trials with children and young people under the age of 18

This section describes requirements regarding an application for trials with medical products or clinical investigations of medical devices involving children and young people under the age of 18. The assumption in the text is that the custodial parent gives surrogate consent. If someone other than the custodial parent gives consent on behalf of the minor, this person assumes the rights described for the custodial parent.

In trials with medical products and clinical investigations of medical devices there are supplementary requirements to the application as mentioned in section 4.0. These supplementary requirements are:

- A copy of a completed application for the Danish Medicines Agency (front page)
- Documentation of the notifier's medical or dental training. (certificate of graduation or authorisation)
- CV indicating the notifier's clinical experience
- Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of trial results. These clauses shall be translated into Danish if they are mentioned in the protocol or attached to the protocol

In terms of finances, supplementary requirements regarding contents apply which are described in detail in section 4.4.1.1. h.

4.4.1.1 Trial protocol

The trial protocol shall contain a description of the following:

- a) **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b) **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the research standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

Trials with medical products initiated by researchers shall also state who is the monitor on the trial.

- c) **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent.

- d) **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made.

Calculation of strain shall be available. It should be stated how the risk is being monitored continuously.

- e) **Trial subjects, including criteria for inclusion and exclusion.** Inclusion and exclusion criteria shall be stated. The gender and age of the child or the youth shall be given. The least vulnerable children should be preferred. That means older children should be preferred before younger children. A healthy child or youth can as a principle rule not participate in medicinal product trials (except trials with vaccine). It should be stated whether the subjects included are patients and/or healthy trials subjects. If pregnant or breast-feeding subjects are included, this shall be stated. A statistical reason for the planned number of trial subjects shall be stated.

Children or young people subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

At the evaluation of research projects involving minors, the committee shall, prior to the approval, ensure that the project cannot with similar benefit be conducted by including legally competent trial subjects, that the surrogate consent is in accordance with the interest of the child or the youth, and that the criteria of section 13 of the Committee Act have been observed.

The protocol shall therefore include a special argumentation for involving persons who cannot give informed consent. According to section 13 of the Act, the trial can be approved if:

A

The project is essential to verify data collected through trials on individuals who are capable of giving their informed consent or through other trial methods, and the project concerns the clinical condition of the child or the youth, and the project provides direct benefit to the patient group.

If it is not a trial with medical products, but a clinical investigation of medical devices, the investigation may also be approved if

B

The project cannot be implemented with the same benefit by including legally competent trial subjects and the project is expected to be of direct benefit to the child or the youth.

or if

C

The project can be carried out only by the inclusion of individuals in that age group, with that disease or condition, and the project is expected to be of considerable benefit to the group of patients of the same age group, with the same disease or condition as the trial subject, and the project entails minimal risk and discomfort for the child or the youth.

The trial protocol shall state which of the categories A, B, or C justifies implementation of the project.

- f) **Side effects, risks and inconveniences** for the child or the youth. The trial protocol shall describe predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. See item n below concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the child or the youth. Therefore, the trial protocol shall describe any safety measures.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials must be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Attention is drawn to the fact that the child or the youth shall receive oral information of the research project, its risks and benefits from a person with knowledge of the project area and with the educational qualifications to be able to communicate the contents to the age group comprised by the project, cf. section 20 of the Executive Order on Information. It is not a requirement that this person has had educational training. The section in the trial protocol shall describe how this requirement will be taken into consideration.

On information to the age group from 15-17, see section 4.4.3.

- g) **Respect for the physical and mental integrity of the child or the youth** and their right of privacy. Statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information about the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h) **Finances.** If the chief investigator receives remuneration for completion of the trial, the size of the remuneration and the rules for payment hereof shall be stated.

The protocol shall also state:

1. Who initiated the biomedical research project,
2. Names of commercial as well as non-commercial sponsors,
3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.

It shall be stated how any excess financial support is to be used.

- i) **Relevant clauses in the contract between sponsor and the location of the trial**, i.e. the physical or legal person responsible for the initiation, management or

financing of the research project and the location of the trial/the chief investigator shall be emphasized in the contract which is to be presented to the committee. These are clauses on financial support for the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of the results which shall be translated into Danish when they are mentioned in the protocol or attached to the protocol, cf. CVK's webpage www.cvk.sum.dk.

- j) **Compensation** for participation in a biomedical research project. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
- k) **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the web address shall be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
- l) **Availability of information** for the minor or the parents. How the trial subject or the parents are guaranteed access to further information on the project shall be stated. For instance reference to a health professional who may be a contact person.
- m) **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a scientific journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). Information of how publication will be made shall be stated.
- n) **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues created by the biomedical research project, including argumentation that the project is sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial and enable the committee to make a strict risk/benefit assessment considering the involvement of trial subjects who cannot give informed consent.

The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall show care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. When regard for the trial subject's integrity and autonomy may be expressed, it shall in any case form the basis for the considerations in the section.

When placebo (or no treatment) is used, it shall be explained that either there is no effective treatment or that the use of placebo is necessary/acceptable for methodological reasons, and that the child or the youth will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained, and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk.

4.4.1.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol regarding purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information about external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.4.1.3 Information for the custodial parents

Surrogate consent shall be obtained from both custodial parents when a child or a youth under the age of 18 participates in a biomedical research project. Therefore, the custodial parent shall be informed of the research project pursuant to section 17 of the Committee Act and section 16 of the Executive Order on Information.

The general rule is that surrogate consent shall be given on the basis of satisfactory information of the nature, importance, scope and risks of the project as well as suitable documentation.

The child or the youth involved in biomedical research projects shall receive **oral** information on the research project. The information shall be provided by a person who has knowledge of the area that the research project concerns and the educational qualifications to communicate the contents to the age group comprised by the project. However, it need not be a person with educational training.

The child or the youth shall be informed of and be involved in the interviews with the parents on the biomedical research project to the extent that the child or the youth understands the situation. However, this does not apply if it may harm the trial subject.

The comments of the child or the youth shall, if these comments are relevant, be taken seriously, cf. section 17 of the Executive Order on Information.

If the **15-17-year-old** trial subject so wishes and the information may clarify the trial and the risks and benefits to the young person, he or she shall also receive **written** information about the project. Both the oral and the written information shall be adjusted to the age of the youth. The information shall be based on the parent information and be attached to the trial protocol, cf. Appendix 2, Participant information for the age group from 15-17.

4.4.1.3.1 Guidelines for oral information

The guidelines for submitting oral information to custodial parents, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact to the parents made?
Through posting or a personal contact?

- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the parents should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.

Information interview with the parents:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the parents have sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerably adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the parents are believed to be unaware, but which are important for their decision, e.g. that remuneration is a taxable income.

After the information interview:

- The parents shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The parents shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The parents shall be informed if, during the implementation of the research project, significant information becomes available on the state of health of the child or the youth.
- If it is feasible, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the parents of the results achieved and of any consequences for the child or the youth.

4.4.1.3.2 Written information

The trial protocol shall also include written information for the custodial parents, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written **parent information** shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial at the beginning of the information.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Application of approved and non-approved medical products, the names of these products as well as dosage and use of randomisation, blind preparations, periods without treatment, including any known interaction with other medicinal products.
- 5) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 6) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 7) The possible benefits of the research project. A distinction shall be made between benefits for the individual child or youth, for others and for scientific progress.
- 8) Circumstances which may result in the involuntary exclusion of their son or daughter from the research project as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.
- 9) Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.

- 10) Possible remuneration for the child or the youth, including information on taxation of the amount.
- 11) Who initiated the biomedical research project.
- 12) Names of commercial as well as non-commercial sponsors.
- 13) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 14) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 15) If an authorisation is used to get access to a patient record, the content of such an authorisation must be further described. It is recommended that it is made clear what the information from the patient record is to be used for (e.g. monitoring, audit, inspection etc), to whom the authorisation is addressed (e.g. sponsor, which employees of the sponsor, monitor etc), and for how long time the authorisation is valid, cf. CVK's webpage: www.cvk.sum.dk.
- 16) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 17) Where the parents may obtain further information on the research project (e.g. from the contact person), and
- 18) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects, cf. section 11 of the Executive Order.

The above concerns requirements regarding the actual application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.4.1.4 Consent from the custodial parents

The committee may only grant authorisation to initiate and continue a biomedical research project that involves children and young people under the age of 18 if consent from the custodial parents is obtained, cf. section 17 of the Committee Act and section 16 of the Executive Order.

Children or young people subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry cannot participate in biomedical trials, cf. section 23(1) of the Act.

The consent shall be in writing, dated and signed or submitted using an electronic signature. Please note that a precondition for involvement of **minors** in trials is consent from both custodial parents. Therefore, both parents have to sign. However, this does not apply if one parent has authorised the other in writing to make a decision regarding the child's participation in a biomedical trial. Such an authorisation should clearly state the purpose (e.g. the child's participation in a trial at "the oncology department") and for how long time the authorisation is valid. There are no legal requirements for an authorisation. The signatures of two deponents may be required if there is a need to certify that the signature is genuine and that the signer is legally competent.

The consent shall be an expression of the interest of the child or the youth, i.e. expected will. Regardless of a surrogate consent, the trial cannot be completed if the trial subject objects to it, cf. section 17(2) of the Executive Order. An objection is also any resistance that the trial subject does not formulate orally, but is indicated by the person's attitude, body language or resistance against physical interference.

If the minor comes of age during the term of the research project, informed consent shall be obtained from the trial subject before the project can continue, cf. section 19 of the Executive Order.

The trial protocol shall be accompanied by a copy of the declaration of consent.

The trial protocol should be accompanied by one of the ready-printed declarations (S5-S6) of the committee system concerning "Consent from the holder of custody for the child to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If an authorisation is used to get access to the patient record, the authorisation must be included as an independent document (and may not form part of the declaration of consent).. If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall ask for consent for the child/ the young person is involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and as soon as possible after the written and oral information. The consent shall be given to the chief investigator or a person authorised by him/her to give the oral information. This person shall have direct connection with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that the written information has been submitted to the custodial parent. He or she is also entitled to receive a copy of the declaration of consent. Original declarations of consent shall be stored by the chief investigator, and the chief investigator is responsible for providing a copy of the declaration of consent to the trial subject or the custodial parent.

The consent shall be given to the chief investigator or a person authorised by him/her who is connected to the project. Original declarations of consent shall be stored by the chief investigator.

4.4.2 Trials with legally incompetent adults

This section describes the application requirements where legally incompetent adult trial subjects are involved and where the trial deals with medicinal products or medical devices. In such trials the guardian or the next-of-kin and the general practitioner alternatively the medical officer of health gives surrogate consent.

Regarding emergency trials with medicinal products involving legally incompetent adults, see section 4.6.2.

In trials with medicinal products and in clinical investigations of medical devices there are supplementary requirements to the application as mentioned in section 4.0. These supplementary requirements are:

- A copy of a completed application for the Danish Medicines Agency (front page)
- Documentation of the notifier's medical or dental training. (certificate of graduation or authorisation)
- CV indicating the notifier's clinical experience
- Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of trial results. These clauses shall be translated into Danish if they are mentioned in the protocol or attached to the protocol

In terms of finances, supplementary requirements regarding contents apply which are described in detail in section 4.4.1 f.

4.4.2.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the scientific standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

Trials with medical products initiated by researchers shall also state who is the monitor on the trial.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent

- d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.

- e. **Trial subjects, including criteria for inclusion and exclusion.** The inclusion and exclusion criteria shall be stated. The gender and age of the trial subjects shall be given, including whether the subjects included are patients and/or healthy trial subjects. If possible, a statistical reason for the planned number of trial subjects shall be given.

Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

At the evaluation of research projects initiated on the basis of surrogate consent, the committee shall, prior to the approval, ensure that the project cannot with similar benefit be conducted by including legally competent trial subjects. The committee shall also ensure that the surrogate consent is in accordance with the interest of the trial subject and that the criteria of section 13 of the Committee Act have been observed.

In connection with medicinal product trials, the protocol shall therefore include a special argumentation for involving persons who cannot give informed consent. According to section 13 of the Act, a trial with medicinal products can be approved if:

A

The project is essential to verify data collected through trials on individuals who are capable of giving their informed consent or through other trial methods, and the project concerns the clinical condition of the trial subject, and the project provides direct benefit to the patient group.

If it is not a trial with medicinal products, but a clinical investigation of medical device, the investigation can be approved if

B

The project cannot be implemented with the same benefit by including legally competent trial subjects and the project is expected to be of direct benefit to the trial subject.

or if

C

The project can be carried out only by the inclusion of individuals in the particular age group and with the disease or condition concerned, and the project is expected to be of considerable benefit to the group of patients of the same age with the same disease or condition as the trial subject, and the project entails minimal risk and discomfort for the trial subject.

The trial protocol shall state which of the categories A, B, or C justifies implementation of the project.

