Logo: Tel Aviv Medical Center
R&D Division

SOP of Tel Aviv Medical Center
Guidelines for Clinical Trials in Human Subjects, Institutional Helsinki Committee
(hereafter: TASMC Charter)

References: in accordance with Public Health Regulations (Clinical Trials in Human Subjects) – 1980
Including 2006 update

SOP Title: Clinical Trials in Human Subjects - Institutional Helsinki Committee of Tel Aviv Medical Center	**SOP No.: 09.2.1 (11)** **Category: Helsinki Committee**
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Background

The institutional Helsinki Committee acts according to the Guidelines for Clinical Trials in Human Subjects, in accordance with the Public Health Regulations, 1980, with their appendices and revisions to 1999), while implementing the principles of the Declaration of Helsinki. The committee discusses applications for clinical trials in human subjects and approves them, and also discusses research applications in the field of social sciences (psychology, social medicine and applications including questionnaires).

The institutional Helsinki Committee hereby declares that is acts according to the provisions of the Ministry of Health and provisions of the current Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP) (Appendix 6).

A clinical trial in human subjects, as defined in the Regulations, is:

1. Use of a drug, radiation or a chemical, biological, radiological or pharmacological substance, against the approval granted for its use according to the legislation, or when the use mentioned above is not accepted in Israel for the purpose requested, or has not yet been examined in Israel, which may or is intended to affect human physical or mental health, in adults or in fetuses, in whole or in or part, including the genetic system.
2. Performing any non - standard procedure, action or examination in a human subject.
3. In addition, the committee discusses the following activities:
4. Any procedure intended to serve as part of a human trial / study protocol, even if it includes standard methods.
5. Performing any non - standard procedure, action or examination in a human subject, and performing procedures not yet routinely performed in the institution.
6. Requests of bodies outside the institution, with no need for follow up and control.

General

These guidelines regulate the manner of application, approval and control of clinical trials and studies in human subjects. The guidelines define the pathway of clinical trial applications handling, requirements regarding the manner of conducting them, and the manner of supervising them. Every trial, including the design, approval, performance, documentation and reporting, should be carried out while ensuring strict compliance with the: principles of the Declaration of Helsinki, Public Health Regulations, 1980, with their appendices and revisions up to 1999 (hereafter: the Regulations), Genetic Information Act 2000 (hereafter: Genetic Information Act), provisions of the MOH guidelines, provisions of the current Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP E6) (Investigational Products):

Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP E6)

Provisions of the current Standard for **Clinical Investigation of Medical Devices for Human Subjects**
ISO 14155-1, 14155-2 (2003):
As well as circulars and guidelines published by the Ministry from time to time.

Meeting the requirements of the above guidelines is aimed at protecting the trial participants and ensuring that the rights, safety and wellbeing of the trial participants are maintained, and that the information collected during the study is reliable.
In case of any contradiction between the above guidelines, the valid guideline is the one issued by the Ministry of Health. For issues with no obligating guidelines in the Procedure of the Ministry of Health – the guidelines will be based on international standards (defined below).
The Guidelines of the Ministry of Health, with all their appendices and forms, are available on the website of the Department of Clinical Trials, Pharmaceutical Administration, Ministry of Health: **www.health.gov.il/drugs**.

General definitions according to the guidelines of the Ministry of Health

1. "**Special population**" – Pregnant women, minors*, patients whose judgment capability is impaired due to their physical or mental state, and people who are held in legal custody.

2. "**Adverse events in a clinical trial**":
   a. **ADVERSE EVENT** (**AE**): An untoward medical event experienced by a clinical trial participant treated with an investigational product, which is not necessarily related to treatment with the investigational product.
   b. **SERIOUS ADVERSE EVENT (SAE) :** An adverse event which is:
      - Death
      - Life threatening
      - Causing hospitalization or prolonging the duration of existing hospitalization (for example, due to the need for medical intervention, or due to the risk of disability or a life threatening condition)
      - Causing incapacity or significant and/or persistent disability, or
      - A congenital defect
   c. **ADVERSE DRUG REACTION (ADR**) or **ADVERSE DEVICE EFFECT (ADE)**: An adverse event associated with treatment with the investigational product to some extent.
   d. **SERIOUS ADVERSE DRUG REACTION** (**SADR**)/ **SERIOUS ADVERSE DEVICE EFFECT (SADE**): A serious adverse event associated with treatment with the investigational product to some extent.
3. "**Director General**" - Director General of the Ministry of Health or a person appointed by him for matters related to these regulations, in whole or in part.
4. "**Good Clinical Practices" (GCP)** – Working procedures and methodology designed to ensure the wellbeing and rights of study participants, as well as the quality and efficacy of the study.
5. "**International procedures**" – Two international quality standards, ethical and scientific, for design, performance, documentation and reporting of studies involving human subjects.

* A minor is a person below the age of 18 years, based on the Act of Legal Competence and Legal Guardianship - 1962

For investigational products: Harmonized Tripartite Guideline for Good Clinical Practice - ICH-GCP (**hereafter**: ICH-GCP).

For a medical device: The international standard for clinical studies in human subjects with medical devices: ISO 14155-1, 14155-2: Clinical Investigation of Medical Devices for Human Subjects GCP (**hereafter**: **ISO14155**).

6. "**Helsinki Committee of the hospital or medical institution**" – An independent committee, the composition, ways of appointment and the legal quorum of which are defined in the regulations. Its duty is to ensure the rights, safety and wellbeing of the subjects enrolled in the clinical trial by evaluating and approving the clinical trial protocol and the informed consent form, among other activities. In addition, the committee is responsible for routine monitoring of the trial, including modifications made in the protocol and in the informed consent form, and for supervising the clinical trial, as detailed in section 18 of these guidelines.
7. "**Supreme Helsinki Committee**" – An independent committee, the composition, ways of appointment and the legal quorum of which are defined in the regulations. Its duty is to provide its expert opinion on trials related to genetic research in human subjects, unnatural female fertilization, and other issues which the Director General requests to discuss, including trials regulated by the Genetic Information Act.
8. **"Central committee for clinical trials in human subjects"** – A committee consulting to clinical trials appointed by the Director General of the Ministry of Health, in any of the following subjects (or in any other subject to be decided in the future):
   - **a.** Medicinal products (medications)
   - **b.** Medical devices and equipment
   - **c.** Products containing living human cells and tissues and xenotransplantation
9. **"Association**" – Any relationship of paid employment, or commercial or business relationship, or family or personal relationship, including subordination at work, which may raise a concern of the existence of conflict of interests or dependence, except for reimbursement of expenses or payment for participation in committees according to this procedure.
10. **"Investigator or Principal Investigator"** – A certified physician or a certified dentist serving as an investigator responsible for conducting the clinical trial at the trial site as defined in the trial protocol.
11. **"Sub-Investigator"** – Any person in the study staff, who was appointed by the Principal Investigator, and is under his supervision at the study site, to perform critical procedures related to the study and/or for taking important decisions related to the study.
12. "**Sponsor**" – A person, including a corporation or an institution, responsible for initiation, management and funding of the clinical trial.
13. **"Sponsor-Investigator**" – A person, excluding a corporation or an institution, who is both the sponsor and the Principal Investigator of the clinical trial, whether by self funding or third party funding, regardless of the source of funding. This person bears the responsibilities of both the Principal Investigator and the sponsor.
14. "**Recognized country**" – any of the following:
    a. USA;
    b. European Union member state;
    c. Switzerland;
    d. Norway;

e. Iceland;

f. Australia;

g. New Zealand;

h. Japan;

15. "**Investigational Product**" – A medicinal product (medication; or placebo), a medical device, a medicinal product containing living cells and tissues, a cosmetic product, a food product, a food supplement, a homeopathic product or a medicinal herb, etc. A product studied or used as a reference product in a clinical trial in human subjects, including a product approved for marketing used differently from the registered manner of use, or off-label use (for a non-registered indication) or used for the purpose of acquiring additional information about the registered use.

16. "**Multicenter trial in Israel**" – A clinical trial conducted in more than one medical center in Israel.

17. "**Director of a medical institution** " – The medical director, or acting director of the hospital or of the medical center at which the clinical trial is conducted, with respect to the regulations, all or some of them.

18. "**Monitor**" – A person responsible for monitoring during a clinical trial in human subjects, who underwent relevant professional training for this purpose.

19. "**Monitoring**" - Real time control of procedures performed during a clinical trial in human subjects, the aim of which is to ensure that clinical trial performance, documentation and reporting are carried out in accordance with the clinical trial protocol, GCP procedures, approval granted for the study and applicable legal provisions.

20. "**Clinical trial / clinical study**" – A clinical trial in human subjects, as defined by the regulations"

(1) Use of a medication, radiation or a chemical, biological, radiological or pharmacological substance, against the approval granted for its use according to the legislation, or when the use mentioned above is not accepted in Israel for the purpose requested, or has not yet been examined in Israel, which may or is intended to affect human physical or mental health, in adults or in fetuses, in whole or in or part, including the genetic system.

(2) Performing any non - standard procedure, action or examination in a human subject.

In addition, a clinical trial in human subjects includes special clinical trials, as defined in the fourth supplement to the Regulations.

The aims of a clinical trial in human subjects, as defined by the Helsinki Convention, are to improve the treatment, diagnosis and prevention of diseases, and to contribute to the understanding of disease etiology and pathogenesis.

21. **"A genetic trial / genetic study"** – A study in which a biological sample is taken, and DNA is extracted from it to obtain genetic information, regulated by the Genetic Information Act. Except for: clinical genetic testing (detection and identification of mutations in a known gene, related to a known disease), as well as studies aimed at testing DNA products (RNA, protein expression or enzyme activity).

22. "**Sample bank**" - Application for establishing/ or approval of a DNA sample bank for medical or research purposes (in accordance with the guidelines of Supreme Helsinki Committee for Genetic Studies in Human Subjects for establishing and using genetic sample banks and according to the circular of Director General, Ministry of Health 01/05)

23. "**A special clinical trial**" – A clinical trial, which the Director of the medical institution is authorized to approve. This clinical trial does not require approval by the Ministry of Health

in addition to the approval of the institutional Helsinki Committee, as defined in the fourth supplement to the Regulations and included in the list provided in Chapter 6 of these guidelines.

24. "**A non-special clinical trial**" – A clinical trial which requires approval by the Ministry of Health after it has been approved by the institutional Helsinki Committee.

25. "**A study which is not a clinical trial in human subjects**" – A study involving collection of information from people, interaction with them (a study of questionnaires), or a study in which information is collected from existing medical records without involving the patients (Appendix 2).

26. "**Medical device/ equipment**" – A device, an accessory, a chemical substance, a biological or a biotechnological product used for medical treatment or required for operating a device or an accessory used for treatment, which is not designed to act, by itself, on a human body as medication therapy.

27. "**A recognized medical device**" – A medical device for which any of the following applies:

a. It is routinely used for medical treatment and the Director General has approved its safety;

It has been approved for marketing by the US Food and Drug Administration (FDA) and is being sold in the US;

b. It has been approved for marketing and is being sold in a European Union member state (approved by the CE mark);

28. "**A certified physician**", "**A certified dentist**" – A physician or a dentist who is a holder of an academic degree recognized in Israel – MD, MDD, holders of a license to practice general medicine or dental medicine in Israel, in accordance with Physicians' Ordinance [new version] 1976, and Dentists' Ordinance [new version] 1979.

29. "**A modification in a clinical trial, which the Director of the medical institution is authorized to approve**" - A modification in a clinical trial application which does not require approval of the Ministry of Health in addition to the approval of the institutional Helsinki Committee, included in Section **13** of these guidelines.

30. "**A medicinal product**" – as stipulated in Pharmacists' Ordinance [new version] 1981.

1. Regulations of the institutional committee (hereafter: Charter) – definitions

1.1 The institutional committee supervising clinical trials and studies in human subjects at Tel Aviv Sourasky Medical Center (TASMC) shall be called "Committee for human trials" (Helsinki Committee) of TASMC – hereafter "Committee".

1.2 Committee regulations (hereafter: Charter) are based on the Public Health Regulations (Clinical Trials in Human Subjects) 1980, with their appendices and revisions up to 1999 (hereafter: Regulations, Appendix A), on the provisions of the Regulation of the Ministry of Health (Appendix B), on the recent Declaration of Helsinki (Scotland Revision, 2000 Appendix C) and on the provisions of the international regulations for Good Clinical Practices (Harmonized Tripartite Guideline for Good Clinical Practices) (ICH-GCP) (Appendix D) and additional guidelines defined by the Ministry of Health (such as guidelines for medical devices, guidelines for living cells and tissues, genetic studies).

1.3 Committee Charter implements these regulations and guidelines in accordance with the local conditions and guidelines of TASMC.

2. Duties and authorities

2.1 The duties and authorities of the Committee are:

2.1.1 To ensure the rights, safety and wellbeing of every clinical study subject, with a special emphasis on cases in which the subject may be exposed to risks or side effects, pain and discomfort.

2.1.2 To examine applications for clinical studies/trials in human subjects, to approve, require revisions or reject studies related to TASMC.

2.1.3 To examine the level of investigator's eligibility to conduct the study, including his professional and personal skills.

2.1.4 To verify availability of resources and/or physical conditions required for the study (such as diagnostic equipment or special laboratory tests) in the hospital, or whether they can be purchased by the person performing the study.

2.1.5 To monitor studies at the frequency determined according to the risk level associated with the clinical study, and at least once a year.

2.1.6 To discuss adverse events (such as serious or unexpected side effects) which occurred during the trial.

2.1.7 To halt/stop the study.

3. Composition of the Committee

3.1 The Committee should include at least 7 members, including the Chairman.

3.2 The Committee should include both men and women.

3.3 The Committee Chairman should be a department head (current or former) at the medical center, or a physician holding at least the title of "Associate Professor" at one of the medical schools recognized in Israel.

3.4 At least 3 Committee members should be physicians, who are heads of departments at the medical center, or physicians holding at least the title of "Associate Professor" at one of the medical schools recognized in Israel. At least one of them should be a specialist in internal medicine.

3.5 At least one Committee member should be a public representative (a clergyman, a teacher, a lawyer or a medical ethics expert), who is not affiliated with the medical center and whose major occupation is not related to science.

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3.6 At least one additional member of the Committee should be a professional who is not a physician.

3.7 A representative of the medical administration should take part in the Committee.

3.8 Director of pharmaceutical services of the medical center should be a permanent Committee member.

3.9 A coordinator should be appointed for the Committee, whose duty is to take care of the administrative aspects of Committee's activity, under the supervision of the Research and Development Division of TASMC.

3.10 The Committee coordinator should hold an updated list of the members, approved by the Director of the medical center and the Director General of the Ministry of Health. The list of Committee members should be available to the public.

4. Committee membership

4.1 A Committee member should be appointed by the Director of the medical center following approval by the Director General of the Ministry of Health.

4.2 This rule is applicable to all the members of the Committee, except those who are appointed based on their duties (e.g. representative of the medical center administration and the director of pharmaceutical services).

4.3 A Committee member who wants to resign should notify the Director of the medical center and the Committee Chairman in advance.

4.4 The Committee Chairman should be appointed by the Director of the medical center for a period of up to 5 years, with a possible extension for 5 more years.

4.5 The Director of the medical center should appoint certain Committee members to serve as deputies of Committee Chairman in his absence.

5. Committee meetings

5.1 The Committee should convene at least once a month. Its legal quorum should be at least 5 members, including the Chairman, the public representative, the management representative and a specialist in internal medicine.

5.2 Dates of Committee meetings should be published in advance – the annual schedule should be posted in the hospital website, with personal circulation to the Committee members.