- f. **Side effects, risks and inconveniences** for the trial subjects. The trial protocol shall describe predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc. See item n concerning the application of placebo.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore, any safety measures shall be stated in the trial protocol.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials shall be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

- g. **Respect for the physical and mental integrity of the trial subjects** and their right of privacy. A statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information about the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** If the chief investigator receives remuneration for completion of the trial, the size of the remuneration and the more detailed rules for payment shall be stated.

The trial protocol shall include:

- 1) Who initiated the biomedical research project,
- 2) Names of commercial as well as non-commercial sponsors,
- 3) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
- 4) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.

It shall also be stated how any excess financial support is used.

- i. **Relevant clauses in the contract between sponsor and the location of the trial**, i.e. the physical or legal person responsible for the initiation, management or financing of the research project and the location of the trial/the chief investigator shall be emphasized in the contract which is to be presented to the committee. These are clauses on financial support for the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of the results which shall be translated into Danish when they are mentioned in the protocol or attached to the protocol, cf. CVK's webpage www.cvk.sum.dk.
- j. **Compensation** for participation in a biomedical research project. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects. .

- k. **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited. If websites are used for recruitment of trial subjects, the web address shall be stated. Any advertisement, posting or equivalent shall be enclosed with the application. The text of the advertisement shall constitute a factual presentation of the biomedical research project. The wording shall be without value-laden expressions and shall not arouse unrealistic expectations in the target group of the advertisement.
- l. **Availability of information** for trial subjects. How the trial subject or his/her substitute is guaranteed access to further information on the project shall be stated, such as reference to a health professional who may act as a contact person.
- m. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible, in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- n. **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues created by the biomedical research project, including an argumentation for the project being sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial to enable the committee to make a stricter risk/benefit assessment considering involvement of trial subjects who are unable to give informed consent.

The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall show care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. In any event, the regard for the trial subject's integrity and autonomy shall form the basis for the considerations in the section.

When placebo (or no treatment) is used, it shall be explained that either there is no effective treatment or that the use of placebo is necessary/acceptable for methodological reasons, and that the trial subjects will not in this way be exposed to any risk of serious or irreversible harm. Selection of control group should be explained, and there must be a detailed description of the duration of the use of placebo and safety procedures, cf. CVK's web page www.cvk.sum.dk.

4.4.2.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information

on external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.4.2.3 Information in case of surrogate consent for legally incompetent adults

Surrogate consent is required when the trial subjects involved are unable to give informed consent to participate in the biomedical research project, cf. section 17 in the Committee Act and Section 16 in the Executive Order on Information.

The general rule is that surrogate consent shall be given on the basis of satisfactory information about the nature, importance, scope and risks of the project as well as suitable documentation.

The legally incompetent adult trial subject who is unable to give informed consent shall be informed of and involved in the discussions about the biomedical research project to the extent that the person understands the trial situation, unless this may be harmful to the trial subject. The comments of the trial person shall, if they are relevant, be taken seriously, cf. section 17 in the Executive Order on Information.

If the trial subject obtains or regains his or her legal capacity during the research project, informed consent shall be obtained from the trial subject before the research project can continue, cf. section 19 of the Executive Order.

4.4.2.3.1 Guidelines for oral information

Guidelines for oral information, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact made to the person giving surrogate consent?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the person giving the consent should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.

- Information shall be provided that it is a request for participation in a biomedical research project.
- Information shall be provided about the right to time for reflection after having received the information. The time for reflection depends on the nature of the trial. Basically, it should be at least 24 hours.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the person giving surrogate consent has sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerately and adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the person giving surrogate consent is believed to be unaware, but which are important for the decision, e.g. that remuneration for the participants is a taxable income.

After the information interview:

- The person giving surrogate consent shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The person giving surrogate consent shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The person giving surrogate consent shall be informed if, during the implementation of the research project, important information becomes available on the state of health of the trial subject.
- If it is feasible, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the person giving surrogate consent of the results achieved and of any consequences for the individual.

4.4.2.3.2 Written information

The trial protocol shall also include written information for the participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information for participants and not the title stated on the notification form, the original title shall be stated as well.

- 2) Request regarding participation in a scientific trial at the beginning of the information for participants.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Application of approved and non-approved medicinal products, the names of these products as well as dosage and use of randomisation, blind preparations, periods without treatment, including any known interaction with other medicinal products.
- 5) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 6) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 7) The possible benefits of the research project. A distinction shall be made between benefits for the individual trial subject, for others and for scientific progress.
- 8) Circumstances which may result in the involuntary exclusion of the trial subject from the research project, as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.
- 9) Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.
- 10) Possible remuneration for the trial subject, including information on taxation of the amount.
- 11) Who initiated the biomedical research project.
- 12) Names of commercial as well as non-commercial sponsors.
- 13) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 14) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).

- 15) If an authorisation is used to get access to a patient record, the content of such an authorisation must be further described. It is recommended that it is made clear what the information from the patient record is to be used for (e.g. monitoring, audit, inspection etc), to whom the authorisation is addressed (e.g. sponsor, which employees of the sponsor, monitor etc), and for how long time the authorisation is valid, cf. CVK's webpage: www.cvk.sum.dk
- 16) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 17) Where the trial subject may obtain further information on the research project (e.g. from the contact person), and
- 18) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects.

The above is about requirements regarding the actual application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.4.2.4 Surrogate consent for legally incompetent adults

If a biomedical research project involves trial subjects who are unable to give informed consent to participation in the trial due to age or reduced physical or mental abilities caused by depression, age, mental deficiencies or the like, the committee may give permission to participation in the project if surrogate consent is obtained, cf. section 17 of the Committee Act and section 16 of the Executive Order on Information.

Persons subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

In trials with legally incompetent adults who are not under guardianship, **the next-of-kin and the general practitioner alternatively the medical officer of health** shall give surrogate consent.

A concrete evaluation shall decide who is the next-of-kin. This person may be the trial subject's cohabiting spouse or cohabitor, relatives in direct line and siblings. Often foster children will be considered as next-of-kin. Depending on the circumstances, and especially where there is no spouse, cohabitor or children, those relatives to whom the trial subject is very close or closely related to by marriage may also be considered as next-of-kin. Emphasis is placed on family circumstances and on the closeness of the relationship. The person giving surrogate consent must have the trust of the trial subject and know the subject well. Therefore, a close friend may sometimes give surrogate consent.

Surrogate consent from the **general practitioner** shall be given on the basis of the doctor's knowledge of the trial subject or on the doctor's ability to familiarize himself with the trial subject or with the state of health of the trial subject combined with the doctor's assessment of the content of the biomedical research project, cf. section 22(2) of the Executive Order. The doctor's consent shall be obtained in order to ensure additional security for the legally incompetent adult.

In the absence of the trial subject's general practitioner (in the case of vacation, sickness etc.) or if the trial subject has no permanent general practitioner, the surrogate consent shall be obtained from **the next-of-kin and the medical officer of health**, cf. section 22(3). It is not possible generally to replace surrogate consent from the general practitioner with surrogate consent from the medical officer,

Consent from the general practitioner or the medical officer shall be obtained in order to ensure additional safeguarding of the legally incompetent adult, and surrogate consent must express the best interest of the trial subject.

The general practitioner or the medical officer of health shall, by way of his employment or professional function in relation to the legally incompetent adult, ensure that the consent to the legally incompetent adult's participation in the research project be administered in a manner so as not to harm the trial subject. This may be done on the basis of either the doctor's knowledge of the trial subject or of the doctor's possibility to familiarize himself with the circumstances of the trial subject.

The assessment of whether surrogate consent to participation in a biomedical research project can be given shall be based on a medical assessment of the patient's condition and the complexity and possible consequences of the research project. It is to be expected, therefore, that when consent is given, the doctor has some knowledge of the content of the research project, and that the doctor on the basis of his or her medical knowledge considers that participation in the research project by the legally incompetent adult is justified.

It depends on a concrete assessment of the complexity of the research project what information is needed for the general practitioner or the medical officer to be able to give surrogate consent. In general it would be sufficient that the layman's summary and participant information is sent to the general practitioner or the medical officer. At the same time the chief investigator must ensure that the general practitioner or the medical officer is sufficiently informed of the framework of the surrogate consent, cf. guidance above.

When information is sent to the general practitioner or the medical officer, the chief investigator should, furthermore, ensure that clear contact information is provided so that the doctor can obtain further information about the project if this is needed in the concrete situation.

A **guardian** may give consent if the research project involves a person under personal guardianship. A condition for this is that the guardianship also covers authority to give consent concerning participation in biomedical trials.

Adults who are legally incompetent, for example due to mental deficiencies, including serious dementia or retardation of development or any other form of seriously impaired health, may participate under conditions of surrogate consent in accordance with the regulations in section 17(1) of the Executive Order.

The surrogate consent shall be an expression of the interest of the trial subject and the committee can only give approval if the trial subject is willing to listen to the information that is adjusted to the person's ability to understand. Irrespective of a surrogate consent, the trial cannot be implemented if the trial subject objects, cf. section 17(2) of the Executive Order. Objection also means any resistance that the trial subject does not formulate orally, but is expressed by the attitude, body language of the person or any resistance against physical interference.

If the trial subject obtains or regains legal capacity during the term of the research project, informed consent shall be obtained from the trial subject, cf. section 19 of the Executive Order on Information, before the research project can continue.

The consent shall be in writing, dated and signed or submitted using an electronic signature. A copy of the declaration of consent shall be attached to the trial protocol.

The trial protocol should be accompanied by one of the ready-printed declarations (S7-S8) of the committee system concerning "Surrogate consent to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If an authorisation is used to get access to the patient record, the authorisation must be included as an independent document (and may not form part of the declaration of consent). If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall ask for consent for the person to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and soonest after submission of the written and oral information. Consent shall be given to the chief investigator or a person authorised to communicate oral information. This person shall be directly associated with the research project, cf. section 4(5)

of the Executive Order. The chief investigator shall certify that written information has been submitted to the person giving surrogate consent. He or she is also entitled to have a copy of the declaration of consent. Original declarations of consent shall be stored by the chief investigator who is obliged to distribute a copy of the declaration of consent to the trial subject or the person giving surrogate consent.

The consent shall be given to the chief investigator or to a person authorised by him/her who is associated with the project. Original declarations of consent shall be stored by the chief investigator.

4.5 Trials involving deceased individuals

Section 4.5. deals with the requirements of a duly formulated application concerning biomedical research projects involving deceased individuals.

Research involving deceased individuals can only be made in connection with

- Medical post-mortem examinations pursuant to section 187 of the Health Act
- Donation of the body to science pursuant to section 188 of the Health Act, or

Intervention made outside the provisions of the Health Act, but according to section 18(2) of the Committee Act.

Research may not be carried out in connection with forensic autopsy. And research projects may not be undertaken using biological material removed in connection with forensic autopsies regardless of storage conditions or time.

4.5.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including the nature of the intervention and how much biological material is taken. A possible use of a control group shall be stated. The information shall enable the committee to assess the research standard of the project and ensure that the project contributes to providing new valuable knowledge. If possible, a statistical reason for the planned number of deceased individuals to be included shall be given.
- c. **The object of the trial**. It shall be stated that the project concerns a trial on deceased individuals and whether the research is made on the basis of the provisions of the Health Act regarding a medical post-mortem examination and donation of the body to science, respectively, or according to section 18(2) of the Committee Act.
- d. **Respect for the integrity and right of privacy of the deceased individual**. A statement shall be given that data concerning the deceased individual are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information of the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules of the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- e. **Finances.** It shall be stated in the protocol
 1. Who initiated the biomedical research project,
 2. Names of commercial as well as non-commercial sponsors,
 3. Amounts granted by each sponsor, the way in which the subsidy is included in the research project, and
 4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.

- f. **Availability of information** for the relatives. In case of a minor intervention outside post-mortem, the protocol shall contain information as to how the next-of-kin is guaranteed access to information on the project, such as reference to a person who may act as a contact person.

- g. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. It shall be stated how publication will be made. If the results cannot be published in a journal, publication shall be made in another way (possibly on www.clinicalstudyresult.org).

- h. **Statement of biomedical research ethics.** The protocol shall include argumentation for the project being sound in terms of biomedical research ethics. Respect for the integrity of the deceased shall form the basis for the considerations in the section.

4.5.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis of the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, information about external financial support from private enterprises and foundations, including criteria for inclusion and exclusion without using technical/professional terms.

4.5.3 Information for the relatives

Written information for the relatives shall be attached to the protocol in the event that it is not a post-mortem examination or a donation. The information shall include information on the purpose and method of the project and the nature of the intervention. In addition to this, name, address, e-mail address and phone number of a contact person connected with the research project and information stating who is the chief investigator.

4.5.4 Consent to trials on deceased individuals

As mentioned in item 4.5, research involving deceased individuals shall be based on the provisions of the Health Act or the Committee Act.

Consent for a research project is only required if it is carried out in accordance with section 18(2) of the Committee Act.

In such cases consent shall be obtained from the relatives. When obtaining surrogate consent from relatives, a declaration of consent shall be attached to the research protocol. The pre-printed declaration form of the committee system concerning "Surrogate consent to participate in a biomedical research project" shall be used. Its a standard prepared by the National Committee on Biomedical Research Ethics.

4.6 Trials in emergency situations

Section 4.6 describes the requirements of a duly formulated application for a biomedical research project in emergency situations, cf. sections 20 and 20a of the Committee Act.

4.6.1 Trials in emergency situations that do not involve medicinal products

This section describes the requirements regarding an application in emergency situations that do not involve medicinal products.

In clinical investigations of medical devices there are supplementary requirements to the application as mentioned in section 4.0. These supplementary requirements are:

- A copy of a completed application for the Danish Medicines Agency (front page)
- Documentation of the notifier's medical or dental training. (certificate of graduation or authorisation)
- CV indicating the notifier's clinical experience
- Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of trial results.

Section 20 of the Committee Act describes situations where consent is obtained **after** completion of the trial. It is about the cases where the nature of the research project implies that it can only be implemented in emergency situations where the trial subject is unable to give his/her informed consent and it is impossible to obtain surrogate consent.

Research on this group may be made only if the physical/mental condition making it impossible to obtain informed consent or a surrogate consent is a necessary characteristic element of the research project. It is normally trials involving individuals who are temporarily incapacitated, e.g. unconscious.

It is a requirement that there is reason to assume that the trial subject's health can be improved in the long term.

Such trials cannot be carried out with medicinal products, but in other trials, including clinical investigations of medical devices.

4.6.1.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the scientific standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent

- d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.
- e. **Trial subjects, including criteria for inclusion and exclusion**. The gender and age of the trial subjects shall be stated. If pregnant or breast-feeding subjects are included, this shall be stated. If possible, a statistical reason shall be provided as to the planned number of trial subjects.
- Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.
- f. **Side effects, risks and inconveniences** for the trial subjects. The trial protocol shall describe predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore, the trial protocol shall describe any safety measures.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials must be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

- g. **Respect for the physical and mental integrity of the trial subjects and for their right of privacy.** Statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information of the duty of notification. If biological material is exported to countries outside the EU, it shall be stated that the project is implemented in accordance with the rules under the Act of processing of personal data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** It shall be stated
1. Who initiated the biomedical research project,
 2. Names of commercial as well as non-commercial sponsors,
 3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
 4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.
- i. **Relevant clauses in the contract between sponsor and the location of the trial,** i.e. the physical or legal person taking on responsibility for the initiation, management or financing of the research project and the location of the trial/the chief investigator shall be emphasized in the contract which is to be presented to the committee. These are clauses on financial support for the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of the results which shall be translated into Danish when they are mentioned in the protocol or attached to the protocol.
- j. **Remuneration** for trial subjects. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
- k. **Recruitment of participants.** A description shall be made of where and how trial subjects are recruited.

- l. **Availability of information** for trial subjects. Indication shall be provided as to how the trial subject is guaranteed access to further information on the project, such as reference to a health professional who may act as a contact person.
- m. **Publication of trial results.** The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible, in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- n. **Statement of biomedical research ethics.** The protocol shall include a statement concerning the ethical issues raised by the biomedical research project, including an argumentation for the project being a sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial. The risk assessment shall comprise an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall show care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the trial subject's safety, rights and welfare shall take precedence over scientific and social interests. In any event, the regard for the trial subject's integrity and autonomy shall form the basis for the considerations in the section.

It shall appear from the protocol that subsequent informed consent or surrogate consent will be obtained as soon as possible.

4.6.1.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen to whom and why) in a brief form. The lay person summary shall be included as part of the basis of the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information on external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.6.1.3 Information about the trial

It is stated in section 20(2) of the Committee Act that the chief investigator as soon as possible after the trial shall obtain informed consent from the trial subject or a surrogate consent. The surrogate consent shall be given by the guardian, the custodial parent or the next-of-kin and the general practitioner alternatively the medical officer of health.

The general rule is that surrogate consent shall be given on the basis of satisfactory information of the nature, importance, scope and risks of the project as well as suitable documentation.

Informed consent shall also be obtained if the trial subject regains legal capacity during the term of the research project, cf. section 19 of the Executive Order.

4.6.1.3.1 Guidelines for oral information

The trial protocol shall be accompanied by guidelines for oral information, cf. section 8 of the Executive Order. These guidelines may also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact made to the trial subject or the person giving surrogate consent? Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How to make sure that the trial subject is given the option to have an observer present at the interview?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the person giving the consent should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Information shall be provided that it is a request for participation in a biomedical research project.
- Attention must be drawn to the fact that the trial subject is entitled to have an observer present during the interview.
- Information shall be provided about the right to time for reflection after having received the information.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the trial subject or the person giving surrogate consent has sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerately and adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and

inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.

- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the trial subject or the person giving surrogate consent is believed to be unaware, but which are important for the decision, e.g. that remuneration for the participants is a taxable income.

After the information interview:

- The trial subject or the person giving surrogate consent shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The trial subject or the person giving surrogate consent shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The trial subject or the person giving surrogate consent shall be informed if, during the implementation of the research project, important information becomes available on the state of health of the trial subject. However, the trial subject may have declined this knowledge.
- If it is feasible and the trial subject so wishes, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the trial subject or the person giving surrogate consent of the results achieved and of any consequences for the individual trial subject.

4.6.1.3.2 Written information

The trial protocol shall also include written information for the participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information for participants and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial in an emergency situation at the beginning of the information for participants. It shall be stated that the trial has been initiated.
- 3) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 4) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 5) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:
 What material and how much is removed (e.g. ml per removal or a total)?
 Are there any risks involved in the removal and, if so, what are they?
 What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 6) The possible benefits of the research project. A distinction shall be made between benefits for the individual trial subject, for others and for scientific progress.
- 7) Circumstances which may result in the involuntary exclusion of the trial subject from the research project, as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.
- 8) Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.
- 9) Possible remuneration for the trial subject, including information on taxation of the amount.
- 10) Who initiated the biomedical research project.
- 11) Names of commercial as well as non-commercial sponsors.
- 12) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 13) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 14) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 15) Where the trial subject or the person giving surrogate consent may obtain further information on the research project (e.g. from the contact person), and
- 16) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless this information is given in the information material. The Appendix states the general rights of trial subjects.

The above is about requirements regarding the actual application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.6.1.4 Subsequent consent in emergency trial situations

Section 20(2) of the Committee Act stipulates that the chief investigator as soon as possible after completion of the trial shall obtain informed consent from the trial subject or a surrogate consent. This shall be given by the guardian, the custodial parent or by the next-of-kin and the general practitioner alternatively the medical officer of health.

If surrogate consent has been obtained and the trial subject obtains or regains his or her legal capacity during the term of the research project, informed consent shall be obtained from the trial subject before the research project can continue, cf. section 19 of the Executive Order on Information.

The trial protocol shall be accompanied by a copy of the declaration of consent.

The trial protocol should be accompanied by one of the ready-printed declarations (S1-S4) of the committee system concerning "Informed consent to participate in a biomedical research project" or "Surrogate consent to participate in a biomedical research project" (S7-S8). These are standards prepared by the committee system on research ethics.

If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall ask for consent for the person to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

The chief investigator shall keep a copy of the signed declaration of consent and the chief investigator shall be obliged to give the trial subject a copy of the declaration of consent.

4.6.2 Trials with medicinal products in emergency situations

This section describes the requirements regarding an application for emergency trials with medicinal products, cf. section 20a of the Committee Act. Regarding clinical investigations of medical devices, see section 4.6.1.

In trials with medicinal products there are supplementary requirements to the application as mentioned in section 4.0. These supplementary requirements are:

- A copy of a completed application for the Danish Medicines Agency (front page)
- Documentation of the notifier's medical or dental training. (certificate of graduation or authorisation)
- CV indicating the notifier's clinical experience
- Information on compensation or reimbursement schemes. Reference can be made to the patient insurance scheme if the trial subject is covered by patient insurance, see Act on the Right to Complain and Receive Compensation within the Health Service and Executive Order no. 1097 of 12 December 2003 regarding coverage of the Act on Patient Insurance. If compensation or reimbursement schemes exist, they should be mentioned
- Relevant clauses in the contract between the sponsor and the trial location regarding financial support of the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of trial results

In terms of finances, supplementary requirements regarding contents apply. They are described in detail in section 4.6.2.1 f.

Section 20a of the Committee Act is about the situations where consent is obtained **before** the trial has been completed. Section 20a is about trials with medicinal products where the nature of the trial implies that it can only be carried out in emergency situations where the trial subject is unable to give informed consent, and it is not possible to obtain an *ordinary* surrogate consent from the guardian, the custodial parent, the next-of-kin and the general practitioner alternatively the medical officer of health.

Research on this group may be made only if the physical/mental condition making it impossible to obtain informed consent or a surrogate consent is a necessary characteristic element of the research project. These are normally trials involving individuals who are temporarily incapacitated, e.g. unconscious.

The urgency of the trial decides whether it is an emergency situation whereas difficulties in contacting the next-of-kin, the general practitioner, the custodial parent or the guardian do not

justify application of section 20a instead of the general rules regarding trials with medicinal products based on surrogate consent in section 4.4.

Please note that the assumption is that the project gives the patient group a direct benefit, cf. section 13(1) of the Committee Act.

This consent may be obtained from the trial guardian which is a unit consisting of two doctors, see section 4.6.4 on requirements regarding trial guardian consent.

It is a requirement that there is reason to assume that the trial subject's health can be improved in the long term.

4.6.2.1 Trial protocol

The trial protocol shall contain a description of the following:

- a. **The purpose of the project**, including problem and hypothesis.

There must be a short review of literature possibly supplemented by an actual bibliography. The description shall enable the committee to decide whether there are sufficient grounds for implementing the project, and whether the hypothesis of the project is justified. The description shall also enable the committee to decide whether the project may be justified by the expected therapeutic and public health benefits.

If a similar project has previously been carried out, the researcher shall supply information about this and justify the need for a repetition of the trial.

- b. **Trial method**, including design and planning. Use of control group, randomisation, etc. shall be stated. This information shall enable the committee to assess the scientific standard of the project and ensure that the project contributes to providing new valuable knowledge.

If any surgical intervention is carried out on trial subjects, this shall be stated. If biological material is removed for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, this must be stated; see item (c) below. Section 2.6. describes where a research biobank is established.

Where placebo is applied, this shall be accounted for. Moreover the selection of a control group shall be accounted for.

Trials with medical products initiated by researchers shall also state who is the monitor on the trial.

- c. **Setting up a research biobank**. Information shall be given if biological material is removed from the trial subject for the purpose of storage in a research biobank, cf. Section 2.6.

The following issues must be stated:

- What material and how much is removed (e.g. ml per removal or a total)
- Are there any risks involved in the removal and, if so, what are they?
- What is the purpose of the research biobank?
- What will happen to the material, will it be unidentifiable at the end of the project, will it be passed on to others or exported from Denmark?
- For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Note! Removal of biological material for future research that is not related to the actual project undertaken is considered as the establishing of a biobank with a view to future research. The establishing of such a biobank should not and cannot be approved by the committee system, but should be notified to the Danish Data Protection Agency only.

When at a later point such a biobank is to be used for research, this new project must be notified – either as an additional protocol or as a new protocol and

normally renewed consent must be obtained from the trial subjects. General consent for use of the material for research purposes obtained in connection with the removal of blood and tissue samples is of no legal significance in relation to the Committee Act which requires concrete and current consent.

- d. **Statistical considerations** must be described. They must be sufficient for an evaluation as to whether the project can provide answers to the questions made. Calculation of strain shall be available.
- e. **Trial subjects, including criteria for inclusion and exclusion.** The gender and age of the trial subjects shall be given, including whether pregnant or breast-feeding women are included. If possible, a statistical reason for the planned number of trial subjects shall be given.

Patients subject to confinement pursuant to the Act on Incarceration and other compulsion in psychiatry may not participate as trial subjects in biomedical research projects, cf. section 23(1) of the Act.

- f. **Side effects, risks and inconveniences** for the trial subjects. The trial protocol shall describe predictable risks, side effects, including known long-term side effects, complications and inconveniences involved in participation in the trial and, if possible, the expected frequency of the individual side effects, etc.

Pain, discomfort, fear and other foreseeable risks shall be minimised in relation to the disease and the developmental stage of the trial subject. Therefore any safety measures shall be stated in the trial protocol.