5.3 In case of numerous applications, to prevent delay of study approvals, the Committee Chairman may conduct an additional meeting, at limited quorum, a week before the scheduled meeting. Five members should take part in this meeting, including the management representative and the public representative. The rest of Committee members should be informed of the decisions taken during this meeting as part of the joint protocol of both meetings.

5.4 Committee meetings and its decisions should be documented in writing by the Committee coordinator (without details of voting for/against); the coordinator should forward the complete meeting protocol, including decisions regarding new applications, revisions and extensions, to the Ministry of Health and to the Committee members.

5.5 Decisions relevant to a specific study/ trial should be sent to the Principal Investigator and made available for review by the Sponsor and other regulatory authorities (such as FDA, EMEA).

6. Confidentiality

6.1 All the discussions conducted by the Committee are confidential and should not be disclosed to any person outside the Committee, unless the disclosure is performed officially according to Chairman's decision (for approval by the Pharmaceutical Administration, for professional consultation, due to the request of the study sponsor, etc.).

6.2 The Committee members should make sure that all the relevant documents are returned to the Committee coordinator at the end of the meetings. Material not required for filing or sending to the Pharmaceutical Administration should be returned to the Principal Investigator.

6.3 Every Committee members should sign a document of maintaining confidentiality as part of his membership (Appendix 7).

7. Investigator's declaration regarding his association with the study Sponsor.

7.1 If the Principal Investigator/ or a Sub-Investigator/ or head of the department/ unit in which the study is conducted are associated with the study Sponsor, this should be indicated in the application documents, as a prerequisite for protocol evaluation by the Committee.

7.2 Details of association should include precise information about the nature of association of each investigator or head of department/ unit. This information must be signed by the people declaring association and by the head of department/ unit in the application documents.

7.3 The investigator associated with the Sponsor may not serve as the Principal Investigator. The decision regarding approval of the study, in which the Sub-Investigator/ or head of the department/ unit are associated with the Sponsor company, lies with the Helsinki Committee. The Committee should examine the possible impact of such association on the scientific integrity of the trial and on its ethical aspects.

7.4 The Committee should decide whether the head of the department/ unit or another investigator associated with the Sponsor company should be invited to the Helsinki Committee meeting.

7.5 The Committee may approve participation of an investigator associated with the Sponsor company and or participation of the department/ unit, the head of which is associated with the Sponsor company, require inclusion of an additional independent investigator or reject participation of the above parties in the study.

7.6 The Committee should verify that the association with the Sponsor is indicated in the Informed Consent Form provided to the patient and signed by him.

8. Conditions of conducting a clinical trial in human subjects according to the Guidelines of the Ministry of Health

8.1 A clinical trial in human subjects shall be conducted only if it complies with the

provisions of the Regulations and these guidelines.

8.2 a. A clinical trial in human subjects shall not conducted unless it has been approved by the institutional Helsinki Committee and by the Director of the medical institution, according to the rules defined in the Regulations and in these Guidelines.

b. A non-special clinical trial in human subjects requires approval by the Ministry of Health in addition to approval by the institutional Helsinki Committee.

c. An application for approval of a clinical trial in human subjects may only be submitted by a certified physician or a certified dentist (depending on the study subject), who will be the Principal Investigator of the trial.

d. The Principal Investigator should submit an application for a clinical trial in human subjects to the institutional Helsinki Committee, as detailed in Section 9 of these Guidelines.

8.3 The Helsinki Committee shall not grant approval to conduct a clinical trial in human subjects unless it has been reasonably convinced that the conditions detailed below, and any other conditions, according to its discretion, have been met:

a. The expected benefits for the trial participant and the society justify the risk and the discomfort associated with the trial caused to the trial participant.

b. The currently available medical and scientific information justifies the conduct of the proposed clinical trial.

c. In case of a clinical trial to be conducted in a special patient population, the trial is required to promote the health of this population and cannot be conducted in any other population instead of it.

d. The scientific design of the clinical trial enables answering the study question; it is described clearly, accurately and comprehensively in the study protocol and complies with the principles of the Declaration of Helsinki.

e. The foreseeable risks to the trial participant are minimized, as much as possible, by the use of appropriate research methods, and if possible, by the use of procedures already performed in human subjects or examined in animals.

f. The trial protocol should define clear criteria for selection of trial participants.

g. The informed consent form for the clinical trial should contain a summary of all the required information, as detailed in these guidelines.

h. The study design should contain instructions for maintaining privacy of the participants and confidentiality of the information collected.

i. The study design should contain an ordered mechanism for optimal monitoring of the trial.

j. The Sponsor of the clinical trial must provide appropriate insurance to cover its legal liability in accordance with the laws of the State of Israel against claims filed by clinical trial participants and/or third-party claims, all related to the clinical trial, whether during the duration of the trial or thereafter. The insurance should be expanded to include the legal liability of the medical institution and/or the medical staff and/or the Investigator, resulting from their involvement in the trial, with the exclusion of events resulting from malpractice or intentional deviation from the study protocol.

k. Free supply of the investigational product to the trial participants should be guaranteed throughout the entire period of the trial.

l. The Sponsor, Principal Investigator and the medical institution are capable of and undertake to allocate the resources required for appropriate conduct of the clinical trial, including experienced personnel and necessary equipment.

m. The nature of the commercial agreement with the Principal Investigator and the medical institution in which the trial is conducted does not compromise the appropriate

conduct of the clinical trial.

n. If all or some of the clinical trial participants may be exposed to pressure or inappropriate influence to participate in the clinical trial, appropriate measures have been taken to prevent such pressure or to minimize such influence.
o. The rights and safety of the clinical trial participants should be protected throughout the trial.
p. Any decision made and any medical treatment given to a participant as part of the clinical trial should be under the responsibility of a certified physician or dentist, as relevant.

8.4 A clinical trial in human subjects should be conducted strictly in accordance with the provisions of the Regulations, these guidelines of the Ministry of Health, including the relevant laws mentioned there, the international guidelines and requirements of the study protocol, as approved by the Helsinki Committee, and in accordance with the approval conditions.

8.5 According to the requirements of TASMC, the Principal Investigator should be appropriately qualified for conducting clinical trials (completion of GCP course) and the Sub-Investigator (hereafter: the Investigator) taking part in a clinical trial in human subjects should be appropriately qualified for conducting clinical trials, and skilled and experienced in his field, with respect to the clinical trial conduct.

8.6 Any information related to a clinical trial in human subjects, which may lead to disclosure of a trial participant's identity or details of his medical or genetic condition, should be maintained confidential, subject to the provisions of Article 19 of the Patient's Rights Act 1996, with the mandatory revisions. With respect of genetic information, the results of genetic tests should not be included for study purposes in the medical file, based on Article 30 of the Genetic Information Act.

9. Contents of the application for a clinical trial

General comment:
The content of the application documents varies depending on the nature of the trial: trial with a medicinal product, trial with a medical device; trial with a product derived from living cells and tissues; a genetic trial; a clinical trial not involving the use of an investigational or experimental product; a study which is not a clinical trial. There is a separate application package for each type of trial, as detailed in the table in section 33 of the guidelines and forms provided in these guidelines. The application should contain the following documents and data:

9.1 טופסי בקשה מתוך נוהל ניסיים רפואיים בבני אדם של משרד הבריאות (2006)

9.1 Application forms provided in Guidelines for Clinical Trials in Human Subjects of the Ministry of Health (2006)

*Form 1A - for medicinal products

* Form 1B - for medical devices

* Form 1C - for products containing living cells and tissues

* Form 1D - for genetic trials

*Form 1E - for clinical trials not involving investigational products

* A study which is not a clinical trial in human subjects (a study of questionnaires or collection of data from medical records) (Appendix 12)

* Application for establishment of a sample bank for medical and research purposes (Appendix 16)

9.2 A detailed design of the clinical trial (trial protocol):

9.2.1 Protocol for a trial with an investigational product

In general, the protocol should address the subjects specified in the instructions of the international guidelines, and in particular:

- Name, number, date and version of the protocol
- Name and address of the study Sponsor and the study monitor (if other than the Sponsor)
- Name and title of the person who has signed the protocol
- Background and rationale for the clinical trial, including a review of scientific literature
- Name and description of the investigational product, the clinical indications and summary of existing preclinical and clinical knowledge related to the investigational product. For a trial with a medical device, name of the manufacturer, name of the model, accompanying accessories, identification number of the software version and the manner of use in the trial should also be specified.

  In applications for trials with investigational products, the name of the investigational product and the name of the manufacturer should be specified in the protocol.
- Objectives of the clinical trial
- Parameters to be used for evaluation of the results (endpoints)
- Total number of participants, number of sites planned to take part, phase number and design of the clinical trial - open-label, blind, etc.
- Criteria for inclusion in, exclusion and withdrawal from the clinical trial
- Plan of treatment with the investigational product/ medical device (including dosage, mode of administration, treatment duration and number of treatments)
- Clinical follow up plan (it is recommended to attach a time schedule and/or a flow chart of the trial)
- Laboratory tests and any other relevant test to be performed during the trial and the follow-up period
- Conditions of clinical trial termination
- Methods of safety evaluation and manner of serious adverse event (SAE) reporting (reporting should be performed according to the rules of the guidelines)
- Methods of analysis and processing of the results
- Ethical issues of the trial
- Examples of Case Report Forms (as required)
- Method of investigational product accountability
- Clinical tests, questionnaires

9.2.2 Protocol of a genetic trial

According to the genetic questionnaire, the protocol should include the subjects specified in Part B Section 1: information required for the research proposal as indicated in the instructions for investigators and forms for completion required for application for approval of genetic studies in human subjects, 2005 (Appendix 13)

These guidelines are provided on the website of TASMC.

9.2.3 Protocol of a clinical trial without an investigational product:

- Name, number and date of the protocol
- Name and signature of the protocol author
- Background and rationale for the clinical trial, including a review of scientific literature
- Objectives of the clinical study
- Parameters to be used for evaluation of the results (endpoints)
- Number of participants, and number of sites planned to take part
- Criteria for inclusion in and exclusion from the study
- Time schedule of the study
- If relevant: laboratory tests and any other relevant test to be performed during the study or the follow-up period, location of test performance and handling of samples at the end of the study
- Methods of analysis and processing of the results
- Ethical issues of the trial

9.3 Investigator's Brochure

9.3.1 Investigator's Brochure - medicinal products

The current Investigator's Brochure containing information about the investigational product, as detailed in the international guidelines (ICH-GCP), including:

- A cover page including: details of the study Sponsor, name and/or code of the investigational product, edition number and date
- Table of contents
- Introduction including the scientific rationale
- Physical, chemical, and pharmaceutical data of the final product being investigated in the trial
- Preclinical data: pharmacology, pharmacokinetics and toxicology
- Current clinical data including safety and efficacy information
- Summary of the data, summary of expected risks to the participants and instructions for use of the investigational product

Comments:

An exemption from the obligation to submit the Investigator's Brochure may be obtained from the Ministry of Health in the following cases:

- ❖ The trial involves the use of a registered product approved in Israel for the registered indication.
- ❖ The trial involves the use of a medicinal product previously approved for a clinical trial in Israel, for the same indication and with the same mode of administration.

The clinical trial refers to an additional indication, additional dosing form or additional dosing regimen for a product registered in Israel, as long as the route of administration is the same as that of the registered product and the dose does not exceed the commonly used dose reported in the literature. Relevant publications, such as articles from the professional literature, supporting the rationale of the clinical trial, should be enclosed with the application.

If the mode of administration is different, the specific chapters of the Investigator's Brochure related to the requested mode of administration should be submitted.

- ❖ A bioavailability trial in which one or both of the products are registered in Israel or in a recognized country.

9.3.2 Investigator's brochure - a medical device

The current investigator's brochure containing information about the medical device, as specified in the international guidelines (ISO 14155), and in particular:

9.3.2.1 A cover page, including details of trial Sponsor, name and/or code of the medical device, model number/name, software version, manufacturer's details, version date and number

9.3.2.2Table of contents

9.3.2.3 Introduction, including the background and the rationale for the designated use of the medical device in the trial and for technology development

9.3.2.4 General description of the medical device and the accompanying accessories, indicating the models (including a technical description and the active components) and the software version number

This section should include, among other details:

a. Information about the substances of which the medical device is composed and their suitability for their proposed purpose. (Any medical device must comply with biocompatibility requirements in accordance with the ISO 10993 standard).

b. If the medical device transfers energy to or from the body - the type of energy, its description and quantity in physical parameters, and the rate of energy flow should be indicated.

c. If substances are transferred to or from the body - description of the substances, description of the quantities, and description of their flow rate should be included. If isotopes are used, indicate the dose of radiation received by the clinical trial participant, with reference to the common standards.

d. If the medical device contains a medicinal product - the name of the product, name of the manufacturer, quantity/strength, method of release, and additional information should be indicated, according to standard practices.

e. If the medical device contains a biological substance - description of the substance, its origin, and method of handling it for inclusion in the medical device should be indicated.

f. If the medical device is a measuring device, details of the variables measured and the extent of accuracy should be indicated.

g. Information about sterilization, if relevant (single or multiple use, sterilization site and method), and compliance with the requirements of the circular of Director General: "Instructions for sterilization of medical devices and equipment".

h. If the medical device is a change/modification of "recognized medical equipment" or of a medical device previously approved for use in a clinical trial:

- Name of the original medical device (including the model) and name of the manufacturer.
- Regulatory status of the original medical device, with approval certificates enclosed.
- Description of the modification of the medical device.
- Possible impacts of the modification on performance of the medical device, its safety, efficacy, method of use and clinical action; references from the literature, mathematical proofs and report on preclinical trials should be enclosed.

i. If the medical device is a software or a medical device with incorporated software - identifying details of the version, a brief description of the algorithm, including a macro flowchart (at the level of main functions and routines) should be indicated. A signed validation certificate should be enclosed. An explanation should be provided regarding the manner of handling situations, related to either software or hardware, where a software failure may endanger the trial participant.

9.3.2.5 Explanation on the mechanism of action, performance, and method of use of the device, with instructions of the manufacturer for use/ operation/ installation/ maintenance (as relevant).
Description of the clinical action (with reference to the intended use in suitable patients) and of the indications.

9.3.2.6 Description of preclinical studies and their results: relevant laboratory and animal trials performed to prove the safety and efficacy of the medical device in use for its intended indication. Animal trials should be conducted in accordance with Good Laboratory Practice (GLP) guidelines applicable in the US or in a European Union member state.

9.3.2.7 Summary of the existing clinical experience with the medical device, including previous trials in human subjects, marketing history and reports on serious adverse events in human subjects/ medical device failures.

9.3.2.8 List of the standards (name of the standard, symbol/number, author), the regulatory requirements according to which the medical device was designed/ built/ handled/ tested and a summary of risk analysis.

9.3.2.9 Description of the unique features of the medical device, as compared to equivalent medical devices which are commonly accepted or approved for use (relevant parameters, manners of use, risks and benefits).

9.3.2.10 Summary of the information and guidelines for the Investigator.

9.3.2.11 Manner of accountability.

9.3.2.12Marketing material (if available).

Comments:

An exemption from the obligation to submit material may be obtained from the Ministry of Health in the following cases:

- Exemption from submission of material as detailed in sections 9.3.2.4 (only a summary will be required) and 9.3.2.9 – in cases of recognized medical equipment or a medical device approved for use in a clinical trial in Israel.
- Exemption from submission of material as listed in Section 9.3.2.7– in cases of a medical device previously approved for use in a clinical trial in Israel for the same indication.
- In cases of modification in a medical device approved for use, as detailed in Section 25 in the "Definitions", and/or a medical device previously approved for use in a clinical trial, or use of non-approved devices - the modification and the accessories should be described, and information in accordance with the entire section 2.3.2 specified above should be attached, if relevant.

9.3.3 Investigator's Brochure – medicinal products containing living cells and tissues of human origin.

The current Investigator's Brochure in accordance with
Points to Consider on the
Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products, published by the EMEA CPMP on May 31, 2001. (http://www.emea.eu.int/)

The brochure should include the preclinical information required to prove the efficacy and safety of a medicinal product containing human living cells and tissues (hereafter: the product) intended for use in a clinical trial, and in particular:

9.3.3.1A cover page, including the product name, name of study Sponsor, edition date and number.

9.3.3.2Details of the manufacturer (if the manufacturer is the Investigator - details of the Investigator should be specified): name, address, telephone number, fax number, name of the contact person for clinical trials.

9.3.3.3Manufacturing site.

9.3.3.4Characterization of the product, including:

- Biological description of the final product, with its specifications and intended clinical use (indication)
- Source of the cells/tissue:
  - Autologous (self source), allogeneic (non-self human source)
  - Description of the original cells/tissue
- Mode of administration
- Mechanism of action

9.3.3.5The technology – review:

Rationale, scientific and historical background, existing clinical experience with this technology in human subjects, existing experience in animal models (with references to the literature and copies of supporting articles).

9.3.3.6Characterization of processes:

9.3.3.6.1 The donor:

- ❖ Characterization of the donor: including gender and age, medication therapy administered prior to cell/tissue production
- ❖ Donor Selection
- ❖ Procedure of screening and testing for pathogens (indicating the laboratories/ examining entities). Donor's medical history of the donor should be addressed.

Comment:

The applicants should consider the standards and guidelines of relevant organizations, in accordance with the tissue source.

- ❖ Description of donor registration procedure, with reference to the possibility of tracking the donor if the recipient develops an infectious disease.
- ❖ Procedure of registration and storage of donor's serum with reference to the possibility of testing the serum if the recipient develops an infectious disease.

9.3.3.6.2 Source and characterization of materials used in the manufacturing process:

Description and quality of growth (culture) media and their components.

Details of the tests performed to identify infectious agents.

Components of living sources (human or animal): growth media without the above components are preferable.

Minimal requirements for components of living sources, if used, in accordance with the following circulars of the Ministry of Health:

a. Medical Administration Circular No. 45/97 dated November 10, 1997: "Special requirements for the import of whole blood and its components".

b. Medical Administration Circular No. 32/98 dated May 7, 1998: "Nutrition substrates (media used for growth of material intended for use in humans) produced from living sources or containing components produced from living sources – mandatory registration".

c. Pharmaceutical Administration circular dated April 19, 2001: "Medicinal products containing or exposed to substances with suspected Transmissible Spongiform Encephalopathy (TSE) contamination".

If an updated version of any of these circulars is published, the requirements will be defined in accordance with the updated version.

9.3.3.6.3 Manufacture:

- ❖ Description of the ex vivo manipulation (with emphasis on optimization of the conditions to minimize the risk of infection by infectious agents and of contaminations by other cell types)
- ❖ In Process Controls (IPC)

- Documentation of the in-process procedures and controls
- Infection tests (microbiology, virology, mycology)
- Integrity and function test in each stage

❖ Characterization of the product during development

❖ Flow chart

9.3.3.6.4 Characterization of the final product:

❖ Objectives

❖ Expected and relevant biological activity

❖ Absence of any long term risk

❖ Evaluation of identity, purity, biological activity using appropriate in-vitro methods and, if possible, in-vivo tests in a suitable model (validation of the animal model is required)

❖ Quantitative analysis of the number and fraction of active cells

❖ Stability - test of the phenotypic and genetic characteristics of the cells over time

❖ Toxicity – upper limit of the allowed quantity of residual materials used in the manufacturing process and in tissue culture and animal experiments, if possible.

9.3.3.6.5 Results of in-vitro model experiments

9.3.3.6.6 Results of animal model experiments

9.3.3.6.7 Results of previous human trials

9.3.3.6.8 Description of the Quality Assurance system

Comment:

The brochure should address the laws/ regulations/ circulars of Director General/ standards/ guidelines/ procedures commonly used in Israel and worldwide, compliance with them, and appropriate certificates of compliance with them should be attached.

9.3.4 Investigator's Brochure – xenotransplantation:

Instructions for the Investigator's Brochure are detailed in the document "Instructions for the performance of xenotransplantation", which is available on the website of the Ministry of Health specified on page 5 above.

9.3.5 Investigator's brochure – gene therapy:

The guidelines regarding medicinal products for gene therapy are detailed in the following EMEA document:
Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products, CPMP/BWP/3088/99.

9.4 Certificate of analysis from a recognized laboratory:

This certificate is required for clinical trials with a non-medicinal product (a cosmetic product, a food product, a food supplement, a homeopathic product or a medicinal herb) which is not marketed in Israel.

9.5 Informed consent form (Form 2A - for clinical trials of investigational products and for single patient access to investigational treatment; Form 2B - for genetic trials; Form 2C - for clinical trials without investigational products; Form 3 - informed consent form for a parent/guardian for clinical trials in which the participants are minors/wards/legally incompetent patients. Form 3A, 3B and 3C for trials of investigational products, genetic trials and trials without investigational products, respectively. For trials involving the populations of both adults and minors/wards/legal incompetents, the appropriate consent forms should be attached to the application documents).

An informed consent form should contain a summary of the information about the clinical trial provided to the participant, according to sections 10.4 and 10.5 below, provided that all the information considered as declaration is stated in detail. The form should be written in ordinary language which is clear, coherent and understandable to any person, and in the language spoken by the participant, if possible. (See guidelines for consent form text (Appendix 9)).

9.5.1 Subject information sheet – Information sheet/ Explanation sheet should be attached to each consent form (for an adult and a minor); it provides a brief summary of the major details, clarifies the nature of the study, and explains what is required for participation. It must be emphasized! Participants should not sign this document.

For a study in which minor patients participate, a consent form and subject information sheet for adolescents – above the age of 12 – should be attached.

9.6 Sponsor's declaration of commitment (Form 4A - for clinical trials with investigational products; Form 4B - for genetic trials; Form 4C - for clinical trials without investigational products):

9.6.1 This declaration of commitment should be signed by the Sponsor and approved by Principal Investigator's signature. This declaration of commitment should also be attached to the contract between the Sponsor and the Principal Investigator/medical institution.

9.6.2 In case of a Sponsor-Investigator, this declaration of commitment should be signed by the Sponsor-Investigator and approved by the signature of the hospital director or his designee.

9.7 Declaration of the Sponsor or Sponsor's representative in Israel (Form 5)

9.8 Document checklist: prior to submission of the application to the institutional Helsinki Committee, the Principal Investigator should complete and sign the document checklist (Form 9A, 9B or 9C, depending on the trial type).

9.9 Notice for recruitment of participants (Form 10): if required, the Principal Investigator should attach to the application documents the text of the notice for recruitment of clinical trial participants. The application for release of the notice and the text of the notice require approval by the institutional Committee.

If the Investigator wishes to deviate from this text, he must request approval of the deviation from the Ministry of Health.

9.10 Letter to the attending physician at the HMO (Form 11): If the clinical trial involves performance of medical tests or provision of devices, products or implants, the Investigator should complete this form, with reference to contraindications due to possible interactions between the Investigational Product and the standard treatment.

General comment:
The Ministry of Health / Helsinki Committee of the medical institution may each request additional documents or data in addition to those mentioned above – as relevant.

10. Informed consent procedure

10.1 A clinical trial involving human subjects may not be conducted unless the Investigator[*] has obtained informed consent from the clinical trial participant, after the Investigator has provided an appropriate verbal explanation to the trial participant and the participant has read the informed consent form for the clinical trial. Consent to participate in the clinical trial should be given in writing, on the informed consent form approved by the Helsinki Committee for the specific trial. The informed consent form should be signed by both the participant and the Investigator. A copy of the signed form should be given to the participant.

10.2 If the participant is a minor, legally incompetent, ward, or cannot provide informed consent for medical treatment and has a legally appointed guardian, or if the participant has properly appointed a representative in accordance with Article 16 of the Patient's Rights Act 1996[†] (hereafter: legal representative), the Investigator should obtain the consent of the legal representative, in addition to, or instead of the participant's consent. In this case, wherever the word "participant" appears in this chapter, it also refers to such legal representative. A family member not appointed as a legal representative may not consent instead of the participant.

If the Investigator has any doubt regarding the competence of the participant to provide an informed consent and knows that no legal representative has been appointed for the participant, the Investigator must obtain an assessment of a psychiatrist/geriatrician, who is not involved in the study. The populations listed in this section should not be included in a clinical trial unless their inclusion is essential for improving their health, and the trial cannot be conducted in any alternative legally competent population.

10.3 In order to obtain informed consent, the Investigator should provide the participant with information about the clinical trial, in clear language which is understandable to the participant; the Investigator should make his best efforts to enable the participant to understand the information to the maximal extent possible, with the aim of obtaining a voluntary independent decision, after consideration and without pressure or inappropriate influence.

10.3.1 If the participant is a minor, the Investigator should also provide him with an explanation about the clinical trial in accordance with his level of understanding. The minor can sign a form stating that he received an explanation about the trial. The Investigator must take into account the opinion of the minor regarding non-participation in the clinical trial. A minor who has reached the age of 18 while participating in the clinical trial should sign an informed consent form. The participant may withdraw, limit or modify the consent which was previously provided by him or for him when he was a minor.

In genetic trials – according to Article 27 (A) of the Genetic Information Act, a 16-year-old minor must sign an informed consent form for a genetic trial.

[*] The investigator is the Principal Investigator or a Sub-Investigator.
[†] In certain cases, a power of attorney for medical treatments, as defined by the Patient's Rights Act, may not be sufficient, and a power of attorney for participation in clinical trials may be required

10.3.2 If the participant and/or his legal representative is unable to read the consent form, an impartial witness should be present while the Investigator provides the participant with an explanation and should read to him the text of the informed consent form and any other accompanying material. The trial participant and/or his legal representative should confirm verbally that he has understood what has been said and that his signature constitutes consent to participate in the trial. Only then should the impartial witness sign the consent form, and this signature confirms that the explanation and reading of the material were done voluntarily by the participant, without pressure or inappropriate influence.

10.4 Information about the clinical trial, including:

10.4.1 Explanation of the investigational nature of the procedure, the study objective, providing information about the anticipated duration of participation in the trial and approximate number of participants in the clinical trial.

10.4.2 Description of the various procedures to be performed during the trial period (treatment and follow-up), with a clear distinction between investigational and standard therapeutic procedures; indicating participant's chances of receiving each of the treatments offered in the trial (including placebo, if any).

10.4.3 Description of the expected benefits to the participant or to others, as a result of the trial.

10.4.4 Description of the known or foreseeable risks and/or discomforts to the trial participant, and, if necessary - to the embryo, fetus or breastfeeding infant; declaration that the clinical trial involves a risk to the participant which cannot be predicted in advance.

10.4.5 If the clinical trial involves a risk to the participant - an explanation regarding the medical treatment to be provided to the participant in case of harm to his health and the responsibility for providing such treatment.

10.4.6 Circumstances under which his/her participation in the clinical trial may be discontinued by the decision of the Investigator or the Sponsor.

10.4.7 For a study involving administration of medical treatment to the participant

10.4.7.1 Declaration that participation in the clinical trial will not be associated with any additional financial cost to the participant beyond the cost of the regular treatment required for him.

10.4.7.2 Explanation of alternative treatments, their advantages and disadvantages, if any, to the participant; see guidelines for writing a consent form in Appendix 9.

10.5 In addition, the Investigator should provide the participant with the following information -

10.5.1 Explanation that participation in the clinical trial is completely voluntary, declaration on participant's right to refuse to participate in the trial or to discontinue his participation at any stage of the trial, and a declaration that participant's medical rights will not be harmed due to refusal to participate in the clinical trial or discontinuing participation in the clinical trial.

10.5.2 As relevant, information about possible medical consequences of participant's decision to withdraw from the clinical trial priro to its completion.

10.5.3 Explanation about whom to contact, at any time of day, with any question about the clinical trial, participant's rights, and in case of any health injury as a result of participation in the trial.

10.5.4 Explanation to the patient that the information contained in his file, including medical documents, will be reviewed only by authorized individuals (e.g. Helsinki Committee, the auditing body of the hospital, the Ministry of Health, representatives of the company responsible for the trial and trial monitoring), while maintaining absolute confidentiality, while avoiding disclosure of patient's identity to non-authorized individuals either verbally or in scientific / medical publications.

10.5.5 If the clinical trial involves performance of medical tests or provision of devices, products or implants, the Investigator should obtain participant's consent for informing his attending physician at the HMO, with which he is insured, of his participation in the trial.

10.6 The participant should be informed of any new information discovered during the clinical trial, which may affect his decision to continue participating in the trial. The trial participants should sign an updated consent form as soon as possible. If new participants are still being recruited, they should sign the updated version of the consent form.

10.7 The consent form for genetic trials should particularly address the specific issues related to such trials:

10.7.1 The manner in whcih DNA samples will be handled, kept and stored at the end of the trial.

10.7.2 Confidentiality of genetic information: personal details and results obtained from trial participants are information protected by the right of privacy, and is must be protected in accordance with the provisions of any law. The investigators should restrict the access to places where participant's medical information and genetic test results are stored.

Participant's medical record should not include any results of the genetic trial.

10.7.3 Risks associated with genetic trials: impacts of discovering participant's genetic information on the participant and his family or community; misuse of the genetic information, which may cause harm to the participant and/or his relatives.

10.8 Information about the trial, request for informed consent and the consent form for participation in the trial should not contain any instruction or requirement which may imply a waiver of participant's rights according to any law, or which may exempt the Investigator, the Sponsor, the medical institution or any of their representatives from the obligation or responsibility imposed on them according to any law or agreement.

10.9 **Under special conditions, as detailed below, the Ethics Committee may approve a waiver of the requirement for obtaining informed consent:**

10.9.1 A retrospective study based on unidentified data collected from medical records of patients.

10.9.2 In accordance with the Genetic Information Act, in trials involving the use of only unidentified DNA samples or existing DNA samples from which identifying

details have been removed, thus making it impossible to identify them in any way, there is no requirement for completing an informed consent form.

10.9.3 In addition, exemption from having participants sign informed consent may be obtained in the following cases:

* The samples have been collected before December 2001

* The samples are transferred from laboratories/ institutes in unidentified manner, thus making it impossible to identify them

* The samples have been taken from an existing approved sample bank, and the participants have signed consent for sample use referring to the 2 possibilities as follows:

- "I agree to the use of the samples (unidentified/ identified) provided by me <u>for any lawfully approved trial investigating the disease</u>."

- "I agree to the use of the samples (unidentified/ identified) provided by me <u>for any lawfully approved trial</u> ."

In such case, it should be indicated below:

- Submit the approved consent form to the Committee.

- Indicated the number of samples collected and stored in the tissue bank to be used by the Investigator.

10.9 4 <u>In case of medical emergency</u> - Regarding a clinical trial designed to include only participants in medical emergency, as defined in the Patient's Rights Act 1996, under circumstances where it is impossible to obtain informed consent from the participant, his guardian or legal representative (hereafter: legal representative), and it may be reasonably assumed that participation in the proposed trial is more likely to improve participant's medical condition than any other standard treatment, and outweighs the harm to participant's rights or wellbeing.

In such cases, the Helsinki Committee may approve the conduct of clinical study without the requirement for obtaining prior informed consent from the participant or his legal representative, provided that all the conditions detailed in the appendix to these guidelines are met.

The physician responsible for the clinical trial should declare in writing that:

- ❖ The patient is in a life-threatening condition and the available treatments do not grant equal or better chances for saving patient's life, and it is important to determine the safety and efficacy of the treatment in this patient population.
- ❖ The clinical trial cannot be conducted without a waiver of the requirement to obtain prior informed consent from each participant.