Information on the risk in connection with the use of ionising radiation from X-rays or radioactive materials must be clearly stated in the protocol if such sources are used, cf. Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

- g. **Respect for the physical and mental integrity of the trial subjects** and their right of privacy. A statement shall be given that data concerning the trial subject are protected under the Act on Processing of Personal Data and the Act on the Health Act. It shall also be stated whether the project will be notified to the Danish Data Protection Agency. If the project is not notified to the Danish Data Protection Agency, the reason shall be stated (e.g. if the person responsible for data is not established in Denmark but in a different EU country). If the Danish act on protection of personal data does not apply, it must be stated in the information material given to participants what national laws on the protection of personal data apply. The majority of biomedical trials shall be notified to the Danish Data Protection Agency. The Danish Data Protection Agency provides information about the duty of notification. If biological material is exported to countries outside the EU, it must be stated that the project is implemented in accordance with the rules under the Act on Processing of Personal Data.

Where a researcher wishes to use information from patients' records in the research project, this shall appear from the protocol. What information is to be used and the intended use hereof shall also be stated. The information must be relevant and necessary for the research project. Any subsequent contact to the patients concerned shall take place only if the health person who has treated the patient allows this, cf. S. 46 (1) and (3) of the Health Act.

- h. **Finances.** If the chief investigator receives remuneration for completion of the trial, the size of the remuneration and the more detailed rules for payment shall be stated.

The trial protocol shall include:

1. Who initiated the biomedical research project,
2. Names of commercial as well as non-commercial sponsors,

3. Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial,
4. Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned.

It shall also be stated how any excess financial support is used.

- i. **Relevant clauses in the contract between sponsor and the location of the trial**, i.e. the physical or legal person taking on responsibility for the initiation, management or financing of the research project and the location of trial/the chief investigator shall be emphasized in the contract which is to be presented to the committee. These are clauses on financial support for the project/remuneration of the chief investigator, access for the chief investigator to data and on publication of the results which shall be translated into Danish when they are mentioned in the protocol or attached to the protocol.
- j. **Remuneration** for trial subjects. Any remuneration (including or reimbursement of transport expenses or lost earnings) shall be described, and the amount must be stated. The amount of remuneration shall not be such as to have undue influence on the giving of consent by the trial subjects, cf. Appendix 6 Guidelines on remuneration of trial subjects.
- k. **Recruitment of participants**. A description shall be made of where and how trial subjects are recruited.
- l. **Availability of information** for trial subjects. Indication shall be provided as to how the trial subject is guaranteed access to further information on the project, such as reference to a health professional who may act as a contact person.
- m. **Publication of trial results**. The researcher shall be obliged to publish trial results regardless of whether results are positive, negative or inconclusive. Such results shall be published as soon as possible, in a professionally responsible manner and in accordance with the Act on Processing of Personal Data. If the results cannot be published in a journal, they shall be published in another way (possibly on www.clinicalstudyresult.org). A statement shall be provided as to how publication will be made.
- n. **Statement of biomedical research ethics**. The protocol shall include a statement concerning the ethical issues raised by the biomedical research project, including an argumentation for the project being sound in terms of biomedical research ethics.

The statement shall include a thorough risk/benefit assessment of the trial. The risk assessment shall include an evaluation of side effects and risks calculated in absolute figures and in terms of relative risk without regard for any other benefits. This shall be followed by an assessment of the project in relation to predictable benefits for the trial subjects, for others and for research.

No risk may be of unreasonable extent neither in itself nor in relation to the predictable benefits of the project, cf. section 12(1)(i) of the Committee Act. That is, neither the absolute nor the relative risk may be unjustifiable. Authorised health professionals shall display care and conscientiousness in their work. An upper limit for the acceptable risk is already incorporated in this obligation. According to section 1(3) of the Committee Act, regard for the safety, rights and welfare of the trial subject shall take precedence over scientific and social interests. In any event, the

regard for the trial subject's integrity and autonomy shall form the basis for the considerations in the section.

It shall be stated in the protocol that subsequent informed consent or surrogate consent will be obtained as soon as possible.

4.6.2.2 Lay person summary

A lay person summary shall mean a commonly understandable description of the project. The description shall cover the basics of the protocol (what is to happen with whom and why) in a brief form. The lay person summary shall be included as part of the basis for the committee's evaluation. The aim is to enable the lay persons on the committee to form a research-ethical view of the project.

The lay person summary shall be enclosed with the trial protocol and include:

A description of the indication in the trial protocol of purpose, method, side effects, risks, and inconveniences, trial subjects, including criteria for inclusion and exclusion, information on external financial support from private enterprises and foundations, and a research-ethical account without using technical/professional terms.

4.6.2.3 Information about the trial

It is stated in section 20a, subsection (2) of the Committee Act that the chief investigator as soon as possible after the trial shall obtain informed consent from the trial subject or a surrogate consent. The surrogate consent shall be given by the guardian, the custodial parent or the next-of-kin and the general practitioner alternatively the medical officer of health.

The general rule is that surrogate consent shall be given on the basis of satisfactory information of the nature, importance, scope and risks of the project as well as suitable documentation.

Informed consent shall also be obtained if the trial subject regains legal capacity during the term of the research project, cf. section 19 of the Executive Order.

4.6.2.3.1 Guidelines for oral information

Guidelines for oral information, cf. section 8 of the Executive Order, shall be attached to the trial protocol. These guidelines can also constitute a separate section in the protocol.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact made to the trial subject/the person giving surrogate consent?
Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How to make sure that the trial subject is given the option to have an observer present at the interview?

- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the person giving the consent should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

Generally, it should be pointed out that

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Information shall be provided that it is a request for participation in an emergency trial which has already started.
- The trial subject shall be informed that it is possible to have an observer present at the interview.
- Information shall be provided about the right to time for reflection after having received the information.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the trial subject or the person giving surrogate consent has sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerately and adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on any predictable risks, side effects, complications and inconveniences and state that participation in a biomedical research project may involve unpredictable risks and harm.
- The information shall contain details on alternative treatment methods, cf. section 7(4) of the Executive Order, if the research project also aims at an element of treatment.
- The information shall include details on circumstances about which the trial subject or the person giving surrogate consent is believed to be unaware, but which are important for the decision, e.g. that remuneration for the participants is a taxable income.

After the information interview:

- The trial subject or the person giving surrogate consent shall be informed if, during the implementation of the trial, *new* information becomes available concerning effect, risks, side effects, complications or inconveniences.
- The trial subject or the person giving surrogate consent shall be informed if the trial design of the research project is significantly altered in relation to the safety of the trial subject.
- The trial subject or the person giving surrogate consent shall be informed if, during the implementation of the research project, important information becomes available on the state of health of the trial subject. However, the trial subject may have declined such knowledge.
- If it is feasible and the trial subject so wishes, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the

trial subject or the person giving surrogate consent of the results achieved and of any consequences for the individual.

4.6.2.3.2 Written information

The trial protocol shall also include written information for the participants, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

According to the Executive Order, the written information shall as a minimum include the details mentioned in sections 9, 10, and 12.

The written information for participants shall include the following:

- 1) The title of the project. If an abbreviated title is used on the information for participants and not the title stated on the notification form, the original title shall be stated as well.
- 2) Request regarding participation in a scientific trial at the beginning of the information for participants. It shall be stated that the trial has started.
- 3) Application of approved and non-approved medicinal products, the names of these products as well as dosage and use of randomisation, blind preparations, periods without treatment, including any known interaction with other medicinal products.
- 4) Purpose and method and the importance, nature and scope of the research project, including the practical arrangement of the project and any clinical trials.
- 5) Any predictable risks, side effects, including known long-term side effects, complications and inconveniences by participating in the research project, and that participation in a biomedical research project may involve unpredictable risks and harm.
- 6) If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- 7) The possible benefits of the research project. A distinction shall be made between benefits for the individual trial subject, for others and for scientific progress.
- 8) Circumstances which may result in the involuntary exclusion of the trial subject from the research project, as well as circumstances under which the project as a whole may be discontinued. If there are no situations where the trial subject may be excluded from the trial after inclusion, this shall be stated in the information. However, if for instance diabetes is a criterion for exclusion and the trial subject gets diabetes during the trial period, this may be given as an example of subsequent exclusion from the trial. An example of a discontinuation of the project as a whole may be that serious side effects occur unexpectedly.

- 9) Other possible treatment methods in situations where the project aims at results in terms of science as well as treatment.
- 10) Possible remuneration for the trial subject, including information on taxation of the amount.
- 11) Who initiated the biomedical research project.
- 12) Names of commercial as well as non-commercial sponsors.
- 13) Amounts granted by each sponsor and the way in which the subsidy is included in the research project, including whether the subsidy is paid as a fixed sum or as a remuneration per trial subject, and whether the subsidy is paid directly to the chief investigator, to his/her department/institute, to a common research fund or otherwise.
- 14) Whether the chief investigator is otherwise financially attached to private enterprises, foundations, etc., who may have interests in the research project concerned (it may be stated if other persons in the group of researchers have any such attachment).
- 15) Name, address, e-mail address and phone number of the chief investigator and a contact person connected with the research project.
- 16) Where the trial subject or the person giving surrogate consent may obtain further information on the research project (e.g. from the contact person), and
- 17) A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless the information from this is given in the information material.

If ionising radiation is used, the written information shall contain the details about the actual project included in Appendix 5, Guidelines on the application of ionising radiation in biomedical trials.

Finally, the Appendix, "The rights of a trial subject in a biomedical research project" shall be included with the written information, unless the information from the Appendix is given in the information material. The Appendix states the general rights of trial subjects.

The above issues concern requirements of the application. Reference is made to Appendix 1, Drawing up useful information for participants.

4.6.2.4 Surrogate consent from the trial guardian in trials with medicinal products

Trials with medicinal products in emergency situations can only be conducted if, **prior** to the commencement of the trial, surrogate consent has been obtained from the trial guardian, cf. section 20a of the Committee Act.

Consent from the trial guardian shall be given after satisfactory information on the nature, significance, scope and risks of the project and receipt of suitable documentation. It is a precondition that the trial guardian has access to the trial protocol and written patient information. This material may for instance be made available to relevant doctors on call at a hospital ward where the emergency trial is going to take place.

A trial guardian is a unit consisting of two doctors who give surrogate consent on behalf of the legally incompetent trial subject. The trial guardian shall protect the interests of the trial subject and be independent of the interest of the chief investigator in the research project. The two doctors shall be third parties in relation to the research project and it should be avoided that they are in a subordinate position to the chief investigator. At least one of the doctors shall have professional insight in the area.

The trial guardian may either be a unit of the same two doctors who are contacted for all the trial subjects in a clinical trial or who are appointed ad hoc for individual trial subjects.

The chief investigator must sign a written consent. The written consent need not be signed while the health professional carrying out the project is present. The consent may be verified prior to

commencement, e.g. by telephone. However, the consent shall be given on the basis of information regarding the specific trial and the condition of the trial subject in question.

The trial protocol should be accompanied by the ready-printed declaration (S9) of the committee system. Its a standard prepared by the committee on research ethics.

4.6.2.5 Subsequent consent in emergency trial situations

Section 20a, subsection (2) of the Committee Act stipulates that the chief investigator as soon as possible after completion of the trial shall obtain informed consent from the trial subject or a surrogate consent. The surrogate consent shall be obtained from the guardian, the custodial parent or the next-of-kin and the general practitioner alternatively the medical officer of health.

If surrogate consent has been obtained and the trial subject obtains or regains his or her legal capacity during the term of the research project, informed consent shall be obtained from the trial subject before the research project can continue, cf. section 19 of the Executive Order on Information.

The trial protocol shall be accompanied by a copy of the declaration of consent prepared by the committee system.

The trial protocol should be accompanied by one of the ready-printed declarations (S1-S4) of the committee system concerning "Informed consent to participate in a biomedical research project" or (S7-S8) "Surrogate consent to participate in a biomedical research project". These are standards prepared by the committee system on research ethics. If, in connection with the research project, biological material is removed from the trial subject for the purpose of storing it in a research biobank, the researcher shall request the person concerned for his/her consent to be involved in the research project and for removing biological material for the purpose of storing in a research biobank.

Consent shall be given on the basis of and as soon as possible after the written and oral information. The consent shall be given to the chief investigator or a person authorised by him/her to give the oral information. This person shall have direct connection with the research project, cf. section 4(5) of the Executive Order. The chief investigator shall certify that the written information has been submitted to the trial subject and that communication of the oral information has taken place, cf. section 4(4) of the Executive Order.

The chief investigator shall keep a copy of the signed declaration of consent and the chief investigator shall be obliged to give the trial subject a copy of the declaration of consent.

4.7 Register research projects that incorporate biological material.

This describes the requirements of a valid application that deals with register research incorporating biological material.

See also Section 2.6.2 which describes if a register research involving biological material is involved.

In the case of register research involving fully **anonymous** biological material, cf. below 4.8.

4.7.1 The Trial Protocol.

The trial protocol will describe the origin of the material. For instance, does it originate from a clinical biobank or from a research biobank in a different project? (e.g. biobanks established for general research purposes, donor biobanks, or private biobanks established within the pharmaceutical and the medical industry), cf. Section 2.6.2. and Glossary 11.1. for a further definition of biobank.

If the material originates from **abroad**, the following information should also be included

- Which country the material originates from
- Statement to the effect that the material was removed in compliance with the rules and regulations of the country where removal took place

Moreover, the trial protocol shall meet the relevant requirements of a research protocol as mentioned above in Sections 4.1.- 4.6

This means that if the material originates from legally competent adults, please see Section 4.1.1. on the content of the trial protocol.

If the material originates from children, please see Section 4.2.1, etc.

4.7.2 Informed consent for register research projects that incorporate biological material.

As a general rule, a trial subject shall give informed consent to participation in the research, however, see the rules of exemption in section 4.7.3.

Guidelines for oral information shall be available.

The chief investigator is responsible for providing the information, but the information may be given by a person who has the professional qualifications to communicate the contents of the research project and who is directly associated with the project, cf. section 7(3) of the Executive Order. The guidelines shall apply to the person who provides the information in practice, i.e. the health professional who communicates the information.

Basically, the guidelines shall describe *how* to plan the information process, but also *what* is to be included in the information.

As a minimum the guidelines shall consider:

- Who provides the oral information?
- How is the first contact made to the trial subject or the person giving surrogate consent? Through posting or a personal contact?
- When is the oral information given?
E.g. before or after the written information?
- How to make sure that the information interview is undisturbed?
- How to make sure that the trial subject is given the option to have an observer present at the interview?
- How much time for reflection should be given between the oral/written information and the subsequent signature on the declaration of consent?
- When to ask for consent?
A clear correlation between information and consent is required, i.e. the person giving the consent should be asked to consider consent soon after having received the information, however duly considering the time for reflection.

The guidelines may also include the rules listed below:

Before the information interview:

- Time and place for the interview shall be agreed upon.
- Attention must be drawn to the fact that the trial subject is entitled to have an observer present at the interview.
- Information shall be provided that it is a request to use biological material in a biomedical research project.

- Information shall be provided about the right to time for reflection after having received the information.
- The research shall consider the trial subjects' right to decline knowledge about his or her own health.

Information interview:

- The interview shall be planned carefully.
- The interview shall take place in an undisturbed environment and without interruptions.
- The interview shall be planned so that the person receiving the information has sufficient time to read the written information, listen to the oral information and ask questions.
- The interview shall contain an understandable presentation of the research project without using technical or value-laden terms and communicated considerately and adjusted to the individual in terms of age, maturity, experience, etc.
- The information shall include details on circumstances about which the recipient of the information is believed to be unaware, but which are important for the decision, e.g. that remuneration for the participants is a taxable income.

After the information interview:

- The trial subject shall be informed if, during the implementation of the trial important information about the health of the trial subject turns up, unless the trial subject has clearly indicated that he or she does not want this, cf. section 13 of the Executive Order.
- If it is feasible and the trial subject so wishes, the chief investigator or the health professional in charge of information shall, when reporting the research project, inform the trial subject of the results achieved and of any consequences for the individual.

The trial protocol shall also include written information for the participant, cf. section 9 of the Executive Order on Information. The written information shall be submitted in paper form or electronically. However, you may always require the information in paper form, cf. section 8(3) of the Executive Order.

The written information shall include:

- Project title
- A request as to whether the biological material may be included in the project and information about where the material comes from
- Purpose and method of the research
- Project benefit
- Information about external financial support, including information about the identity of the sponsor
- Any new knowledge about the person who has given the material and how this knowledge will be handled, and
- Name and address of a contact person connected to the project
- A recommendation to read the attached Appendix, "The rights of a trial subject in a biomedical research project", unless this information is given in the information material.

A declaration of consent is also required. As mentioned above, the trial subject shall be informed if, during the course of a project, important information turns up regarding the health of the trial subject. This also applies to information that has nothing to do with the purpose of the research project, cf. section 13 of the Executive Order on Information.

However, section 13 gives the person the right in advance to decline knowledge of this information. This may be particularly relevant if the information concerns a hereditary disease. Prior to any research involving biological material from a person, a clear statement on the declaration of consent is required where the person is able to decline any information about his or her health that may turn up during the project.

It is recommended that the researcher considers whether the declaration of consent should include an option for the trial subject to sign that he/she declines being contacted regarding any knowledge about his or her health resulting from the research (the right to no knowledge). For a project involving biological material from legally competent trial subjects the trial protocol should be accompanied by one of the ready-printed declarations (S10-S11) of the committee system concerning "Informed consent to participate in a register research project". These are standards prepared by the committee system on research ethics.

4.7.3 Exemption from consent in register research projects that incorporate biological material.

The committee may grant exemption from obtaining informed or surrogate consent for participation in research projects involving biological material already removed. This is stipulated in section 16(3) of the Committee Act.

This applies

- If the project does not pose any health risk or in any other way, under the circumstances, may be harmful to the trial subject, or
- If it is impossible or unreasonably difficult to obtain informed consent

Therefore, the trial protocol is to describe these circumstances so that the committee on research ethics may evaluate if the conditions are met for allowing an exemption.

It must be explained whether as part of the project there is any probability that e.g. serious genetic diseases may be found that it will be necessary to inform the trial subjects of.

In case of research projects that involve trial subjects, the committee shall be satisfied that the trial subject **actively** gives his/her informed consent to participation. In case of register research projects, the committee shall not assess whether the trial subject would actively have given his/her consent, had the trial subject been asked. Vice versa, the committee shall be satisfied that the research **does not injure or strain** the subject.

According to the remarks of the act, the committee shall, among other things, assess whether it may be ethically unjustifiable for individual reasons to permit the inclusion of tissue from a trial subject in a research project. For instance, this may concern a personal political or religious conviction which may induce strain on the individual person if he/she participates in the research project.

The commentary of the Committee Act states: "The situation where the collection of informed consent may appear unnecessary is where tissue specimens were previously removed from patients or trial subjects and stored in a biobank. In case of a new register research project using these existing tissue specimens, no (new) medical intervention will be made on the subjects concerned, and typically there will be no further strain on the trial subjects. In these cases, the committees shall safeguard the consideration of individual protection, cf. page 165 of Recommendation 1414, submitted by the task group on biobanks."

According to the Recommendation, the committee shall make an entirely concrete assessment of the research project concerned and in this way safeguard the protection of the individual subject.

In relation to the assessment as to cases where it is impossible or excessively difficult to obtain informed consent, such cases concern very large research projects.

4.8 Research in anonymous biological material

Section 4.8. describes the requirements of a valid application for research in anonymous biological material. This means that it is not possible for the material to be identifiable with individual persons. Data are identifiable with individual persons if it is possible to identify such persons either by name or by code. If just one person has the "key", the material is traceable to a person and is not "anonymous".

If the biological material is **removed** in the actual project, the material is not "anonymous", as the researcher knows who is involved in the intervention.

Therefore, in this section, the situation concerned is where the researcher intends to use material which was already removed from persons and is stored in an "anonymous" form. In such situations, no informed consent can be obtained from the trial subjects. Therefore there is no consideration to be made of any trial subject, but the committee on biomedical research ethics must ensure that the research is made in an ethically responsible manner.

4.8.1. The Trial Protocol.

The trial protocol is to describe the material concerned and the purpose of using the material and the method of the project. What is to happen with the material in the project and how will it be treated?

In case of trials where there is not directly any person to safeguard, the protection interest is different. The trial shall be made in an ethically responsible manner and at the same time it shall create new knowledge.

It must be substantiated that the material is used in an ethically responsible way and that it is used in harmony with the conception of true human dignity.

4.9 Applications for trials with fertilised eggs, stem cells or stem cell lines

Requirements as to the content of the trial protocol are similar to the requirements stated in 4.2.1

The Fertilisation Act implies that it is possible to carry out research related to fertility treatment and research which is not related to fertility treatment. The latter is allowed according to section 25(1)(iii). The committee shall decide whether the project has one of the aims approved under subject (1)(iii).

A protocol describing purpose and method shall be prepared. Information shall be given as to which of the aims under subsection (1)(iii) is involved. The protocol may refer to relevant literature, and any financial issues regarding sponsors shall be stated. Indication shall also be made that the trial results will be published. The included lay person summary shall contain information included in the protocol without using technical/professional terms.

The parents shall give consent to the research according to the general rules in the Executive Order on Information. Cf. also Section 4.2.1.4 regarding rules on consent from the holders of custody. When using a fertilised egg for stem cell research, the couple shall give consent to storage of the fertilised egg and to application in the research project.

A circular letter regarding research involving embryonic stem cells says that. "If the research project is about establishing a stem cell line which will form the basis for a large number of research projects, the couple shall be informed that the project has this purpose. The couple shall also be informed that they will not be asked for consent in case of any subsequent research projects.

It is important that the couple receives this information together with information about the research purpose, the stem cell line may be used for, namely gaining new knowledge to improve the possibilities of treatment of diseases in humans.

The couple shall also be informed that all research projects concerning stem cells and stem cell lines from embryos shall be approved by the committee system on biomedical research ethics, also in those cases where the consent of the couple is no longer required for scientific application of embryonic stem cell lines. The committee system on biomedical research ethics shall assess whether the projects have the purpose allowed."

5.0 Updating informed consent

If, during a trial, important new facts become available about the individual trial subject's health, they must be communicated, together with their practical consequences, to the trial subject even if these facts cannot be immediately related to the purpose of the research project.

The trial subject may in advance have declined to receive information about facts that turn up in connection with the trial. This may be particularly relevant for persons who may be bearers of hereditary diseases and where the purpose of the trial is to uncover any predisposition to serious

hereditary diseases which may not break out for a long period of time. In such cases, a clear written statement by the trial subject declining to receive information of the mentioned nature shall be given before the person concerned is included in the trial.

The Act provides no possibility for the chief investigator of the project to decide whether a trial subject can cope with receiving information about his/her disease. If, during a trial such information turns up, the trial subject shall be informed accordingly unless the trial subject in advance has declined such information.

If, during the course of a trial, new facts turn up about the effects, risks, side effects, complications or drawbacks of the trial, or if the trial design of the research project is considerably changed, the trial subject shall be informed accordingly and renewed consent shall be obtained.

If new knowledge about side effects and risks means that the trial procedure will be changed immediately, a revised version of the written patient information shall be prepared and forwarded to the committee on biomedical research ethics for approval. The trial subject shall then be informed and, on the basis of the new information, renewed written consent to participation shall be obtained.

6.0 Amending a biomedical research project

Substantial amendments to the research protocol may only be made following approval by the committee on biomedical research ethics. However, the sponsor or the chief investigator shall establish the necessary safety measures in order to protect the trial subjects, cf. section 23 of the Committee Act.

Substantial amendments include, for instance, amendments that may influence the safety of the trial subject, interpretation of the scientific documentation on which the project is founded, the implementation or management of the project, such as

- changes in inclusion or exclusion criteria
- trial design
- number of trial subjects
- trial procedures
- trial medicinal products
- changed doses
- duration of treatment
- parameters of effect
- changes concerning chief investigators or trial locations
- changes of the contents in the written information material for trial subjects.
- changes of agreements in sponsor contracts (concerning economy, access to data or publication)

At www.cvk.sum.dk may be seen a list of the most common changes in research projects and what changes are considered significant so that notification is required. The list is not exhaustive and the chief investigator is at all times responsible for notifying significant changes to the committee system.

The chief investigator / the coordinator shall submit a duly formulated application of amendment consisting of:

1. A completed amendment notification form (cf. the notification database)
2. A description of the changes and the underlying reasons
3. Amendment/additional protocol stating changes of the project (if possible including excerpts from the changed documents highlighting textual amendments)
4. Amended trial protocol highlighting changes, dated and stating version no (if many and substantial changes require a new edition)
5. Any revised written participant information and consent when changes require this. If there is a need for renewed consent, this must be described.

Where new information means that the researcher considers changing the experimental procedure or calling a halt to the experiment, the committee shall be informed of this.

If procedures are changed immediately out of consideration for the safety of trial subjects, the background for this decision must be explained to the committee as soon as possible including what safety precautions have been taken and what future safety measures are considered.

If many additional protocols have been submitted for a project, a new version should be produced so that amendments become part of the main protocol. It is recommended that new versions are produced on a current basis so that the committee may maintain an overview of the project.

An additional protocol must fit within the identity of the main protocol. In the case of changes that exceed the significant changes of an existing project that may be approved pursuant to Section 23, these changes amount to a new project that require independent notification.

7.0 Deadlines for case handling

The committee shall decide on the approval of the project within 60 days of receiving the duly formulated application, cf. section 10 of the Committee Act.

The 60-calendar-day period starts from the time when the committee has received a duly formulated application. A valid application shall mean an application which contains the information which the committee system must receive in order to make a research ethical evaluation in accordance with Chapter 4 of the Act.