10.9.5 In special cases, as detailed below, the Helsinki Committee may approve a waiver of the requirement for obtaining a <u>written</u> informed consent:

If the only risk to the clinical trial participant is the disclosure of his identifying information, and this risk is greatly increased by the requirement for a written informed consent; if a waiver of the requirement for written consent is approved in this case, the participant should always have the choice of providing informed consent in writing. In any case, the Investigator must document obtaining patient's verbal consent.

10.9.6 For trials involving a telephone interview/ questionnaire, a telephone consent form documenting the details of the interviewer and the person being interviewed, including time and date, should be submitted to the Committee. (Appendix 10)

11. Rules for approval of clinical trial applications

The final approval of any clinical trial should be granted in accordance with the definitions specified in the Regulations:

11.1 A special clinical trial - The Director of the medical institution should issue the aforementioned approval after the Institutional Helsinki Committee has approved the clinical trial and determined that it is a special clinical trial.

11.2 A non-special clinical trial - The Director of the medical institution should issue the aforementioned approval after the institutional Helsinki Committee has approved the clinical trial and determined that it is a non-special clinical trial, which requires approval by the Ministry of Health, provided that such approval has been obtained.

12. Authorities of the Director of the medical institution

The authority of the Director of the medical institution to approve clinical trials is granted to him by the Director General of the Ministry of Health. This authority is dependent on full compliance with the requirements specified in the guidelines and Regulations, and may be revoked in case of failure to comply with these requirements.

13 Special clinical trials and special modifications which the Director of the medical institution is authorized to approve without additional approval by the Ministry of Health

13.1 Medicinal products (including biological products)

13.1.1 A clinical trial using a medicinal product registered in Israel, or authorized for marketing in a recognized country for a registered indication and at the commonly accepted dose.

13.1.2 A clinical trial, the primary objective of which is to evaluate the efficacy of the product, provided that all the following criteria are met:

- Previous clinical trials aimed at evaluating the safety and efficacy of the product have been conducted and completed in a recognized country, and their results are reported in the study protocol and its appendices.
- The clinical trial involves the same indication, dosing form and mode of administration used in previous trials.
- The clinical trial is not planned to be conducted in a special population.

13.1.3 A clinical trial planned to be conducted simultaneously in several hospitals in Israel, for which approval by the Director General was required and granted for at least one site, provided that the trial protocol and the informed consent version are identical to those already approved by the Director General.

Except for cases in which the Central Committee of the Ministry of Health limits its approval to a certain number of participants and/or sites.

13.1.4 A clinical trial, the objective of which is to evaluate the comparative bioavailability of a generic product versus a registered product, or a product approved for marketing in a recognized country.

13.2 Medical accessories and devices/ medical equipment

13.2.1 A clinical trial using recognized medical equipment for the commonly accepted indication and under the same limitations, provided that the treatment and follow-up of the trial participant do not differ from the standard practice for a patient in the same condition.

13.2.2 A clinical trial, the primary objective of which is to evaluate the efficacy of medical equipment, provided that all the following criteria are met:

- ❖ The medical device complies with all the relevant safety standards relevant for a medical device of the same type.
- ❖ Previous clinical trials aimed at evaluating safety in human subjects have been conducted and completed in a recognized country and their results are reported in the trial protocol and its appendices.
- ❖ The clinical trial involves the same method of use addressed in previous trials.
- ❖ The clinical trial will not be conducted in a special population.

13.2.3 A clinical trial planned to be conducted simultaneously in several hospitals in Israel, for which approval by the Director General was required and granted for at least one site, provided that the trial protocol and the informed consent version are identical to those already approved by the Director General.

Except for cases in which the Central Committee of the Ministry of Health limits its approval to a certain number of participants and/or sites.

13.2.4 The collection of data from adults using recognized non-invasive medical equipment, including weighing, electrocardiography, electroencephalography, thermography, identification of natural radioactivity, diagnostic echography, electroretinography, ultrasound, MRI test, except for collection of data requiring exposure to ionizing radiation.

13.3 Miscellaneous: trials without medicinal products or medical devices/medical equipment

13.3.1 A clinical trial of a non-medicinal product such as a cosmetic product, a food product, a food supplement, a homeopathic product, or a medicinal herb, which is approved for marketing in Israel.

13.3.2 Drawing blood from a vein in a volume not exceeding 450 ml over a period of eight weeks, at a frequency not exceeding twice a week, from healthy adults (not including pregnant women), except for blood sampling for genetic research.

13.3.3 Collection of body fluids, secretions, or non-viable tissues (except for hair, nails, teeth) from adults, in the standard way, except for samples intended for genetic research.

13.3.4 Voice recording as commonly accepted in speech impairment studies.

13.3.5 Moderate physical exercise performed by healthy volunteers.

13.3.6 A clinical trial performed using existing data, documents, recordings, notes, radiology images (e.g. X-rays, ultrasound images, etc.), pathological samples or diagnostic samples taken for medical purposes.

13.3.7 Collection of information using questionnaires (information directly related to the health status, either physical or mental, of the participant/patient or to his medical care).

14. Special modifications:

14.1 Modifications which the Director of the medical institution (or his designee) is authorized to approve without additional approval by the Ministry of Health:

14.2 Modifications in clinical trials with valid approvals.

14.3 Modifications which do not significantly increase the likelihood of risk to the clinical trial participant, do not impair the scientific value of the study, and do not jeopardize the rights, safety, health and wellbeing of the study participants, including:

- Administrative modifications
- Increase in the number of clinical trial participants, if not initially limited by the Ministry of Health (for example, due to high rate of withdrawal from the clinical trial, which is not related the investigational product).

14.4 Extension of approval validity

14.4.1 Extension of approval validity period should be granted after receipt of the report, as required, for example, in the following cases:

- The clinical trial was planned in advance for a period exceeding the validity period of the approval
- The initiation date of the clinical trial was delayed due to technical or logistical reasons
- Recruitment of trial participants was slower than expected

15. Procedure of handling clinical trial applications or requests for modification in a clinical trial

The Principal Investigator should submit the clinical trial application or the request for a modification in the trial to the institutional Helsinki Committee.
Submission of a new application for a trial is performed electronically using the clinical trial software (Matarot) according to the guidelines of the Ministry if Health 2006.
Following completion of the electronic application and its online submission, via Matarot software, as a request for review or as a report to the Committee, one copy should be printed and signed by the Investigators, and copies should be prepared for submission to the Committee. (Appendix 8)
Documents such as: updates, reports etc., should be sent online and submitted as a hard copy signed by the Principal Investigator. Principal Investigator's signature is required for all the application documents submitted to the Committee.

The Helsinki Committee should discuss the clinical trial application or the request for a modification in the trial and decide whether to approve or reject the application. The Helsinki Committee should also decide, according to the criteria and definitions specified in section 16, whether the Director of the medical institution is authorized to approve the clinical trial or the modification in the trial, or whether additional approval by the Ministry of Health is required.
In general, the Helsinki Committees must follow a written working procedure. Specifically, all the decisions (approvals and rejections) made by the committee should be clearly explained and documented in writing in the protocol of the meeting, and within the study card in Matarot software. The protocol of the Committee should document the decisions regarding both new

applications and existing applications with valid approvals (modifications, validity extensions and reports).

16. Handling new applications for special clinical trials - in the medical institution

16.1.1 The Helsinki Committee should forward to the management representative, authorized by the Director of the medical institution, its decisions, documented in the discussion protocol, regarding applications for clinical trials which have been approved by it and which the Director is authorized to approve without additional approval by the Ministry of Health. A copy of the approval by the institutional Helsinki Committee (Form 6) should be sent to the Principal Investigator.

16.1.2 The Committee should issue an approval for the clinical trial to the Principal Investigator, signed by the Director, specifying the conditions and limitations (Form 7). A copy of the Director's approval should be transferred to the director of the medical institution's pharmacy (if required). Scanned signed approvals are filed in the study file at the Helsinki Committee and are stored in the study card in Matarot software.

16.2 Approval of a study which is a not a clinical trial in human subjects

16.2.1 According to the circular of Director General of the Ministry of Health (No. 15/06) dated June 6, 2006, a study which is a not a clinical trial in human subjects is defined as one of the following two types of study:

a. A study involving collection of information from human subjects while interacting with them.

b. A study involving collection of information from medical, nursing, psychological, social and other para-medical records of patients without involving the patients,

provided that the study does not involve performance of any procedure or physical examination, or the use of any medication, radiation or any chemical, biological, radiological or pharmacological substance in the participant.

16.2.2 In such studies, the Principal Investigator does not have to be a holder of a MD or DMD degree, but may be a holder of at least a M.Sc. degree, with professional knowledge and experience enabling him to carry out the study as specified in the application.

16.2.3 The application forms for a study which is a not a clinical trial in human subjects are different from the forms detailed above, and are available at the website of the hospital's Helsinki Committee and at the website of the Ministry of Health.

16.2.4 The Helsinki Committee, in its current setting, will serve as a sub-committee for this purpose; it will discuss and approve these studies since its composition and activity do not contradict the guidelines of Director General for approval of such studies.

Approval of the institutional Helsinki Committee is issued on Form 4, and Director's approval on Form 5.

The Investigator may initiate the trial only after receipt of Director's approval.

16.3 Handling applications for special modifications in clinical trials- in the medical institution

Procedures of approval of amendment /addition in a previously approved trial:

16.3.1 According to the guidelines of the Ministry of Health and in accordance with approval of the Director of the medical institution authorized to approve studies, the working procedures of the Helsinki Committee determine that all the modifications required prior to the study approval (revisions) and during the study should be submitted to the Committee by the Investigators and approved by the Committee Chairman, his deputies or Committee members reviewing the application, except for substantial modifications in non-special trials, which should be submitted to the Ministry of Health for review and approval, in accordance with the decision of the Chairman or his deputies.

16.3.2 If modification/ amendment of a protocol previously approved by the Committee is required, the Principal Investigator should submit the application in writing on Form 12 (in guidelines of the Ministry of Health, Appendix 18 in these guidelines), including a brief summary (in Hebrew) justifying the modification/s required and specifying the locations of modifications made in the protocol or in the accompanying forms. In addition, a detailed document indicating all the above modifications (old version vs. new version) should be enclosed.

16.3.3 Protocol modifications the meaning of which is inclusion of a special population (children, pregnant women, etc.), or genetic testing which has not been previously approved, will require discussion by the Committee and referral to the trial as a non-special trial according to the guidelines of the Ministry of Health.

16.3.4 If the Chairman (or his deputy in his absence) decides that the Committee should discuss the requested modifications/revisions, this subject should be raised during the next Committee meeting and recorded in the protocol.

16.3.5 The Chairman (or his deputy in his absence) is authorized to approve administrative protocol modifications without waiting for Committee's approval.

16.3.6 The Chairman (or his deputy in his absence) is authorized to approve updates of the trial (such as Investigator's Brochure and consent form), provided that they exert no impact on the participants, without waiting for Committee's approval.

16.3.7 During Chairman's discussion, all the applications for modifications submitted for Committee's approval are discussed.

The documents are approved and signed by the Committee Chairman or one of his deputies on the date of the discussion.

16.3.8 Approval of these documents should be documented in Matarot software during the days following the discussion, on the date of the discussion. The scanned approved and signed documents should be sent by mail, email or fax within 2 weeks from the date of discussion during which approval was granted.

16.3.9 If modifications in the protocol and/or in the Investigator's Brochure requiring payment are requested, the application should be approved in Matarot software after receiving payment from the study Sponsor. The time interval between the date of approval of the modification request by the Chairman and the date of modification approval in the software depends on review of the request and date of payment. Approval for the amendment should be provided on Form 12 of the Ministry of Health (Approval of institutional Helsinki Committee) (Appendix 18). Electronic approval in the software is not valid unless the printed and signed approval has been received.

16.3.10 Chairman's approvals are kept as scanned documents in the "Study documents" file; the Investigator must print and keep these approvals in the study file and transfer a copy to the study Sponsor.

16.4 Procedures of validity extension for a previously approved trial:

16.4.1 The Director of the medical institution has authorized the Helsinki Committee Chairman to provide Committee's decisions regarding validity extension for approved clinical trials; the approval for extension of trial validity is provided on Form 7A, which bears Chairman's signature (from Form 6A – Committee's approval, therefore this form is not being issued) and signature of the Director of the medical institution, and indicates the updated versions and dates of application documents, in accordance with section 6.4.2 of the guidelines of the Ministry of Health.

In accordance with this approval, approval for extension of the clinical trial validity is issued to the Principal Investigator; the approval specifies the conditions and limitations (Form No. 7A). The Principal Investigator is responsible for forwarding a copy of the approval to the director of the institutional pharmacy (if required).

Approval for validity extension signed by the Committee Chairman and by the hospital Director should be filed in the study file at Helsinki Committee, after the documents have been scanned and stored in the study documents in Matarot software. The Principal Investigator must print the approval and transfer a copy of the approval to the study Sponsor.

16.4.2 The Helsinki Committee coordinator transfers a periodic report to the Ministry of Health on all the validity extensions and study completions; this reporting is a monitoring tool of the Helsinki Committee and the Ministry of Health, and the computerized registry of valid clinical trials at the Ministry of Health is being updated based on these reports.

16.5 Handling applications for non-special clinical trials and non-special modifications - in the medical institution

Once a month, the coordinator should forward the following documents to the Ministry of Health:

a. A full protocol of the meeting.

The protocol is sent to the Department of Clinical Trials – Pharmaceutical Administration and to the National Coordinator of Clinical Trials with Medical Devices

b. The applications for clinical trials requiring additional approval by the Ministry of Health, including Helsinki Committee approvals (Form 6) of these applications:

- **Applications** for clinical trials with **medical devices** and medical procedures, as well as applications for clinical trials with products containing **living cells and tissues** should be forwarded to the National Coordinator of Clinical Trials with Medical Devices in **5 copies**;
- **Applications** for **genetic** trials and trials of in-vitro fertilization – should be forwarded to the Clinical Trials Division **in 13 copies**.
- **All the other applications** for clinical trials should be forwarded to the Department of Clinical Trials at the Pharmaceutical Administration **in one copy**:

c. Non-special modifications

d. Reports mentioned in section 16.4.2 above

* The modifications and the reports should be forwarded to the relevant departments in accordance with the type of the trial.

16.6 Handling applications for non-special clinical trials and non-special modifications - in the Ministry of Health

16.6.1 Based on the protocol of the Helsinki Committee meeting regularly sent to the Ministry of Health, these applications are entered into the computerized database of clinical trials and labeled by application numbers of the Ministry of Health according to the name of the medical center; the study should be identified by that number in any future correspondence.

Each medical center participating in the study will receive a separate application number; a unique number is given to each site even for a single multicenter study.

16.6.2 Procedures of handling a new application:

The Ministry of Health examines the application, and decides on the way of handling it in accordance with one of the 3 following options:

16.6.3 The clinical trial is approved:

The Ministry of Health sends an approval (Form 8) to the Helsinki Committee Chairman and to the Director of the medical institution. The Committee issues to the Principal Investigator an approval for the clinical trial (Form 7), signed by the Director and specifying the conditions and limitations (if any). The approval should be filed in the study file at the Helsinki Committee, after it has been scanned and stored in the study documents in Matarot software. The Principal Investigator must print the approvals, store them in the study file and transfer a copy of the approval to the study Sponsor and to the director of the institutional pharmacy (if required).

The Investigator may initiate the trial only after receipt of Director's approval.

16.6.4 The application should be transferred for expert opinion:

The Ministry of Health should send a notice to the Chairman of Helsinki Committee, who should inform the Investigator via the Committee coordinator. The notice should include details of the documents or data required for further processing of the application.