The time-limit of 60 calendar days may be interrupted once by the committee as the committee may request information in supplement to the otherwise duly formulated application, cf. section 10(2) of the Committee Act. The time-limit is interrupted until the committee has received the supplementary information.

In the event of a request for amendment of an approved biomedical research project, the committee shall decide on any approval of the amendment within 35 days of the receipt of a duly formulated application for amendment.

8.0 Control of biomedical research projects

The regional committee shall monitor that the biomedical research project is carried out in accordance with the authorisation given. However, this does not apply to clinical trials of medicinal products where the Danish Medicines Agency is the supervisory authority.

The regional committee is also the controlling agency when a project is implemented following final approval of the National Committee on Biomedical Research Ethics. Control may be implemented by inspection on the location of the trial.

The committee may follow the course of a project and request that the final research report or publication be sent to the committee. The committee may request a reasoned statement from the chief investigator or the sponsor in cases where the project is not completed, cf. section 22(2) of the Committee Act. This shall also apply to trials involving medicinal products.

8.1 Duty to report in connection with biomedical trial except trials involving medicinal products

The chief investigator shall immediately inform the committee if serious side effects or adverse events occur during the project. The report shall be accompanied by comments on any consequences for the trial.

If these are serious side effects or adverse events resulting from the project, the chief investigator shall provide the information that the committee asks for.

Once every year during the entire trial period, the sponsor or the chief investigator shall submit to the committee a list of all serious expected and unexpected adverse reactions and all serious events encountered during the period. The information shall include the safety of the trial subjects.

The material submitted must be in Danish or in English. If the list of serious side effects and serious events is in English, a summary in Danish must be included.

Please note that

- Reporting on side effects shall relate to the approved research project
- Comments may be sent electronically, e.g. on a CD
- The comments shall be in Danish
- The chief investigator's assessment of the side effects occurring is included in the material

The reporting obligation also includes trials with medical devices.

8.2 Duty to report in connection with trials involving medicinal products

Immediate reporting of suspected, unexpected serious adverse reactions (SUSARS) shall be made to the Danish Medicines Agency only.

Once every year during the entire trial period the sponsor or the chief investigator shall submit to the committee a list of all serious expected and unexpected adverse reactions and all serious events encountered during the period and provide information about the safety of the trial subjects.

The material submitted must be in Danish or in English. If the list of serious side effects and serious events is in English, a summary in Danish must be included.

Please note that

- Reporting of side effects shall relate to the approved research project and not only to any substance which may have been tested in several projects or possibly only tested outside Denmark
- Comments may be sent electronically, e.g. on a CD
- The comments shall be in Danish
- The chief investigator's assessment of the side effects occurring is included in the material

Regarding the contents of the list of side effects, the committee follows the guidelines issued by the Danish Medicines Agency.

9.0 Fees

The regions that finance the operation of the regional committees shall determine a fee per project notified by the research institutions, etc. and by private undertakings and hospitals. However, the fee shall not exceed an amount corresponding to the project's expected share of the relevant committee's total annual expenditure, cf. section 28(1) of the Committee Act.

It has been agreed that the fee for notifying a project shall be DKK 4000 and for a supplementary protocol DKK 1500.

Reference is made to the secretariats of the regional committees for further information on rates.

10.0 Complaints procedure

The chief investigator whose application for the approval of a biomedical research project has been declined may bring the decision before the National Committee on Biomedical Research Ethics, which is the final administrative complaints board, not later than 30 days from receipt of the decision from the regional committee, cf. section 25(1) of the Committee Act.

Any individual who is a party to the case as defined by the Danish Public Administration Act may bring a project before the National Committee on Biomedical Research Ethics not later than 30 days from the decision of the regional committee.

Any decision concerning approval and rejection from the regional committee, but also legal issues concerning the procedure of the case may be brought before the National Committee on Biomedical Research Ethics. A party as defined by the Danish Public Administration Act is a subject who has a significant and individual interest in the outcome of the case.

Where a rejection from the regional committee is submitted by an individual entitled to complaint, the project shall be initiated only when and if the National Committee on Biomedical Research Ethics has given its approval.

Where an approval is submitted to the National Committee on Biomedical Research Ethics by a party to the case, the complaint shall have a delaying effect which means that a project shall not be commenced or must be discontinued until an approval is given by the National Committee on Biomedical Research Ethics.

11. GLOSSARY

Serious events:

Any event that – regardless of for instance medicine dose - results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in significant or persistent disability or incapacity, or a congenital anomaly or birth defect in the trial subject during the trial period itself.

A duly formulated application:

An application fulfilling the form and contents requirements as stated in section 4 of the Guidelines.

Biomedical research project:

A biomedical research project means an activity planned according to scientific methods which aims at producing new, valuable knowledge about human biological and psychological processes, either in relation to healthy people or for the purpose of preventing, recognising, palliating, treating or curing diseases, symptoms or pain, including affecting bodily functions.

Side effects:

Harmful or undesirable reactions resulting from participation in the trial, for instance a reaction to a test preparation regardless of dose.

Donor biobank

A donorbiobank is a collection of human biological material that typically has been donated by healthy persons with a view to treatment of a concrete patient or a further defined group of patients (e.g. egg, semen and blood banks).

Exclusion criteria:

A description of the circumstances excluding a person from participating in a concrete biomedical research project; it could for instance be that the person in question is breastfeeding or pregnant.

Research biobank:

A research biobank is defined as the collection of biological material which is accessible as an integrated part of a concrete research project, cf. Circular of 13 June 2005 from the Ministry of the Interior and Health about research biobanks.

Chief investigator:

A person engaged in a profession acknowledged for the performance of research, for instance through employment as a researcher or a PhD student or any other employment with actual research who is responsible for the practical implementation of the trial in a certain trial location.

Trial subject:

An individual who participates in a biomedical research project as either a recipient of test preparations or a participant in a control group.

Research protocol:

A research protocol is a document that describes the objective(s), design, methodology, planning, statistical considerations, research ethical considerations, finances, publication issues and information for the trial subjects in connection with a biomedical research project etc.

Non-intervention trials involving medicinal products:

Non-intervention trials involving medicinal products are trials where one or more medicinal products are prescribed in the usual manner in accordance with the terms of the marketing authorisation. The decision to prescribe the medicinal product is clearly separated from the decision to include the patient in a trial. The actual treatment does not take place in accordance with a trial protocol but falls within current practice. No additional diagnostic or monitoring procedures are carried out and epidemiological methods must be used for the analysis of collected data.

Informed consent:

A decision to participate in the research project made following satisfactory information about the nature, importance, scope and risks of the project and following receipt of suitable documentation. The decision is made voluntarily by a person capable of consenting. The consent must be in writing, dated and signed or given using an electronic signature.

Inclusion criteria:

A description of the conditions to be fulfilled by the participants in a biomedical research project, for instance that they must be over 18 years old and have a specific diagnose.

Trials involving medicinal products:

Clinical trials involving medicinal products include trials intended to discover or verify the clinical, pharmacological or other pharmacodynamic effects on humans, including to identify any side effects or to study pharmacokinetics for the purpose of obtaining knowledge about the safety or efficacy of medicinal products on humans.

Lay person summary:

A description of the research protocol's stated purpose, method, side effects, risks and inconveniences, trial subjects, including inclusion and exclusion criteria, as well as a research ethical account without the use of technical/specialist terms.

Multi-centre trials:

A multi-centre trial means a trial carried out in accordance with one and the same trial protocol, but in different locations in Denmark with different chief investigators and with one coordinating chief investigator.

Legally competent people:

People who are over 18 years old and capable of making decisions. This means that they have not been declared legally incompetent or incapable of making decisions on their own affairs.

Register research projects involving human biological material:

Register research projects, as defined by the Committee Act, shall mean projects where the subject-matter of the research is one or more existing registers. "Register" ('filing system') shall mean any structured set of personal data which are accessible according to specific criteria, whether centralised, decentralised or dispersed on a functional or geographical basis, cf. S.3(3) of the Act on Processing of Personal Data.

When the register involves blood samples, cell swabs, tissue, cells etc. it is also a biobank.

Register research involving human biological material which can be traced back to an individual is therefore research in *already removed* biological material (see sections 2.6.2 and 4.7).

Guidelines for communication of oral information:

Guidelines aimed at the person who is in practice to provide the participants in a biomedical research project with oral information. The guidelines may for instance specify that an information interview may only take place following agreement on the time and place of the interview, and the guidelines may specify whether the oral information is to be given before or after the written information.

Sponsor:

An individual or a corporate body assuming the responsibility for the implementation, management or financing of a biomedical research project.

Surrogate consent:

A decision made by the next-of-kin and the general practitioner or alternatively by the medical officer of health or the custodial parent or the guardian. The decision concerns the trial subject's participation in the research project and shall be made following satisfactory information about the nature, importance, scope and risks of the project and after receipt of suitable documentation. The consent shall be in writing, dated and signed or given using an electronic signature.

Incompetent adults:

Individuals who are covered by the definition in section 5 of the Act on Guardianship where no guardianship has been established.

Appendix 1. Drawing up useful information for participants

(August 2008)

Generally about information for participants

In connection with scientific trials involving trial subjects, rules have been laid down on how to inform trial subjects about participation in the trial. These rules can be found in "Executive Order on Information to and Consent from Trial Subjects Involved in Biomedical Research Projects." These rules are also elaborated in "Guidelines about notification etc. of a biomedical research project to the committee system on biomedical research ethics".

The written information

There are rules on both the oral and the written information for trial subjects. This Appendix only addresses the drawing up of written information.

It is very important that the information is intelligible and thorough. It is also important that the information is not too extensive and confusing for the trial subject. Furthermore, it is very important that the language in the written information is targeted at the people who are going to read it.

Attention to a number of general linguistic and communicative effects may render the text more readable:

- Throughout the text it should be clear who is the sender of the text and who is conducting the trial.
- The use of the passive voice (is given, is taken) should be reduced to the extent possible.
- When medical terms are used, these should always be translated into everyday language in a parenthesis, and translation should be provided consistently throughout the text.
- The use of words that fall totally outside the world of health care (e.g. cup, drawing lots) should be avoided in the text.
- To the extent possible questions should be avoided in headlines as such questions presume views on the part of the reader that may be non-existing.
- Side effects should preferably be listed as 'frequent/not serious' and 'seldom/serious' so as to make decoding easier for the reader. A separate box may be used.
- Always conclude the text by reminding the reader that the text is meant to assist him or her in taking a decision, and that further questions are always welcome

It is recommended that a 3. person reads the information to check whether the information is easily understandable.

If the information is extensive it is recommended that a summary on maximum 1 page is enclosed.

The written information does not necessarily have to follow the order suggested in the following pages. Instead the researcher should assess which information is the most relevant for the project in question. This information should come first in the written information.

The following pages describe the requirements of a trial involving legally competent trial subjects. Reference is made to the stricter requirements of the Executive Order – and the Guidelines – regarding information if the trial subject is for instance a minor or a legally incompetent adult. Special guidelines have been drawn up regarding information for the age group from 15 to 17.

Proposed contents of the information for participants

1. Front page/heading
2. Introduction
3. Purpose of the trial
4. Benefits of the trial
5. Side effects, stress, risks, complications and inconveniences - preferably listed in a box
6. Other possible treatments
7. Exclusion from and discontinuation of trials
8. Trial plan
9. Contact person
10. Information about financial matters
11. Access to trial results
12. Special issues regarding trials involving medicinal products
13. Special issues regarding information for parents giving consent to participation in trials involving children in the age group from 10 to 15
14. Conclusion that requests the person to decide on participation in the trial .

Appendices:

- "The rights of a trial subject in a biomedical research project"
- The pre-printed consent form issued by the Danish National Committee on Biomedical Research Ethics

Structure and contents

1. Front page/heading

- Title: for instance "Information for participants about participation in a scientific trial involving individuals with (disease)". The heading should be as readable and as inviting as possible.
- It must be clearly stated that it is a scientific trial and not a routine examination, a diagnostic examination or a treatment.
- The target group for the trial must be stated on the front page, e.g. healthy people or patients – including which patients.
- The formal name of the protocol. If an abbreviated title is used on the information and not the title stated on the notification form, the original title must be stated as well.
- The name of the relevant department and hospital.
- Footer with issue no., date and protocol number.
- To the extent possible questions should be avoided in headlines as such questions presume views on the part of the reader that may be non-existing. E.g. 'What side-effects occur?' (Presumes that there are always side-effects). Rather use 'Side-effects of the trial' or 'The trial's side-effects'.

2. Introduction

- Neutral terms such as "request for participation", "ask for" and the like should be used.
- I must be clear who the sender of the text is and who conducts the trial. E.g. 'The trial is a collaboration between XX, XX and XX and we request whether you are prepared to participate'. Remember to maintain consistent clarity on these issues throughout the text.
- It is a good idea to explain the significance of research and of trials so that the person understands why his or her participation is requested.
- Explain that a refusal to participate in the trial or any later discontinuation of participation will not influence the person's right to present or future treatment.

- When describing the principle of voluntariness, it may be explained that the researchers benefit from knowing why a participant decides to leave the trial as this may influence results, but that individuals of course are free not to provide this information.

3. Purpose of the trial

- The purpose and method must be explained to the trial subject in plain language and without unnecessary medical terms. When medical terms are nevertheless required, these should always be translated into everyday language in a parenthesis and translation should be provided consistently throughout the text. The description must be objective and not create expectations of unrealistic results. It should be pointed out that it is not known whether the trial may benefit the participants – and that this is the reason for conducting the trial.
 - Information about the use of and the names of approved and non-approved medicinal products.
 - The use of randomisation, blind preparations and treatment-free period must be described. In this connection terms from other semantic fields should be avoided, e.g. 'drawing lots'.
 - The general procedure, including the use of invasive examination methods, must be described. Reduce any use of the passive voice, e.g. '10 blood samples are drawn'.
 - It must be clear how many trial subjects are involved.
- If biological material is removed from the trial subject for use in the concrete research project, the purpose shall be stated.

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

4. Benefits of the trial

- The information must include whether the trial subject may or may not expect to benefit directly from the trial. This does not mean the direct benefit that the trial subject may gain through participation in the trial in terms of additional care or remuneration for his or her participation.
- Furthermore, it should be stated whether the trial will be of general benefit for instance to future patients or to science.

5. Side effects, risks, complications and inconveniences

- Any known and predictable side effects, risks, complications and inconveniences in connection with the trial must be disclosed. Information about side effects must be provided regardless of whether they are temporary, long-term, frequent or rare.
- In addition, it must be stated that there could be unforeseeable side effects or risks in connection with participation in the trial, including any control treatment. This is often the case when testing of non-approved medicinal products.
- Information must be provided about inconveniences, which are the practical difficulties and discomforts suffered by trial subjects, such as absence from work due to visits for check-ups, blood tests or the like.
- Side effects, risks and complications should preferably be listed in a box so that decoding is easier for the reader.
- Side effects, risks and complications should preferably be listed as 'frequent/not serious' and 'seldom/serious'.

6. Other possible treatments

- The trial subject must be informed of any other possible treatments in cases where the aim of the trial is both scientific and therapeutic.

7. Exclusion from and discontinuation of trials

- Trial subjects must be informed of any circumstances that may result in their involuntary exclusion from the trial and any circumstances under which the trial as a whole may be discontinued.

8. Project plan

- How long will the trial take?
- How many visits?
- How will the treatment be given? And by whom?
- Which examinations will be involved?

It may be useful to tabulate the project plan if it involves many visits. This will provide a quick overview. Avoid using both a table and plain text to explain the same thing.

Reduce any use of the passive voice (is given, is taken) in the text. Use e.g. 'The nurse draws the blood samples' rather than 'blood samples are drawn' so that the reader knows whom he or she is going to meet.

Never use words from other semantic fields in the text. E.g. *drawing lots*, *a cup of blood*, *a spoonful of blood*. Such words are associated with matters that in the patient's mind are far from the world of health care. Rather use more neutral words such as e.g. '*random distribution*', '*decilitre*' and '*millilitre*'.

When medical terms are used these should always be translated into everyday language in a parenthesis – and translations should be consistently provided throughout the text. E.g. 'electrocardiogram (measuring of the heart's impulses)'

9. Contact person

- The information must contain the name, address and telephone number of the chief investigator and at least one contact person associated with the trial. If the contact person can only be contacted at certain times, these should be stated.
- It is recommended that the chief investigator or another professionally competent person is the contact person.
- Introduce the contact person at the beginning of the text and make the identity of this person clear throughout the text in order not to create a distance vis-à-vis the reader.

10. Information about financial matters

- If the researcher receives any funding from private enterprises, foundations etc. in connection with the trial, this should be stated. The names of any sponsors and the amounts from each sponsor must be stated. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial.
- It must be made clear whether the financial support is given as a fixed amount per trial subject (perhaps within a specified number) or as a lump sum for the entire project, and whether the money is paid to the researcher, to his/her department/institute, to a joint research fund or other recipients. It must also be stated how any excess financial support is to be used.
- Information about whether the chief investigator has any financial connection with the enterprises or foundations interested in the scientific trial in question. (It may also be stated whether other researchers in the group have such affiliations).

11. Access to trial results

- It must be explained where, when and how the trial subject will be able to obtain information about the trial results, negative as well as positive. This could for instance be in the form of a telephone number, a website or the like where the trial subject may obtain the information.
- If a trial subject after completion of the trial is allowed to receive information of which treatment he or she has been given, it would be appropriate to write in the information for

participants that “completion of the trial” means that tests of all the trial subjects included should be completed and the data processed. In this way, the misconception that trial subjects can obtain information as soon as they have completed their participation in the trial is avoided. It may be explained that it could take some time before information on results can be provided (preferably further specified if possible).

12. Special issues regarding trials involving medicinal products

In connection with trials involving medicinal products, a trial card may be provided saying that the trial subject is involved in a trial with medicinal products, the full title of the project and the name of a contact person to be contacted in case of injuries or accidents.

13. Special issues regarding information for parents giving consent to participation in trials involving children in the age group from 10 to 15

Generally, the aim should be to formulate the information in a language which is easy to understand. Information for parents giving consent on behalf of their children should to the extent possible be expressed in a language and in a form that encourages the parents to involve the children in understanding the purpose and methods of the trial. The text may be supplemented by a drawing showing the clinical situation.

Conclusion:

Always provide a summary by way of conclusion of the text. Request that the person takes a decision and preferably let the person know that any further questions are welcome. E.g. ' We hope that this information has given you sufficient understanding of what it means to take part in this trial and that you feel that you have a basis for taking a decision on your possible participation. If you would like to get more information please contact XXXX Kind regards XXXX

Appendix 2. Information for participants in the age group from 15 – 17

(August 2008)

Structure and contents

If 15 – 17-year olds participate in a scientific trial, special rules apply. According to the Executive Order on Information and Consent, permission may only be given if the youth is informed about the trial by someone with knowledge of the project area and also with the educational qualifications required to communicate the information, cf. section 20 of the Executive Order.

Usually, surrogate consent must be obtained from parents or a guardian. However, exemption from this rule may be granted in case of trials that do not involve medicinal products. See below. The procedure for obtaining surrogate consent is described in section 4.2.1.3 in the Guidelines.

Please note that minors who reach the age of 15 during the trial period are covered by the provisions regarding the 15 – 17-year-olds. Similarly, trial subjects who reach the age of 18 during the trial period are covered by the provisions regarding adults.

Information in connection with surrogate consent

15 – 17-year-olds are entitled to written information if they so wish and if the information will help them understand the scientific trial, its risks and benefits, cf. section 20(3) of the Executive Order.

The written information shall:

- Be adapted to the age and ability of the young person both in terms of language and contents. The heading should state who the target group is.
- Mention the most important issues, including risks and benefits involved in the trial.
- Make it clear who is the sender of the text, both in the introduction and throughout the text.
- Contain explanations of any medical terms – consistently throughout the text.
- Take special circumstances into account. If the young people are often in contact with the health service, they will probably be in a better position to understand the information than if they are rarely in contact with the health service.

We recommend that someone in the relevant age group is asked to read the information for the participants in order to determine whether the text is suitable.

About the oral information:

- It is important that the information for the 15 – 17-year-olds is targeted at the trial subject in terms of both language and contents.
- The information shall include the most important issues of the trial, including risks and benefits.

The oral information shall be based on the written information to the parent/guardian.

Information where an exemption from the surrogate consent has been granted

15 – 17-year-olds may participate in scientific trials if an exemption from the requirement regarding surrogate consent is granted, if the trial does not involve or only to a limited extent involves intervention or if the trial is not considered to involve any risk or stress for the trial subject, such as blood samples etc., i.e. trials not involving medicinal products. In such cases the custodial parent shall receive the same information and be involved in the decision-making of the 15 – 17-year-old. This ensures that the parents are informed and able to support the youth in his or her decision-making, cf. section 21 of the Executive Order.

The written information shall:

- Be adapted to the age and ability of the young person both in terms of language and contents. The heading should state who the target group is.
- Be exhaustive but with emphasis on the most important issues involved in the trial, including risks and benefits.
- Make it clear who is the sender of the text, both in the introduction and throughout the text.
- Contain explanations of any medical terms – consistently throughout the text.
- Take special circumstances into account. If the young people are often in contact with the health service, they will probably be in a better position to understand the information than if they are rarely in contact with the health service.

The written information shall contain information about:

- The objective and method and the importance, nature and scope of the scientific trial, including the practical arrangement for the trial and any clinical trials.
- Why research and trials are undertaken
- Any predictable risks, side effects, including known long-term effects, complications and inconveniences of participating in the scientific trial, and the fact that participation in biomedical trials may involve unpredictable risks and stress. Possibly listed clearly in a box.
- The aim of any removal of biological material for use in the given research project

If a research biobank is established, the trial subject shall be informed as to:

What material and how much is removed (e.g. ml per removal or a total)?

Are there any risks involved in the removal and, if so, what are they?

What is the purpose of the research biobank?

What will happen to the material, will it be unidentifiable after the termination of the project, will it be passed on to others or exported from Denmark?

For how long will the material be stored? For instance, will it be destroyed after the termination of the project?

Please note that if the trial subject has been informed that the material will be destroyed after use, the material cannot be used for future research projects.

It should be described whether the trial subject will have his/her material destroyed if he/she may subsequently wish this to be done.

- The possible benefits of the scientific trial. A distinction must be made between the benefit for the individual trial subject and the benefit for others and for scientific progress.

The fact that any refusal to participate in the trial or any later discontinuation of participation will not influence the young person's right to present or future treatment.

- Any circumstances that may result in the involuntary exclusion of the trial subject from the trial and in which circumstances the trial as a whole may be discontinued.
- Other possible treatments in cases where the purpose of the trial is both scientific and therapeutic.
- Who has initiated the biomedical trial and whom the participant will meet during the trial.
- The names of both commercial and non-commercial sponsors.
- The amounts from each sponsor and the way in which the financial support is included in the scientific trial, including whether the financial support is given as a lump sum or as an amount per trial subject, and whether the money is paid to the chief investigator, to his/her department/institute, to a joint research fund or another recipient. The application of the financial aid shall be stated, showing which part of the aid goes to the researcher as e.g. a personal fee and which part of the amount is allocated to payment of salary to assisting staff, laboratory tests or other examinations, respectively. The reason for this is that it is up to the

committee to assess whether the amount of the fee is reasonable in relation to the researcher's expenses for implementing the trial.

- Whether the chief investigator has any other financial association with the scientific trial.
- The name, address, e-mail address and telephone number of the chief investigator and a contact person associated with the scientific trial.
- A conclusion that summarizes the aim of the text – deciding on possible participation in the trial.

We recommend that someone of the relevant age is asked to read the information for participants in order to determine whether the text is suitable.

For a more detailed version of the Guidelines please see Appendix 1 "Drawing up useful information for participants".

About the oral information

- It is important that the information for the 15 – 17-year-olds is targeted at the trial subject both in terms of language and contents.
- The information need not be exhaustive, but must mention the most important issues involved in the trial, including risks and benefits.

The oral information shall be based on the written information.

Appendix 3. Ethical guidelines concerning biobanks

Cancelled. Please see Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics sections 2.6 and 4.7.

Appendix 4. Guidelines on research with pre-implantation diagnostics

Cancelled. Please see Guidelines about Notification etc. of a Biomedical Research Project to the Committee System on Biomedical Research Ethics, sections 2.9 and 4.9 regarding application for trials with fertilised eggs, stem cells or stem cell lines.

Appendix 5. Guidelines on the use of ionising radiation in biomedical trials

(May 2006)

General provisions

Any use of ionising radiation from X-ray sources or radioactive substances in biomedical trials results in radiation of the trial subject.

The risk involved in the radiation itself depends on the size of the radiation dose. The clinical investigator may obtain information about the radiation dose for the individual procedures from a responsible hospital physicist who must, according to the National Board of Health rules, ensure that such information is available.^{1,2} In cases where it is impossible to obtain the information from a responsible hospital physicist, the National Institute of Radiation Hygiene³ will provide assistance.

In connection with certain procedures the absorbed dose for a particular tissue or the mean dose for organs must be stated, for instance skin dose in case of intervention radiology and dose for tumour and surrounding tissue in case of radiotherapy. In case of long-term screening the total radiation dose is not known in advance, but it should be stated whether there will be a risk of deterministic damage.

Classification of research projects

The below-mentioned classification is based on guidelines from the International Commission on Radiation Protection (ICRP) and the European Commission.^{4,5}

Category I: Effective doses under 0.1 mSv for adults:

This category involves a risk of total stochastic damage from exposure to radiation of normal trial subjects in the order of 1 to 1 million or less. This risk may be regarded as insignificant. Consequently, the research project may be approved although the usefulness is small and the project is only expected to "increase our knowledge".