If the experts recommend approval of the application, the Ministry of Health should send an approval as detailed in section 16.6.3 above. If there is no recommendation to approve the trial, the application should be transferred for discussion at the Central Committee for Clinical Trials.

16.6.5 The application should be transferred for discussion at the Central Committee for Clinical Trials or at the Supreme Helsinki Committee:

A notice should be sent to the Chairman of Helsinki Committee, who should inform the Investigator via the Committee coordinator. The notice should include details of the documents or data required for further processing of the application.

The Central Committee for Clinical Trials and the Supreme Helsinki Committee of the Ministry of Health convene every 6-8 weeks, and discuss applications for which the entire material required has been received 2-3 weeks prior to the discussion date.

Following discussion at the Committee and having received its recommendations and decisions, the Ministry of Health should send the decision to the Chairman of Helsinki Committee, who should inform the Investigator via the Committee coordinator.

- If it has been decided to approve the application, an approval should be provided according to section 16.6.34 above.
- If supplemental material is required for another discussion regarding the application, the process detailed in section 16.6.4 should be repeated.
- If it has been decided to reject the application, a clearly explained response should be sent. If the decision of the Central Committee or of the Supreme Committee is appealed, the Investigator should be granted the opportunity to present his claims to the Committee personally, after submitting them to the Ministry of Health in writing, and after the appeal has been received by the institutional Committee.

16.7 Handling applications for non-special modifications – in the Ministry of Health

Once a month, the Helsinki Committee coordinator should forward to the Ministry of Health any application for a modification in a clinical trial which is not included in section 14 above and detailed in section1 6.3.1.

16.8 A multicenter trial in Israel:

According to the requirement of the Ministry of Health, the trial Sponsor is responsible for notifying the Ministry of Health of his intention to perform a multicenter clinical trial in Israel, upon receiving Helsinki Committee's approval for the trial at least at one of the medical centers expected to participate in the trial.

The notice should include the following details:

- Study subject.
- Protocol number and date.
- Names of the medical institutions (expected to participate in the trial).
- Names of the Principal Investigators (expected to participate in the trial).
- Date of approval by the institutional Helsinki Committee (of the first institution, at least) + Committee's decision regarding classification of the trial as a special/ non-special trial.

After the application for a multicenter trial has been approved by one of the handling procedures detailed above, and after the approval has been sent to the Helsinki Committee of at least one medical center and to the Sponsor, the Sponsor should notify the rest of the study sites expected to participate in the trial of approval by the Ministry of Health.

The institutional Helsinki Committee should discuss the application and approve it by a special procedure based on the approval granted by the Ministry of Health to one site, and the Director of the medical institution will be able to issue approval for the trial.

17. investigational treatment in a single patient

The Committee Chairman may approve a clinical trial by expedited procedure in the following cases and according to the following rules:

17.1 Exceptional cases in which Committee's approval for treatment, defined as investigational, in a single patient is required, and delay in approval has an immediate impact on patient's health and life. Investigational treatment in a single patient is treatment with a novel investigational product not registered in any country worldwide, for which there may be no data available in the professional literature based on previous clinical trials. The aim of this treatment is to save patient's life in medical emergency or compassionate treatment.

17.2 If the novel medication is no registered in any recognized (Western) country, or if the medication is registered but the requested indication is not approved in the State of Israel, the Helsinki Committee Chairman (or his deputy in his absence) may approve it for the patient in the setting of individual investigational treatment on compassionate basis **without the need to convene or inform the Committee members**. This is based on the guidelines of the Ministry of Health for approval of a non-registered medicinal product according to Regulation 29 of Pharmacists' Regulations (medicinal products) 1986.

17.3 The content of an application for investigational treatment in a single patient is specifiedin the table in Section 33 of these guidelines.

17.4 Submission of the following documents:

Form 2 – (29C) – designed for overall handling for a number of patients if the medication is registered worldwide, but not registered in Israel (Appendix 21).

Form 3 (29C) – designed for individual handling for a medication registered worldwide but not registered in Israel (if registered in a recognized (Western) country, signature of the Helsinki Committee Chairman is not required) (Appendix 22).

Designated consent form (Consent form for use of a medication which is not included in the "Hospitalization services basket" (Appendix 24).

The attending physician should contact the Committee Chairman or coordinator, and attach a written explanation to the application form, Form 3 (29 C); the Committee Chairman (or his deputy in his absence) may decide whether such an application should be approved via an expedited procedure or by the Committee plenum. Subsequently, the application should be forwarded to the Pharmaceutical Administration at the Ministry of Health, to the pharmacist in charge of approvals according to Regulation 29 A(3) of Pharmacists' Regulations – for final approval.

17.5 Compassionate use of experimental medication or urgent compassionate treatment - for an individual patient.

In case of treatment with or use of a medication not registered anywhere in the world, the experimental medication has no name. If the treatment is urgent – life-saving and/or has never been administered to humans - since the time interval is short, the application should be submitted for approval to the Committee Chairman, to the hospital Director, to the pharmacy director, and sent to the Director General of the Ministry of Health and to the Director of Department of Clinical Trials at the Ministry of Health for information.

The following documents should be submitted:

- Form 4 – Physician's order for compassionate use of experimental medication or urgent compassionate treatment - for an individual patient.
- Consent form - Since there is no designated consent form in the guidelines of the Ministry of Health, Form 2A should be completed and adjusted to the experimental treatment.
- Patient's anamnesis, treatment protocol, relevant supporting documents.

The attending physician should contact the Committee Chairman or coordinator, and attach a written explanation to the application form, Form 4; the Committee Chairman (or his deputy in his absence) may decide whether such an application should be approved via an expedited procedure or by the Committee plenum (Appendix 23).

18.1 Working procedures of the institutional Helsinki Committee

18.1 Procedures before the meeting

18.1.1 The application for approval of a clinical trial should be submitted by the Principal Investigator. The Principal Investigator may be a senior physician, who is a permanent employee of the TASMC, after the Committee has verified his resources and after he has received approval of the head of department, institute or clinic at which he works (if he is not the head).

18.1.2 The TASMC Helsinki Committee should examine any research proposal submitted to it within the period of time specified in the application schedule.

18.1.3 Prior to the Committee meeting, the Principal Investigator is responsible for submitting the following documents to the Committee:

18.1.3.1 A package of updated application documents for clinical trial approval according to the guidelines of the Ministry of Health as relevant to the study subject (Form 1A for medicinal products, Form 1B for a medical device, Form 1C for cells and tissues, including the trial protocol synopsis) – **an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers**.

18.1.3.2 Trial protocol (**5 copies**) including:

- Protocol name, number and date
- Name and address of the study Sponsor
- Name and signature of the protocol author
- Background and rationale for the clinical trial, including references published in the literature
- Objectives of the clinical trial
- Parameters to be used for evaluation of the results (endpoints)
- Number of participants, number of sites planned to take part in the trial
- Type and design of the clinical trial - open-label, blind, etc.
- Criteria for inclusion in, exclusion and withdrawal from the clinical trial
- Plan of treatment with the investigational product/ medical device (including dosage, mode of administration, treatment duration and number of treatments, schedule)
- Possible risks and side effects
- Laboratory tests and any other relevant test to be performed during the trial and the follow-up period

- Conditions of clinical trial termination
- Methods of analysis and processing of the results
- Method of investigational product accountability
- Risk analysis for the trial participant as a result of his participation (for a medical device only)

18.1.3.3 Investigator's Brochure (**4 copies**) if required by the guidelines of the Ministry of Health.

18.1.3.4 Certificate of Analysis from a recognized laboratory (this certificate is required for a trial with a non-medicinal product not marketed in Israel (e.g., a cosmetic product, a food supplement, a homeopathic product or a medicinal herb) (5 copies).

18.1.3.5 Informed consent form(s) (Form 2 in guidelines of the Ministry of Health), including written information about the trial to be given to the participant, and if necessary, an update of the consent form, or informed consent form for parents or legal guardian in case of a minor / ward / legally incompetent (Form 3 in guidelines of the Ministry of Health) or translation to additional languages as required, including a certificate of accurate translation by a qualified translator – **an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers**.

18.1.3.6 Sponsor's commitment declaration (Appendix 4 in guidelines of the Ministry of Health) or a written explanation of the reason for not submitting it) – an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers.

18.1.3.7 Information on the way of recruiting study participants and on financial compensation, if any.

18.1.3.8 Information on insurance for the study participants.

18.1.3.9 Any other document that the Committee may require from the Investigator in order to make its decisions.

18.1.3.10 Declaration of the clinical trial Sponsor verifying the application documents (Appendix 5 in guidelines of the Ministry of Health) – **an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers**.

18.1.3.11 A list of clinical trial application documents (Appendix 9 in guidelines of the Ministry of Health) – **an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers**.

18.1.3.12 Text of the notice to be published for recruitment of participants to the clinical study (Form 10 in guidelines of the Ministry of Health), if required – **an electronic copy for each Committee member and a hard copy for the Chairman and the reviewers**.

18.1.3.13 Text of the Letter to attending physician (Form 11 in guidelines of the Ministry of Health), if required – **an electronic copy for each**

Committee member and a hard copy for the Chairman and the reviewers.

18.1.3.14 Since the Principal Investigator is usually well known to the Committee members, it is not necessary to attach a CV to every clinical trial application. If necessary, the Committee may require a CV document in order to ensure that Investigator's qualifications are suitable for conducting the study requested for approval. The Principal Investigator must ensure that his and Sub-Investigators' updated CV documents are available for review at the study site at any time.

18.1.3.15 Beginning on June 1, 2007, the Investigator must attach a certificate of GCP training.

18.1.3.16 Principal Investigator's responsibility: In case of prolonged absence of the Principal Investigator, exceeding the period of two months, he should notify the Helsinki Committee and attach updated forms. The Committee Chairman should approve the appointment of Principal Investigator's deputy on the relevant forms.

18.1.4 In general, all the documents should be submitted to the Committee coordinator 21 days prior to its meeting. If there are exceptional circumstances and the Principal Investigator cannot meet these timelines, he should request coordinator's approval for late document submission. It is the responsibility of the Principal Investigator to ensure that Committee members receive the documents in a timely manner to enable them to review the documents before Committee meeting.

18.1.5 For each application, one or two Committee members will be appointed as "reviewers", whose duty is to comprehensively examine the material submitted.

18.1.6 Discussion of the application for the study during the Committee meeting may be held in the presence or in the absence of the Investigator. The Committee Chairman (or his deputy in his absence) is authorized to decide whether the discussion on approval of a clinical study requires participation of the Investigator in the Committee meeting.

18.1.7 A Committee member may ask the Committee Chair to invite the Investigator or to obtain additional background material. In such a case, the Investigator will be invited to the Committee meeting and/or will be requested to provide additional material as requested, even if this was not required initially.

18.1.8 If Investigator's presence at the discussion is required, he will be invited in writing by the Committee coordinator. The Principal Investigator or a Sub-Investigator, who is an **expert** in a field relevant to the study subject, will present the application.

18.1.9 The Committee may request the presence of experts who are not Committee members, if this is necessary for making decisions related to a specific study.

18.2 Course of Committee's discussion:

18.2.1 The Principal Investigator (if his presence is required) will present the trial in brief and will answer the Committee members' questions.

18.2.2 The Investigator will then be asked to leave the room. The reviewer(s) will raise their hesitations or comments, and then the other Committee members will express their opinions.

18.2.3 The following subjects (and others, as required) should be discussed during the Committee meetings:

18.2.3.1 Whether the trial meets the ethical and scientific standards of not harming the rights, health, safety or welfare of the participant.

18.2.3.2 Whether the informed consent reflects the protocol and is consistent with participants' age range, i.e.: According to guidelines of the Ministry of Health, Form 2 for adults and Form 3 for a minor / ward / legally incompetent present the information in a clear and reliable manner, and are prepared according to the laws and regulations of the State of Israel.

18.2.3.3 For studies in which written informed consent cannot be obtained prior to the procedure (e.g., in emergency situations), the Committee should explicitly determine whether the proposed protocol and/or its additional accompanying documents unequivocally meet the ethical requirements and the valid laws and regulations.

18.2.3.4 Procedures of recruitment to the trial. If the volunteers receive compensation, this should be examined by the Committee in order to prevent using the financial factor as a means of forcing a person to participate in the trial. The entitlement to and the sum of compensation should be determined before trial initiation, and this information should appear in the informed consent form and in any other written information presented to the volunteer.

18.2.3.5 Whether the Principal Investigator or other Investigators participating in the trial are associated with the Sponsor or the project, and whether this has any impact on the quality of the study or on protection of participant’s rights and safety.

18.2.3.6 The Committee should determine the duration of conducting the trial.

18.2.3.7 The Committee should determine whether amendments are required or whether limitations should be added such as the frequency of interim reports, supervision of the course of the trial, etc.

18.2.3.8 The Committee should verify the qualifications of the Investigator(s) and the resources available to him/them for conducting the study.

18.2.4 Participation in the discussion will be allowed only for Committee members who are neither dependent on nor associated with the Investigator or the Sponsors of the particular study, and for an expert who is not a member of the Committee, if invited to provide an expert opinion.

18.2.5 Decisions of the Committee will be made by majority vote. An Investigator who is also a Committee member may not participate in voting on his study. An expert who is not a Committee member may not participate in voting.

18.2.6 The Committee coordinator should document the meeting discussions in writing (protocol), clearly identifying the trial being discussed, the date of discussion, the documents examined and the reasons for Committee's decisions. Individual remarks of each participant should not be documented. Possible Committee's decisions are as follows:

- Recommendation for approval (conditional or unconditional), based on the criteria specified in guidelines of the Ministry of Health
- Demand for revisions/ clarifications
- Reject / no approval
- Suspension or cancellation of previous approval

18.2.7 If one of the Committee members is an Investigator involved in the study, it should be explicitly indicated that the he did not participate in Committee's discussions concerning his study.

18.2.8 The following issues should be explicitly indicated by the Committee in its decisions:

18.2.8.1 That no one may participate in a clinical trial until it is officially approved.

18.2.8.2 That no deviation from the approved protocol is allowed, unless a revision has been suggested and approved by the Committee and the Director.

18.2.8.3 That no one may participate in several studies simultaneously

18.2.8.4 That the association of the Investigator(s) with the study/company/project has been examined.

18.2.8.5 That the Investigator is obliged to inform the Committee immediately of any serious or unexpected adverse events observed during the study, which may harm participants' health or safety.

18.2.9 Based on the criteria and definitions specified in the regulations of the Ministry of Health, the Committee should determine whether the Director of the medical center is authorized to approve the clinical trial or the modification made in the trial (a "**special**" trial), or whether additional approval by the Ministry of Health is required (a "**non-special**" trial).

18.2.10 The Investigator should be informed of the decisions made.

18.3 Handling an application for a "**special**" clinical trial:

18.3.1 The Committee Chairman should approve the application for a “special” clinical trial without additional approval by the Ministry of Health (Form 6 in guidelines of the Ministry of Health).

18.3.2 The Director of the medical center, or a person authorized by the Ministry of Health to act on his behalf, should approve conducting the clinical trial by the Principal Investigator. The approval should specify the conditions and limitations (Form 7 in guidelines of the Ministry of Health).

18.3.3 A multicenter trial in Israel: If the trial has been approved by the Ministry of Health for another medical institution, and the Committee has discussed and approved the application, it is not necessary to forward it to the Ministry of Health for further approval. The Director of the medical institution is authorized to approve the trial.

18.3.4 If the Committee has basically approved the trial but required certain technical modifications for final approval, the Principal Investigator should forward the written amendments to the Committee Chairman /his deputy (in his absence). The Chairman, having ensured that the required amendments were actually performed, should approve the trial and sign Form 6.