Category IIa: Effective doses within the area of 0.1-1 mSv for adults:

This category involves a total risk in the order of 1 to 100,000. In order for a research project to be approved, it should be possible to justify its usefulness based on the fact that the project is expected to result in "increased knowledge and health benefits".

Category IIb: Effective doses within the area of 1-10 mSv for adults:

This category involves a total risk to the radiated individual in the order of 1 to 10,000. In order for a research project to be approved, its usefulness to society must be somewhat greater as the project is expected to be "aimed directly at diagnosis, cure or prevention of disease".

Category III: Effective doses over 10 mSv for adults:

Here, the risk to the radiated individual is estimated to be higher than 1 to 1,000. This involves a moderate risk in connection with one-off exposure, but may be considered to be close to unacceptable in case of long-term or repeated exposure. In order to justify examinations in this category, the usefulness must be "considerable and related to the protection of life or prevention or palliation of serious disease". Doses should be kept below the threshold for deterministic effects unless higher doses are necessary for the therapeutic effect.

The table below may be used for adult trial subjects under the age of 50. For each of the above categories the dose figures may be increased by a factor of 5 to 10 for people over the age of 50. If authorisation is given for a research project involving radiation of children, the corresponding dose figures must be reduced by a factor of 2 to 3 due to a higher risk of genetic damage.

Social usefulness	Risk in relation to usefulness	Risk category (Stochastic damage – see definitions)		Corresponding effective dose area (adults) mSv
Small	Insignificant Small	Category I	10^{-6} or less	<0.1
Medium to moderate	Small to medium	Category IIa	approx. 10^{-5}	0.1 - 1
		Category IIb	approx. 10^{-4}	1 - 10
Significant	Moderate	Category III	10^{-3} or more	>10 (see note a)

a: Must be kept below deterministic thresholds except for therapeutic trials.

Information for trial subjects

Information about the risk in connection with exposure to radiation must be clearly stated in the project description to the committee on biomedical research ethics and in the information for the trial subject. This information must be so extensive that the trial subject is able to make a decision on the size of the risk.

In most diagnostic procedures the effective dose can be used as a measure of the likely stochastic radiation damage. In order to illustrate the size of the effective dose, a comparison could be made with background radiation. In Denmark the average background radiation is 3 mSv per year. A radiation dose of 10 mSv thus corresponds to 3 years' background radiation.

For each Sievert (Sv) the risk of inducing an incurable cancer is increased by 5% in relation to the population. By exposure to a dose of 20 mSv = 0.02 the risk increases by 5% x 0.02 = 0.1%. This risk is added to the general risk of 25% so that the total risk is 25.1%.

For healthy trial subjects the risk of damage may be specified as an increased risk of dying of cancer. In Denmark this risk is 25% and an effective dose of 20 mSv will increase this risk by 0.02 [Sv] x 5 [% per Sv] = 0.1% to 25.1%.

In case of radiation with a risk of deterministic damage, for instance in connection with lengthy X-ray screening, the trial subject must be informed of this risk.

Definitions

Medical radiation:

Medical radiation comprises all X-ray examinations, nuclear medical examinations and radiation therapy included in a project.

Radiation damage and risk:

Ionising radiation causes stochastic and deterministic damage. Cancer and genetic damage are regarded as stochastic damage, and the risk of stochastic damage is the sum of the risk of cancer and genetic damage. With large radiation doses, deterministic damage appears on the individual cells. The radiation dose must exceed a threshold dose before the damage becomes significant, and the extent of the damage increases with the radiation dose.

Radiation dose for trial subjects:

For X-ray examinations and nuclear medical examinations the radiation dose for the trial subject must be specified by the effective dose in mSv (milliSievert). For radiotherapy and radiation that may cause deterministic damage the absorbed dose for the radiated tissue area must be specified.

Effective dose:

The effective dose is a calculated mean value of the radiation dose for the trial subject's tissue and organs. The calculation is described in detail in the National Board of Health's Executive Order no. 823 of 31 October 1997 on Dose Limits for Ionising Radiation.¹

Background radiation:

Ionising radiation is part of the daily impact on humans, among other things because nature contains radioactive substances. The most important source of background radiation is the ionising radiation from space and the radiation from the radioactive substances such as potassium-40, radium, radon and thorium occurring naturally in ourselves and our surroundings. The radiation dose from background radiation is accumulated year by year throughout our lives. Background radiation varies according to the substratum we live on and the design and condition of our homes.

References:

- Executive Order no. 975 of 16 December 1998 on Medical X-Ray Systems for the Examination of Patients.
- Executive Order no. 954 of 23 October 2000 on the Use of Open Radioactive Sources in Hospitals, Laboratories etc.
- The National Institute of Radiation Hygiene.
- Radiological Protection in Biomedical Research. ICRP Publication 62, Annals of the ICRP, Oxford Pergamon Press, 1992.
- Guidance on medical exposures in medical and biomedical research, Radiation protection 99, European Commission. Available at europa.eu.int/comm/environment/radprot/99/rp-99-da.pdf

Appendix 6. Guidelines for remuneration or other payment for voluntary trial subjects

(September 2010)

Section 14(1)(ii) of the Committee Act stipulates: *"The committee may only grant authorisation if any remuneration or other payment for participation in a biomedical research project will not influence the giving of consent"*.

Remuneration or other payment for trial subjects in connection with participation in biomedical trials may not be such as to constitute payment for work performed, and it may not be the payment or the remuneration that motivates participation in the trial and the giving of consent. Consent shall be based on the trial subject's voluntary acceptance of participation in research that aims to generate new knowledge within biomedical research.

The rules on taxation of fees for trial subjects and tax rules concerning among other things compensation for transportation costs, are not considered in the present Appendix, and reference is made to the tax authorities for further information on these rules.

At the end of this Appendix there is a glossary of key concepts used (other payment, trial patient, incompetent person, healthy trial subject, lost earnings, transportation costs, inconvenience compensation and guardian).

A distinction is made between four types of remuneration in connection with participation in biomedical trials:

1. Compensation for documented loss of earnings
2. Compensation for documented transportation costs
3. Inconvenience compensation.
4. Other payments

Any remuneration or other payment for trial subjects must be stated and described in the research protocol and in the written information for participants, and it shall be explicit whether payments are made currently or in connection with the termination of the trial as well what payments are due if the trial subject decides to opt out of the trial before this is foreseen or is excluded on the basis of a decision taken by the chief investigator. Furthermore, it shall be made clear in the written information for participants whether payments are subject to taxation.

The National Committee on Biomedical Research Ethics recommends the following principles and rates:

Healthy trial subjects

Healthy trial subjects may receive all types of remuneration.

Thus documented loss of earnings may be compensated. For persons in gainful employment such compensation may be as a maximum amount to full coverage of earnings lost.

Documented transportation costs may be covered.

Inconvenience compensation may be paid on the basis of a concrete assessment of the trial including invasiveness, duration, pain and discomfort.

In the case of "other payment", an assessment shall be made as to whether the payment is liable to influence the giving of consent, and in connection with this assessment a distinction shall be made between on the one hand payments that are an integral part of the biomedical trial and that are necessary for the carrying out of the trial (e.g. free food in the case of trials that concern the significance of nutrition or supply of plaster in the case of a wound healing project), and on the other hand payments that are offered to the trial subject after termination of the project (cinema tickets, 6 bottles of red wine, MP3 player etc.). "Other payments" that are offered after termination of the project may possibly be awarded against the background of a concrete assessment of the trial but based on the same ethical criteria and considerations that form the basis of assessment with regard to inconvenience compensation.

Trial patients:

Inconvenience compensation can as a starting point not be offered. However it might be possible to offer inconvenience compensation if the research project does not imply any possible treatment benefit for the trials patient.

"Other payments" to trial patients may only be offered when these payments constitute an integral part of the trial and are necessary for the carrying out of the trial, cf. below.

Transportation costs may be covered as well as compensation for lost earnings for trial patients who take part because they have a specific condition and when attendance is not part of the treatment of this condition.

The committees may approve coverage of documented transportation costs and documented loss of earnings for a trial patient who takes part in a trial that concerns the treatment of his or her condition if this means that the trial patient has transportation costs and loss of earnings that exceed what would have been required for attendance for standard treatment. Participation in the trial may, for instance, require more frequent attendance than would otherwise have been necessary.

In the case of "other payment", an assessment shall be made as to whether the payment is liable to influence the giving of consent, and in connection with this assessment a distinction shall be made between on the one hand payments that are an integral part of the biomedical trial and that are necessary for the carrying out of the trial (e.g. free food in the case of trials that concern the significance of nutrition or supply of plaster in the case of a wound healing project) and on the other hand payments that are offered to the trial subject after termination of the project (cinema tickets, 6 bottles of red wine, MP3 player etc.).

Specifically on children and incompetent adults

By way of introduction it should be noted that the rules on approval of biomedical trials with the participation of incompetent persons have been made more stringent with regard to both children and adults.

Children/parents

With regard to children inclusion in a biomedical trial requires consent from the holder of custody. The expenses that may be involved in participation in a trial (loss of earnings and transportation costs) will in some cases affect only the child/adolescent, in other cases it will be the holder of custody that has to bear the cost.

The rules on compensation for lost earnings and transportation costs are the same for children as for adults.

Often it will be the parents who have expenses because of the participation of the child/adolescent in the trial, and in such cases the parents may receive compensation for transportation costs and lost earnings.

Compensation for lost earnings and transportation costs etc. may **not** be offered to parents if compensation for these costs is provided for under other legislation, e.g. the Services Act.

Incompetent adults

The above mentioned rules and rates on payments to healthy trial subjects and trial patients also apply to incompetent adults.

It should be noted that some incompetent adults may be incompetent at the time of inclusion though at a later time during the trial they may become competent and also possibly be considered to be healthy trial subjects.

Glossary:

Other payments.

This is a broad concept which covers various payments (e.g. cinema tickets, 6 bottles of red wine, MP3 player etc.).

Trial patients.

By trial patients are understood individuals who participate in a biomedical trial because the individual in question has or is suspected to have a disorder or condition which is required for participation in the trial. The individual may for instance take part in the trial as part of examination

or treatment at the hospital, and the trial may be of diagnostic or therapeutic value to the individual. Individuals may also participate solely because they have the condition in question, and they may already be receiving appropriate treatment for this condition, but the trial patient "contributes" with his or her condition and the trial may nevertheless be considered to be of some value and relevance to the trial subject although it does not play a role in relation to ongoing diagnostics or treatment.

Incompetent persons.

An incompetent person is a person who is unable to give informed consent to the participation in a trial either because of age or because of his or her mental or physical functional level caused by mental condition, age, development retardation or the like.

The Committee Act does not distinguish between permanent incompetence (e.g. persons with Alzheimer's) and temporary incompetence (e.g. unconscious persons who recover competence at a later point).

Incompetent adults will most often be represented by a guardian or closest relative.

Healthy trial subjects.

In this Appendix healthy trial subjects are understood to be:

1. Persons who are in good health and who have no known acute or chronic disease.
2. They may also be persons who have a known disorder which is not relevant to the disease under consideration in the project (e.g. a patient with a tennis elbow who takes part in a diabetes project). From the point of view of the project, this person is to be regarded as healthy.

The individuals concerned will not themselves benefit from participation as trial subjects, and their participation will not affect any future possibility for treating any condition they might have.

Loss of earnings.

In this Appendix compensation for lost earnings is understood as compensation for documented loss of salary as a consequence of participation in the trial.

Transportation costs.

In this Appendix coverage of documented and reasonable transportation costs means that it can be approved that documented transportation costs are covered. That costs should be reasonable means that as a general rule the cost of the cheapest means of transportation may be covered unless special conditions apply.

Inconvenience compensation.

In this Appendix inconvenience compensation is understood to mean a payment by way of compensation for participation in a trial offered on the basis of a concrete assessment of:

- Duration in time,
- invasiveness,
- Discomfort, or
- Pain.

The compensation may as a maximum be based on the rate for adult unskilled workers and shall be calculated as an allowance per hour. In special cases and based on a concrete assessment the rate may be doubled or tripled.

If for instance a trial subject participates in a trial that lasts 8 hours, this is covered by the concept "duration in time". If the trial subject is exposed to an invasive and/or painful intervention during the trial, the committee may allow that the rate for **some** of the eight hours is doubled or tripled based on a concrete assessment.

There can be no compensation for duration in time concurrently with compensation for loss of earnings.

Guardian etc.

A guardian is understood as a person who acts on behalf of the legally incompetent person in connection with among other things personal matters. For children and young people under 18, the holder of custody is automatically considered guardian unless the individual in question is under guardianship. In the case of shared custody both parents are guardians. Legally incompetent adults who are not under guardianship, are usually represented by their closest relative.