18.4 Handling an application for a "**non**-**special**" clinical trial:

18.4.1 If the application for a “non-special" trial has been approved by the Committee, the coordinator should forward to the Ministry of Health (Department of Clinical Trials, Pharmaceutical Administration) Form 6 signed by the Chairman, one copy of the protocol (for trials with medicinal products) and the Investigator's Brochure (if available), with a cover letter from the Chairman. The application should be further handled as specified in guidelines of the Ministry of Health.

18.4.2 For clinical trials with medical devices, cells and tissues, and medical procedures, 5 copies of the forms should be forwarded to the National Coordinator for Clinical Trials with Medical Devices for further handling, as specified in guidelines of the Ministry of Health.

18.4.3 For clinical trials associated with genetic material, 13 copies of the protocols and additional relevant documents should be forwarded to the Ministry of Health (Department of Clinical Trials, Pharmaceutical Administration) for further processing by the Committee for Genetic Trials, as specified in guidelines of the Ministry of Health.

18.4.4 If the trial is approved by the Ministry of Health, the approval should be sent to the Committee Chairman and a copy should be sent to the Director of the medical center.

18.4.5 The Director of the medical center, or a person authorized by the Ministry of Health to act on his behalf, should grant approval to the Principal Investigator to conduct the clinical trial. The approval should specify the conditions and limitations (Form 7 - Director’s approval in guidelines of the Ministry of Health). A copy should be sent to the Committee Chairman, to the director of the institutional pharmacy (if required) and to the Sponsor.

18.4.6 If amendments or supplemental documents are required, a notice should be sent to the Helsinki Committee Chairman, who should notify the Investigator and the Sponsor about the process of application handling after the supplemental documents are received. If the application is to be discussed at the National Committee for Clinical Trials, an appropriate notice should also be sent to the Sponsor; the Sponsor will be requested to forward additional copies of the application documents to the Ministry of Health, as required, as specified in guidelines of the Ministry of Health.

18.4.7 The Investigator may initiate the trial only after receipt of **written** Director's approval (Form 7 in guidelines of the Ministry of Health).

18.4.8 The approval is valid for one year.

19. Clinical trial contractual agreement

Every contractual agreement between the Sponsor and the Principal Investigator conducting the clinical trial requires approval by the Committee for binding contracts with commercial companies and by the CEO of the Research Fund appointed for this purpose by the Director of the medical institution. Approval by the Director of the institution, as mentioned above, is also required for any binding contract between the Sponsor or Sponsor's representative and between the Principal Investigator or any other Investigator taking part in the clinical trial, who is associated (as defined above) with the clinical trial.

The Principal Investigator and any other Investigator taking part in a clinical trial conducted at the medical center must obtain prior approval of the director, authorized by the Director of the medical institution, to receive any financial compensation either directly or indirectly related to the clinical trial. Failure to obtain the aforementioned approval constitutes a deviation from the guidelines of the Ministry of Health.

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All the provisions of the Civil Service Regulations regarding binding contracts with commercial companies apply to this agreement. (Appendix 3)

19.1 The agreement should include the following details, among others:

19.1.1 Names of all the parties signing the agreement, including the Principal Investigator, the Sponsor and/or Sponsor's representative and the medical institution or the institutional research fund.

19.1.2 The clinical trial protocol, number and date of the protocol, and dates of any protocol amendments.

19.1.3 Declaration of commitment by the Principal Investigator to conduct the clinical trial in accordance with the ICH-GCP rules (and/or ISO 14155 for trials with medical devices) and requirements of the guidelines of the Ministry of Health.

19.1.4 Estimated number of participants, budget of the clinical trial and payment dates

19.1.5 Name of the medical institution's business unit or research fund to which the payments should be transferred.

19.1.6 Declaration of commitment by the Sponsor of the clinical trial to arrange for appropriate medical insurance, including insurance against third party claims resulting from the clinical trial (see Appendix 4 – Guidelines for insurance coverage for conducting clinical trials).

19.1.7 Declaration of commitment by the Principal Investigator and the medical institution for reasonable and proper cooperation with the Sponsor in case of a legal claim related to the clinical trial.

19.1.8 Declaration of commitment by the Sponsor not to refer in commercial publications, either directly and/or indirectly, to the name of the institution at which the clinical trial is conducted and/or to the name of any employee of the institution involved in the clinical and its results, and not to use their names as people recommending the quality of the investigational product and/or medical device.

19.1.9 Sponsor's declaration of commitment (Form 4, guidelines of the Ministry of Health) should be attached to each agreement; the text of the declaration should be compliant with requirements of the guidelines for binding contracts with commercial companies.

19.1.10 The Director of the medical institution must ensure that there is no conflict of interests between conducting the trial at the medical institution by the commercial company and the Investigator, who is an employee of the medical institution.

Comment:

For trials in which the Sponsor is a Sponsor-Investigator, the Investigator should submit to the Helsinki Committee the application documents for conducting the trial, which should include a detailed estimate of the trial cost, information regarding funding sources (if any). Approval to conduct the trial constitutes agreement of the medical institution to insure the trial subjects and the study staff involved in the clinical trial.

20. Publication

No information about the clinical trial should be published in the media or in any other way (except for professional scientific journals, upon agreement of the parties) for purposes other than recruitment of participants. The text of a standard notice for recruitment of healthy volunteers and patients is available in Form 10 of the guidelines of the Ministry of Health. If the text differs from the aforementioned text, approval must be obtained from the Ministry of Health. Controlled prospective clinical trials, consistent with the guideline specified in the circular of Director General No. 32/05 dated September 4, 2005, must be registered at the NIH clinicaltrials.gov website (Appendix 15).

21. Labeling of investigational products for clinical trials

The principles for labeling investigational products are defined in the guidelines of international regulations. In addition, packages of investigational products provided to patients treated in clinical trials must be labeled as follows:

- "For Investigational Treatment Only", or "For Clinical Trial Use Only" in Hebrew and/or in English* in clear and legible print letters, in a color different and distinguishable from the background.
- Name and/or code of the investigational product
- Name or code of the manufacturer
- Expiry date, retest date (if any)

Comment:

Medicinal products registered in Israel and used in studies should be labeled "For clinical trial use only" with any identification feature of the trial – on the label. All these requirements are in addition to the standard labeling according to the Pharmacists' Regulations (Medicinal Products) 1986.

22. Import of an investigational product for a clinical trial

22.1 The import documents (supplier's invoice/ order/ proforma invoice) and approval of the trial by the Director of the medical institution (Form 7) should be attached to any application to the Ministry of Health for approval of import of an investigational product shipment for a clinical trial.

* For trials in which the informed consent form has been written in languages other than Hebrew and English, the label "For investigational treatment only" or "For clinical trial use only" must also be added in the additional languages

22.2 If the approval has expired before completion of the clinical trial, the Investigator should make his best efforts to provide the entities handling the investigational product import with a valid approval of the trial by the Director of the medical institution.

22.3 In special cases, the importer may obtain an import authorization before all the conditions mentioned in sections 22.1 and 22.2 have been met. To obtain this special authorization, the importer must contact the Ministry of Health in writing, attach a valid Helsinki Committee's approval, and undertake that:

a. Medicinal products for the trial will be stored in the importer's pharmaceutical company or in the institutional pharmacy. Investigational medical devices / other investigational products which are not medicinal product should be stored by the importer.

b. The investigational products will not be distributed and will not be used before approval to conduct the clinical trial is received from the Director of the medical institution.

c. The importer knows that this process does not guarantee approval of the clinical trial by the Ministry of Health.

d. If the trial is not approved, the importer will be responsible for returning the investigational products to the overseas sender or to destroy them.

23. Supply of the investigational product for the clinical trial

The clinical trial Sponsor is responsible for supplying the investigational product (IP) to the medical institution in which the trial is being conducted. The Principal Investigator / the medical institution are responsible for storing and dispensing the investigational product to the patients. Medicinal products should be supplied, stored and dispensed by the institutional pharmacy, unless decided otherwise by the Helsinki Committee.

24. Modifications in application documents

Any request for modification in the content of the clinical trial application documents should be submitted by the Investigator to the institutional Helsinki Committee, indicating the date of modification, with the revised documents attached.

Modifications are handled by the Helsinki Committee as specified in section 16.3.1 above.

Applications for modifications in clinical trials should be submitted on Form 12 (Appendix 18).

25. <u>Reporting guidelines</u>

25.1 Unless stated otherwise, the Principal Investigator must submit a written interim report on the trial progress **once a year as part of the application for validity extension**.

25.1.1 The Principal Investigator must immediately report to the Committee Chairman in the following cases:

- Any protocol deviation or modification, the aim of which is to prevent exposure of the trial subjects to any risk;

- Any protocol modification which may endanger or significantly affect the trial subjects (as stated in Form of the guidelines of the Ministry of Health);

- Any serious or unexpected adverse event during which patient's death or harm to patient's health has occurred, or which has resulted in termination of the trial. In case of a multicenter trial, any aforementioned adverse event should be reported, even if it occurred in another site participating in the trial. Form 13 and Form 14 of the guidelines of the Ministry of Health);

- Any new information which may affect the safety level of the trial;

- In case of Principal Investigator's absence for a period exceeding two months, he must delegate authorities to his deputy – subject to submitting a written report to the Committee and receiving Chairman's approval.

25.1.2 In case of death, the Committee Chairman must report to the Director of the medical institution. The Director should appoint an independent review committee according to the guidelines of the Ministry of Health, Form 14 of the guidelines of the Ministry of Health (Appendix 20).

25.1.3 In case of a serious adverse event (SAE) which occurred during a trial conducted in TASMC, the Principal Investigator must immediately report it using Form 13 of the guidelines of the Ministry of Health (Appendix 19). The Committee Chairman should confirm receipt of the report by his signature and if necessary, report to the Committee.

25.1.4 For a multicenter trial, the Principal Investigator is also obliged to report on any serious adverse event which has occurred in another site, of which he has been informed by the Sponsor. The Committee should demand obligation to forward such information as part of the trial approval process. Based on the data, the Committee Chairman should decide whether continuation of the trial in TAMSC may be approved.

25.1.5 The Committee Chairman should received the report and update the Committee members regarding further handling and follow up of a patient injured due to a serious adverse event.

25.1.6 For clinical trials in which the Principal Investigator is the **Sponsor**, the Helsinki Committee should forward its conclusions to the Ministry of Health, including conclusions regarding a possible association between the event and the affected persons' participation in the clinical trial, within 30 days or together with the protocol of its next meeting.

25.1.7 In case of unexpected adverse events (SUSARs):

- A periodic report (quaternary/ semi-annual) should be transferred by the Sponsor via the Principal Investigator, accompanied **by a table summarizing the adverse events by type and incidence**.

- If the case involves the same medicinal product used in several studies conducted by the same Principal Investigator - one submission of reports is allowed, while the Principal Investigator should indicate all the names of the studies and Helsinki numbers associated with the product in an accompanying letter.

25.1.8 Annual Safety Report: should be submitted as part of the interim reports/ final report. If no interim reports are required, the Principal Investigator should submit the report within one month following trial completion.

25.1.9 Confirmation of the trial completion report should be provided on the designated form of final report, transferred to the Investigator, with a copy to the Ministry of Health as part of routine reports.
Report confirmation should be stored as a scanned document in the "study documents" folder in Matarot software; the Investigator should print and keep these confirmation letters in the study file and transfer a copy to the study Sponsor.

25.1.10 Once a year, the Director of the medical center should submit to the Ministry of Health an annual report on the clinical trials which have been/ are being conducted at the institution. The report should be submitted on Form No. 15 provided in the guidelines of the Ministry of Health. Date of reporting: date of the fiscal year end, and no later than 3 months after this date.

26. **Management of safety information reports** (according to the guidelines of the Ministry of Health, including February 2010 update)

Safety information about the investigational product collected as reports during the clinical trial affects the safety of trial subjects.

The aim of these reports is to enable regular control of the course of the trial until its completion by all the entities involved in trial conduct and approval.

During a clinical trial, reports are transferred from the Investigator to the Sponsor and from the Sponsor to the Investigator over the period starting on the date of receiving Director's approval until the last subject enrolled in the study at his site completes the treatment and the follow up periods, unless determined otherwise by the trial protocol or by the guidelines specified by the Sponsor.

Timelines for reporting refer to calendar days, rather than working days.

The Principal Investigator should report a serious adverse event (SAE) which has occurred at our institution on Form 13, according to the guidelines of the Ministry of Health (Appendix 19).

Confirmation of reporting on SAE, including an unexpected SAE (SUAE), which has occurred at another institution or center; Report confirmation should be stored as a scanned document in the "study documents" folder in Matarot software; the Investigator should print and keep these confirmation letters in the study file and transfer a copy to the study Sponsor.

Comment:

The following requirements are imposed in addition to the mandatory reporting to the study Sponsor, in accordance with the clinical trial protocol and the international guidelines (ICH-GCP).

26.1 **Safety reports on serious adverse events (SAEs) which occurred during a clinical trial**

26.1.1 Responsibility of the Investigator in trials funded by a Sponsor

26.1.1.1 Report on death: to the institutional committee Chairman

The Principal Investigator should immediately report any case of death of a subject included in a clinical trial conducted under his responsibility, within 48 hours of being informed of the event, to the Chairman of the institutional Helsinki Committee, who should report to the director authorized by the Director of the medical institution.
The Principal Investigator should report by Form No. 13 (and relevant documents, such as: illness summary, death summary, Sponsor's report and Principal Investigator's cover letter, should be attached).
After investigation of the death case is completed at the hospital and Helsinki Committee's decision regarding the trial is obtained, a report should be forwarded to the Ministry of Health on Form 14 (Appendix 20) and a copy should be transferred to the Principal Investigator, who is responsible for transferring it to the study Sponsor.
(The comment at the end of section 26 also applies to Investigator's responsibility).

26.1.1.2SAE reporting to the Sponsor:

The Principal Investigator and/or a Sub-Investigator must report any SAE which occurred in a study conducted under his responsibility to the Sponsor.
Reporting should be immediate after being informed of the event, according to the timelines specified by the Sponsor in the trial protocol. The Investigator should notify the Sponsor of any new information relevant to the event by follow up reports.

This procedure is carried out simultaneously with reporting to the institutional Helsinki Committee Chairman; the Investigator should report by Form 13 and report of the Sponsor.

The Sponsor receiving the SAE reports from the Principal Investigator or the Sub-Investigator should perform initial assessment and update all the investigators participating in the study by safety reports, including information about unexpected SAEs, for which the association with the investigational product use cannot be ruled out (hereafter: SUSARs- Suspected Unexpected Serious Adverse Reactions), within a fixed period of 7 days in case of death and up to 15 days in other cases.

26.1.1.3Safety reports (SUSARs) received from the Sponsor:

Upon receipt of the reports from the Sponsor, the Principal Investigator or the Sub-Investigator should forward them to the Helsinki Committee. The reports should contain information on any unexpected SAEs which occurred at his site or at other sites in Israel or overseas, for which an association with the investigational product cannot be ruled out.
* The Principal Investigator or the Sub-Investigator should decide whether the reports received from other sites require reporting to the Helsinki Committee, based on possible association with the investigational product and SAE severity, and forward individual reports to the Committee.
* The Principal Investigator or the Sub-Investigator should submit a periodic (quaternary or semi-annual) report to the Helsinki Committee upon its receipt from the Sponsor. This report should include a concentrated list of the events and a summary of major issues raised with respect to the safety of the investigational product.

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Comment :

This requirement applies to clinical trials sponsored by the Principal Investigator at the medical institution and by another Sponsor, such as a commercial company, a corporation, an institution, etc.

26.1.2 Responsibility of the Principal Investigator in trials sponsored by him (Sponsor-Investigator)

Case of death:

The Principal Investigator should immediately report any case of death of a subject included in a clinical trial conducted under his responsibility, within 48 hours of being informed of the event, to the Chairman of the institutional Helsinki Committee, who should report to the director authorized by the Director of the medical institution.
The Principal Investigator should report by Form No. 13 (and relevant documents, such as: illness summary, death summary and Principal Investigator's cover letter, should be attached).

After investigation of the death case is completed at the hospital and Helsinki Committee's decision regarding the trial is obtained, a report should be forwarded to the Ministry of Health on Form 14 and a copy should be transferred to the Principal Investigator.

26.1.2.1Other SAEs:

The Principal Investigator and/or the Sub-Investigator must report any SAE which occurred in a study conducted under his responsibility to the Helsinki Committee Chairman; reporting should be immediate after being informed of the event, according to the timelines specified below: a life-threatening SAE within 7 days of being informed of the event, other SAE - within 15 days of being informed of the event. The report should be submitted to the Chairman of the institutional Helsinki Committee on Form 13.

The Principal Investigator should notify the Helsinki Committee Chairman of any new information relevant to the event by follow up reports.

Comment: In relevant cases, the Sponsor-Investigator should communicate with the manufacturer/ marketing authorization holder of the investigational product/ medical device, report adverse events and receive the most recent safety information regarding the investigational product/ medical device in order to perform evidence based safety assessment during the study.

26.1.3 Responsibility of the medical institution / institutional Helsinki Committee:

26.1.3.1Case of death:

The Helsinki Committee Chairman informed of the death case should immediately investigate the event. If the he concludes that the death is not related at all to use of the investigational product and/or to patient's participation in the trial, he should report the event and this conclusion to the Helsinki Committee and to the Ministry of Health, within 30 days of being informed of the event.
If the Committee Chairman concludes that an association between the death and use of the investigational product and/or patient's participation in the trial cannot be ruled out, he should appoint an investigation team, including at least one senior physician involved in the relevant field. The team should discuss the

case within 14 days of being informed of the event, and decide whether there is an association between the event and use of the investigational product and/or patient's participation in the study.

If it is decided that there is an association, the team should also decide whether the trial may be continued, whether the trial should be stopped (stop recruitment of new patients), or whether a recommendation should be issued to the Helsinki Committee to terminate the trial.

The Committee Chairman should report his conclusions and decisions to the director appointed by the Director of the medical institution, to the Director of Department of Clinical Trials at the Ministry of Health and to the Principal Investigator.

If it is decided to stop or to recommend termination of the trial - the Helsinki Committee Chairman (or deputy Chairman) should instruct the Investigator, in writing, to stop the trial. The director appointed by the Director of the medical institution should be informed of this decision of the investigation team, and in exceptional cases, it should be discussed by the institutional Helsinki Committee at its next meeting, and the Committee should decide whether or not to accept the team's decision.

The Helsinki Committee should report the results of investigation team's discussion and Committee's decisions to the Director of the medical institution and to the Ministry of Health – on Form 14 (Appendix 20); a copy should be also sent to the Principal Investigator.

Comment: According to guidelines of the Ministry of Health, no investigation team is appointed in studies conducted in patients with metastatic cancer.

26.1.3.2Other SAEs:

The Helsinki Committee should inform the Ministry of Health regarding its decisions on events for which it was determined that association with the investigational product cannot be ruled out.

26.1.3.3Safety reports (SUSARs) received from the Sponsor:

Upon receipt of reports from the Sponsor, the Principal Investigator or the Sub-Investigator should forward them to the Helsinki Committee. The reports should include information about unexpected SAEs which occurred at his site and at other sites in Israel and overseas, for which an association with the investigational product cannot be ruled out.

* The Principal Investigator or the Sub-Investigator should decide whether the reports received from other sites require reporting to the Helsinki Committee, including his opinion on possible association between the events and the investigational product and their severity, and whether the study may be continued in its approved design.

The Helsinki Committee is exempt from sending these reports to the Ministry of Health.

26.1.4 Sponsor's responsibility

In general, the Sponsor should report to the Ministry of Health, the Investigators and all the parties involved in the trial according to the ICH-GCP guidelines, and in particular about:

- ❖ <u>Unexpected SADR or SADE which occurred at sites in Israel, according to the following time schedule:</u>

  a. Cases of death or life-threatening events should be reported within 7 days of Sponsor's notification of the event.

  b. All the other events should be reported within 15 days of Sponsor's notification of the event.

- ❖ Investigator's Brochure safety update - Safety Addenda. The updates should be forwarded to the Ministry of Health upon their inclusion in the Investigator's Brochure.

- ❖ Conclusions of the Independent Data Safety Monitoring Board regarding protocol modifications, continuation or termination of a trial. The conclusions should be forwarded to the Ministry of Health within 7 days Sponsor's notification of the conclusions.

- ❖ Any notice of termination of the clinical trial for any reason must be forwarded within 7 days of the decision.

-The Sponsor is responsible for the ongoing evaluation of the investigational products safety.

-The Sponsor should notify all the parties involved in conduct and approval of the trial, that is the Investigators, the Helsinki Committee and the Ministry of Health, of any findings which may affect the safety of trial participants, or findings which have an impact on the method of trial conduct, or findings which may affect the decision of the bodies that approved the trial.

-The Sponsor is **exempt** from forwarding to the Ministry of Health reports on unexpected SADRs or SADEs occurring at **overseas sites** participating in the same trial protocol used in Israel, or in other trial protocols involving the same investigational product, which are conducted only at overseas sites.

26.1.4.1Safety reports (SUSARs)

The Sponsor should report to the Helsinki Committee via the Principal Investigator, as specified above (see section 26)

The Sponsor should notify the Investigator of any SAE which occurred in the trial, defined by him as a SUSAR, according to the following time schedule:

A case of death or life threatening side effects should be reported within 7 days of Sponsor's notification of the event. All the other events should be reported within 15 days of Sponsor's notification of the event.

In addition, the Sponsor should periodically forward to the Investigator a concentrated list of all the SUSARs which occurred in the trial, at the frequency to be determined by the Sponsor based on the specific parameters of the trial, including: the study population, the investigational product, manner of treatment etc., at frequencies of quarterly up to semi-annually. The periodic report should be accompanied by a summary of major issues raised with respect to the safety of the investigational product during the time period addressed in the report.

The reports should be forwarded to the Helsinki Committee in a blinded manner.

26.1.4.2Reporting to the Ministry of Health

Reports on SUSARs which occurred in the trial should be forwarded to the Ministry of Health by the trial Sponsor as part of the Annual Safety Report, describing all the new safety information about the product. The report should be accompanied by a summary of major issues raised with respect to the safety of the investigational product during the time period addressed in the report. The Sponsor should forward the annual report within 30 days of the final approval and circulation of the report.

The reports should be forwarded to the Ministry of Health beginning from the date of Director's approval (Form 7) granted to the first Investigator at the first study site until closure of the last study site in Israel.

26.2Additional safety reports

Responsibility of the Sponsor and the Principal Investigator – The Sponsor should forward the following safety information to the Investigator, and to the Helsinki Committee via the Investigator:
New findings related to the study conduct or to the development of the investigational product, which may affect the safety of trial participants, e.g.: a significant safety finding in a recently completed animal study (such as carcinogenicity), lack of efficacy of the investigational product used to treat a life threatening disease.
Conclusions of the Independent Data Safety Monitoring Board regarding protocol modifications, continuation or termination of the trial.
Any notice of termination of the clinical trial for any reason. In case of termination of a special clinical trial, the Ministry of Health should be informed whether the trial was terminated due to special safety reasons, such as due to an SAE.
Investigator's Brochure safety update - Safety Addenda. The updates should be forwarded
to the Ministry of Health upon their inclusion in the new version of the Investigator's Brochure for the investigational product. This requirement is applicable only to those investigational products for which the relevant trial protocol has been discussed at the Central Committee of the Ministry of Health.

The Sponsor should forward the aforementioned safety information to the Ministry of Health as well.

The information should be forwarded to the Investigator and to the Ministry of Health within 15 days of Sponsor's notification of the information or 15 days of the date of final approval of the report/Investigator's Brochure.

26.3 Failure of the investigational medical device:

The Principal Investigator should report immediately, within 48 hours of being notified of the event, to the Chairman of the institutional Helsinki Committee on any failure of a medical device/accessory which may affect the safety and efficacy of the medical device.

The Investigator should report using the Sponsor's report form or Form 13, and summarize his opinion regarding continuation of the trial, and the Helsinki Committee Chairman should make a decision, as relevant.

If the Helsinki Committee Chairman has decided that the failure may affect the course of the trial, the failure should be reported to the Ministry of Health within 15 days of notifying the Helsinki Committee Chairman of the failure event.

27. Reports on the course of the clinical trial and its completion

The aim of the reports is to enable ongoing control of the course of the clinical trial until its completion by the Helsinki Committee.

27.1Interim report / extension of trial validity

Procedures of extending validity of a previously approved trial:

27.1.1 The Principal Investigator is responsible for extending validity of the approval two months prior to its expiration. The application for extension should be submitted in **writing**. The letter should include a brief summary of the trial to date (including the number of participants recruited and side effects, if occurred), and the reason for the extension request.

27.1.2 The Committee Chairman (or his deputy in his absence) is authorized to decide whether extension of the trial validity requires a discussion at the Committee. If not, the Chairman should approve the extension and notify the Committee members in writing at the next Committee meeting.

27.1.3 The extension approval should be provided on Appendix 7A of the Ministry of Health (Director's approval), but should also include Committee's approval and signature of the Committee Chairman (as detailed in sections 27.1.5, 16.4.1).

27.1.4 Investigator's responsibility

Two months prior to the end of the period approved for the clinical trial, the Principal Investigator/ Sub-Investigator should take actions to extend validity of the approval, if required, as follows:

The Investigator should submit to the institutional Helsinki Committee a progress report for the trial.

As specified in section 16.4, the application should be completed and submitted electronically using Matarot software (Report to the Committee). The Investigator should print 1 copy, sign it and submit it to the Committee. (An unsigned application cannot be handled).

The progress report for the clinical trial should include the following items:

- Date of the report;
- Name of the clinical trial;
- Recent number, date and version of the protocol;
- Recent date and version of the consent form;
- Name of the Principal Investigator and name of the department;
- Date of the clinical trial approval by Director of the medical institution and approval validity;

- ❖ Application number and approval number at the Ministry of Health;
- ❖ Number of participants recruited to the clinical trial as compared to the number planned for recruitment at the site;
- ❖ Number of participants withdrawn from the clinical trial, and the reasons for withdrawal;
- ❖ Number of participants who discontinued their participation in the clinical trial, and the reasons for discontinuation;
- ❖ Details of adverse events observed;
- ❖ Interim results of the trial (if possible);
- ❖ Reason for the application to extend validity of the clinical trial.

27.1.5 Helsinki Committee's responsibility

The Helsinki Committee should discuss the application for extension of the clinical trial validity upon receipt of a copy signed by the Principal Investigator. The approval for extension of the trial validity is granted on Form 7A (including signature of the Chairman from Form 6A – Committee's approval, which is therefore not issued), indicating the recent versions and dates of the application documents, in accordance with section 6.4.2 in guidelines of the Ministry of Health, and should be signed by the Director of the medical institution, as specified in section 16.4.1. The original approval is sent to the Principal Investigator, who should forward it to the Sponsor, a copy should be filed in the study file at the Helsinki Committee and stored as a scanned document in the "Study documents" folder in Matarot software.

If approval by the Ministry of Health is required to extend the trial validity, the approval (Form 8A) should be sent to the Chairman of the institutional Helsinki Committee, with a copy to the Director of the medical institution. The Helsinki Committee should issue an approval for extension of the trial validity (Form 7A), as specified above.

Approval of the Director of the medical institution for extension of the trial validity (Form 7A) should be sent to the Principal Investigator, who should forward a copy of the approval to the Sponsor.

An investigator who fails to fulfill his obligation to submit a progress report on the aforementioned date, if the trial has not yet been completed, will be obliged to submit an application to renew the trial as a new application.

If additional patients have been included and/or new information has been collected in the course of the trial during the period of approval expiration, the investigator may not use this information as part of the trial results.

The Helsinki Committee routinely forwards the progress reports for the studies, including the meeting protocols, to the Ministry of Health, as specified in section 16.4.2.

27.2 Report on completion of the clinical trial

27.2.1 Investigator's responsibility

Upon completion of the clinical trial, the Principal Investigator/ Sub- Investigator should submit to the institutional Helsinki Committee a **completion report** for the trial, which should include the following items:

- ❖ Date of the report;

- Date of approval of the clinical trial by the Director of the medical institution (if the trial validity has been previously extended, the extension dates should be indicated);
- Application number in the computerized registry of the medical institution and approval number at the Ministry of Health;
- Name of the Principal Investigator and name of the department;
- Subject of the clinical trial;
- Recent number and version date of the protocol;
- Recent number and version date of the informed consent form;
- Number of participants recruited to the clinical trial as compared to the number planned for recruitment at the medical institution;
- Number of participants withdrawn from the clinical trial according to Investigator's decision and the reasons for withdrawal;
- Number of participants who discontinued their participation in the clinical trial according to their own decision and the reasons for discontinuation;
- Details of adverse events observed;
- Results of the clinical trial to date (if published);
- Date of completion of the clinical trial (after the last subject recruited to the trial at the site completes his participation in the trial);
- Report on collection / destruction of all the investigational products at the site (if relevant);
- Details of the duration and site of trial document storage.

27.2.2 Helsinki Committee's responsibility

The Helsinki Committee routinely forwards the completion reports, including the meeting protocols, to the Ministry of Health, as specified in section 16.4.2 above.

Following final processing of the clinical trial results, the study Sponsor should forward the results or a copy of the paper (if published) to the Ministry of Health; this applies to applications requiring approval by the Ministry of Health.

The Helsinki Committee forwards a concentrated file of studies which have been completed, cancelled or terminated to contact coordinators at the medical center (R&D Division, Commercial unit and Research grants).

27.3 Annual report

The Helsinki Committee coordinator forwards a report to the Ministry of Health, following approval by the Director of the medical institution, on clinical trials which have been conducted/ are being conducted at his institution. The report should be submitted on Form No. 15 in the guidelines of the Ministry of Health.

Date of reporting: date of the fiscal year end, and no later than 3 months after this date.

According to the requirement of Ministry of Health, the Helsinki Committee should forward information and/or documents related to certain trials indicated in Form 15.

These reports will be used as a control tool for the Ministry of Health, with respect to the extent of compliance of Helsinki Committee's decisions and the process of approving the applications with the guidelines rules.

Comment :

The Director of the medical institution may be exempted from submission of the annual report to the Ministry of Health if the Helsinki Committee has appropriately forwarded full protocols of all the meetings conducted during the year. The exemption may be granted upon Director's request submitted to the Ministry of Health.

27.4 Completion or termination of the clinical trial

27.4.1 The notice of completion / termination of the clinical trial should indicate the reason for termination of the trial in addition to the details specified in section 27.2.1.

27.4.2 Suspension or termination of the trial by the institutional Committee**:**

The Committee is authorized to suspend or to terminate a trial which is not conducted according to the approval conditions or in which unexpected harm has been caused to the participants. The reason for any suspension or termination must be explained in writing and immediately reported to the Director of the medical center, to the Principal Investigator, to the pharmacy, and if required, to the Ministry of Health – Director of Department of Clinical Trials at the Pharmaceutical Administration.

27.4.3 Termination by the Sponsor or planned completion:

The Sponsor should notify the Investigator and the Department of Clinical Trials at the Ministry of Health (pharmaceuticals or medical devices, as relevant). The Investigator should notify the Chairman of the Helsinki Committee in writing; the Committee should confirm this notice, handle the study closure procedure and notify the Director of clinical trials authorized by the Director of the medical center (hereafter: the Director) and the Ministry of Health.

27.4.4 Termination by the Investigator:

The Principal Investigator or the Sub-Investigator should notify the Sponsor and the Helsinki Committee. The Committee should confirm the report and handle the study closure procedure in accordance with section 27.2.1 above.

27.4.5 In case of termination of the trial by the Ministry of Health, the Ministry of Health should notify the Director of the medical institution, the study Sponsor, the Investigator, and the pharmacy director, if required.

28. Collection/return/destruction of investigational products (for medical devices – only in relevant cases) used in a clinical trial which was completed or terminated:

The study Sponsor must ensure that investigational products are collected/returned/destroyed and that their use is discontinued upon completion or termination of the clinical trial. The investigational products should be collected/returned/destroyed in accordance with Standard Operating Procedures (SOP) of the Sponsor and in accordance with the SOP of the Unit for clinical trials at the institutional pharmacy.

28.1 Reporting:

Upon completion of collection/return/destruction of the investigational product, the Sponsor should report to the institutional Helsinki Committee, with a copy to the Ministry of Health.

The report should include:

- Identifying details of the clinical trial, as specified in section 27.2, including the date of trial initiation.
- Date of the notice of termination of the clinical trial, and the reason for termination.
- Details of the quantities of the investigational product/medical device (as relevant) distributed in that medical institution; how many were used in the clinical trial and how many were returned. In case of a medical device intended for repeated use – number of times used.
- Summarizing report of the course of the clinical trial up to its termination, as specified in section 27.2.

29. Further provision of the investigational product following completion of the clinical trial

Approval for compassionate use of a study drug following completion of the trial:

29.1 If it becomes clear, following completion of the clinical trial, that treatment with the study drug should be continued, the Principal Investigator should notify the Helsinki Committee Chairman in writing and recommend that further treatment with the investigational product is required for the health of the patient participating in the trial, and that no other alternative medical treatment is available for him. The patient will continue receiving the investigational product in accordance with a written planned follow-up protocol, free of charge, even after completion of the clinical trial, for a period not exceeding 3 years, except for any of the following cases:

a. The investigational product has been approved for marketing in the State of Israel for the requested indication and is available from the HMO with which the patient is insured[1].

b. Development of the product has been discontinued or the clinical trials with the product were not successful.

c. Administration of the investigational product for such a prolonged period of time may endanger patient's health due to insufficient information about the long term safety of the product.

d. If the investigational product is not a medicinal product, such as: a cosmetic product / a food product / a food supplement / a medicinal herb.

29.2 The decision regarding further administration of the investigational product lies with the institutional Helsinki Committee, which may re-evaluate its decision from time to time. The Principal Investigator and the Sponsor have the right to appeal this decision to the Director General of the Ministry of Health or person appointed by him for this matter.

[1] Clarification: according to the Healthcare Basket or via the supplemental insurance, provided that the out of pocket sum does not exceed the approved out of pocket sums.

Comment :

If the trial Sponsor is the Principal Investigator and the trial is not financed at all by a commercial company, the Helsinki Committee may exempt the Investigator from the obligation to continue providing the investigational product after completion of the trial. For this purpose, the Investigator should apply to the Helsinki Committee in writing and explain the reason for his exemption request. The committee should report its decision to the Ministry of Health in the meeting protocol.

29.3 Further provision of the investigational product following completion of the clinical trial is subject to the following conditions:

29.3.1 The Principal Investigator should submit for Committee's approval a planned follow up protocol, written by the Principal Investigator, for treatment extension, including the treatment plan, follow up plan, a new consent form for treatment extension and CRF. Further treatment will be administered as part of the follow up protocol to be approved by the Sponsor and the institutional Helsinki Committee. (Appendix 3.1)

29.3.2 Further treatment should be administered according to a planned follow-up protocol to be written by the Principal Investigator and approved by the Sponsor and the institutional Helsinki Committee.

29.3.3 Further treatment should be administered to the participant after approval by the Director of the medical institution, as commonly accepted for clinical trial applications.

29.3.4 The Principal Investigator is responsible for continuous monitoring of patient's health condition and for reporting to the Helsinki Committee on any adverse events which occurred during the treatment extension, as commonly accepted for clinical trials.

29.3.5 The Principal Investigator should report to the Helsinki Committee on the progress of patient's treatment at least once a year.

29.3.6 The medical institution at which further treatment is to be provided should arrange for appropriate insurance to cover the liability of the medical institution and the Principal Investigator towards the patient in view of further administration of the investigational product following completion of the clinical trial.

30. **Supervision of clinical trials**

30.1 Supervision by the Helsinki Committee:

The institutional Helsinki Committee is responsible for supervising the clinical trials approved by it and by the Director of the hospital. The Committee should receive periodic reports from the investigators responsible for the trial at least once a year. For trials associated with high risk to the participants, according to committee's judgment, the Committee should require more frequent reports, as relevant.

In addition, the Committee should receive routine reports on adverse events which occurred during the trial and discuss them.

The committee should follow investigators' reports, contact the Investigator about two months before completion of the trial, and remind him to submit a progress report or a trial completion notice to the committee, as relevant.

30.2 Supervision by the medical institution according to the SOP of the institutional auditing body with all its updates. (Appendix 11)

According to the guidelines of the Ministry of Health, the management of the medical institution is responsible for appointing an auditing body to review and monitor the clinical trials approved at the institution. This body id independent and is appointed by the hospital management.

The SOPs of the auditing body are available in the SOPs folder of the Helsinki Committee.

The coordinator of the auditing body reports to the Helsinki Committee Chairman; the reports are filed in designated control folders.

The composition of the auditing body and validity of the appointment are specified in the circular of Director General 7/05 dated March 6, 2005.The duty of the auditing body is to examine compliance of the actual trial conduct with the approved trial design.

The auditing body should report its activities and findings to the management of the medical institution and to the Helsinki Committee every six months. The management of the medical institution is obliged, according to the SOP, to forward the report to the Ministry of Health.

30.3 Supervision by the Ministry of Health

The Ministry of Health should supervise the medical institutions (by carrying out sample audits) and examine, among other parameters, compliance of the actual clinical trial conduct with the approved protocols, provisions of the law and regulations of the Ministry of Health.

31. Document storage

All the documents related to Committee's activity and meetings, including meeting protocols, list of Committee members, submitted documents, correspondence and Director's decisions, should be filed and stored for a period of at least 7 years following completion of the clinical trial (according to the regulations of the Ministry of Health).

All the entities involved in sponsoring, approval, conduct, and control of the clinical trial are obliged to keep the trial documents, as detailed below:

31.1 The institutional Helsinki Committee / Director of the medical institution should keep the following documents for at least 7 years following completion of the clinical trial:

- SOPs (Charter) of the committee
- List of committee members who discussed approval of the clinical trial
- Documents submitted for discussion
- Meeting protocols
- Correspondence
- Director's decisions

31.2 The Sponsor/Principal Investigator should keep all the application documents, including the documents submitted to the Helsinki Committee for approval, and all the documents collected during the clinical trial, for at least 15 years following completion of the trial.

31.3 The pharmacy should keep the approval for the clinical trial, the import authorizations - if the pharmacy is an importer, or the certificate of receipt of goods, as well as documents relevant to dispensing drugs for a certain trial, for at least 7 years following completion of the trial.

Comment :

At the end of the storage period, the medical institution can arrange with the Sponsors for further storage at Sponsors' sites. Clinical trial documents kept by the medical institution should not be destroyed without prior agreement with the Sponsor.

32. Service fees

The Director of the medical institution should collect from the Sponsor, as defined in these guidelines, service fees for handling the application for approval of a clinical trial in human subjects in that center. A fee of 800 NIS should be collected for any modification or addition to the clinical trial approval.

33. Package of the application documents required for submission of the request for clinical trial approval*

Trial type / Documents	Trial with an investigational product – medicinal product	Trial with an investigational product – medical device	Trial with an investigational product – cells and tissues	Genetic trial[1]	Trial with no investigational product	Investigational treatment for a single patient
Application form	**1A**	**1B**	**1C**	**1D**	**1E**	**Letter to the committee[2]**
Trial protocol	√	√	√	**√	√	√
Investigator's brochure[3]	√	√	√			
Relevant literature[4]	√	√	√	√	√	√
Consent form - Participant - Guardian	**-2A -3A**	**-2A -3A**	**-2A -3A**	**-2B -3B**	**-2C -3C**	***√
Sponsor's declaration of commitment	**4A**	**4A**	**4A**	**4B**	**4c**	
Sponsor's declaration regarding document identity	**5**	**5**	**5**	**5**	**5**	
Letter to attending Physician at the HMO	**11**	**11**	**11**			
Document list	**9**	**9**	**9**	**9**	**9**	
Notice for recruitment of participants[5]	**10**	**10**	**10**	**10**	**10**	
Declaration on financial involvement or association	√	√	√	√	√	

[1] Further details on the information required for genetic trials are available in the **Instructions for investigators and forms for submission of applications for approval of genetic studies in human subjects, 2005**. These guidelines are available at the website of the Pharmaceutical Administration.

[2] Application letter to the committee, including detailed and current information about the disease course, the treatments given to the patient, and the proposed investigational treatment.

[3] Cases in which the requirement for submission of the Investigator's Brochure may be exempted are listed in section 2.3 of the guidelines.

[4] With each application for a clinical trial for which submission of the Investigator's Brochure is not required, current articles relevant to the study subject should be submitted.

[5] This form should be submitted if required.

Comment :

* Please read the instructions before submitting the applications (Appendix 8)

** Genetic questionnaire Part B should be attached to the genetic application as an appendix to the protocol, and subject information leaflet - as an appendix to the consent form (see appendices 13, 13.1).

*** Form 4 Application and consent form for compassionate use (Appendix 23)

34. Additional forms of the Ministry of Health for use after approval of the trial

Form 6 - Approval of the institutional Helsinki Committee to conduct a clinical trial in human subjects
Form 7 - Approval of the Director of the medical institution to conduct a clinical trial in human subjects
Form 4 - Approval of the institutional Helsinki Committee to conduct a trial other than a clinical trial in human subjects
Form 5 - Approval of the Director of the medical institution to conduct a trial other than a clinical trial in human subjects
Form 5A - Approval of the Director of the medical institution to extend the validity of approval to conduct a trial other than a clinical trial in human subjects
Form 7A - Approval of the Director of the medical institution to extend the validity of approval to conduct a clinical trial in human subjects
Form 8 - Approval of the Ministry of Health to conduct a clinical trial in human subjects
Form 8A - Approval of the Ministry of Health to extend the validity of approval to conduct a clinical trial in human subjects
Form 10 - Text of the notice for recruitment of clinical trial participants intended for publication in the mass media
Form 12 - Application form for modifications in a clinical trial in human subjects
Form 13 - Form for Investigator's notice of an SAE experienced by a clinical trial participant
Form 14 - Form for notification of death of a clinical trial participant – Report of event investigation and Helsinki Committee's conclusions
Form 15 - Annual report on clinical trials in human subjects approved by the Director of the medical institution

35. Modifications and interpretation of the guidelines

35.1 These guidelines are subject to modifications and updates, as recommended by the Committee and based on approval of Committee's recommendations by the Director of the medical center, and in accordance with the law provisions.

35.2 In case of any doubt, these guidelines should be interpreted according to the majority of opinions expressed by the Committee members participating in the meeting, and this decision is valid and obligating.

36. References

Guidelines of the Ministry of Health effective from April 1, 2006.

37. Circulation

Director for clinical trials appointed by the medical institution.

Chairman of the Helsinki Committee and his deputies.

Institutional Helsinki Committee members.

Team of the Research and Development Division and Heslinki Committee.

Members of the auditing body.

All the investigators of TASMC must be informed of these guidelines by electronic circulation on the website of the medical institution.

38. Applicable documents

38.1 Public Health Regulations (Clinical Trials in Human Subjects) 1980, including all amendments and additions until 1999.

38.2 ICH-GCP (E6), 1996 Harmonized Tripartite Guideline for Good Clinical Practice

38.3 Standard for human clinical studies with medical devices:

ISO 14155-1, 14155-2: Clinical Investigation of Medical Devices for Human Subjects (2003)

38.4 Guidelines for gene therapy products

Notes for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products, CPMP/BWP/3088/99

38.5 Genetic Information Act, 1999.

38.6 Helsinki Committee guidelines for genetic trials, 2005

38.7 Prohibition of Genetic Intervention Act – (Human Cloning and Genetic Modification of Reproductive Cells), 1999.

36.8 Patient's Rights Act, 1996.

38.9 Pharmacists' Regulations (Medicinal Products), 1986.

38.10 Circular of Director General (Instructions for Sterilization of Medical Devices and Accessories), 1999.

38.11 Circular of Director General “Xenotransplantation”, 2000.

38.12 Circular of Director General on living cells and tissues, 2001.

38.13 Guidelines of the Ministry of Health for binding contracts with commercial companies, 2004.

38.14 Circular of Director General “Supervision and Control of Clinical Trials in Medical Institutions in Israel”, 2005.

38.15 Conditions for Administration's Consent, File of Publications, 1999, Page 1.

38.16 Circular of Director General “Registration of Clinical Trials in the NIH Database”, 2005.

39. Appendices

Appendix 1 Guidelines of the Ministry of Health - Exemption from Informed Consent Form for a clinical trial in medical emergency.

Appendix 1.1 Appendix A and Appendix B for medical emergency

Appendix 2 Guidelines of the Ministry of Health - Section of insurance in binding contracts with commercial companies for clinical trials in government hospitals.

Appendix 3 Guidelines of the committee of contracts for research purposes and research budgets.

Appendix 3.1 Investigator's guidelines for application for extension study – administration of investigational product following completion of the trial.

Appendix 4 Guidelines for approval of insurance coverage for clinical studies.

Appendix 5 General information for a clinical study participant.

Appendix 6 ICH-GCP declaration.

Appendix 7 Obligation for maintaining confidentiality for Helsinki Committee members.

Appendix 8 Guidelines and information for submitting applications for studies.

Appendix 9 Helsinki Committee guidelines for writing an informed consent form.

Appendix 9.1 Consent form text regarding contact information for trial participants in case of questions.

Appendix 10 Telephone consent form (for adults and minors)

Appendix 11 SOP of the auditing body for clinical trials.

Appendix 12 SOP of the sub-committee for a study other than a clinical trial.

Appendix 13 Genetic questionnaire - Information required in the application for approval of a genetic trial protocol (addendum to the study protocol).

Appendix 13.1 Consent form for pan-genomic study.

Appendix 14 Institutional SOP for safety reports.

Appendix 15 SOP for clinical trials registration at the NIH website.

Appendix 16 SOP for application to establish a sample bank for medical and research purposes.

Appendix 17 Guidelines for arranging studies with biological pathogens, as required by the law

Appendix 18 Form 12 – Application form for reports and amendments.

Appendix 19 Form 13 - Form for Investigator's notice of an SAE experienced by a clinical trial participant

Appendix 20 Form 14 - Form for notification of death of a clinical trial participant – Report of event investigation and Helsinki Committee's conclusions.

Appendix 21 Form 2 for using a medicinal product not registered in the medical institution (collective) (29C)

Appendix 22 Form 2 for using a medicinal product not registered in the medical institution (individual) (29C)

Appendix 23 Form 4 – For experimental compassionate use or urgent treatment on compassionate use basis.

8.2.1.1.1.1.1.2

Appendix 24 Consent form for use of a medication not included in the basket of hospitalization services.