

**Ministry of Health
Pharmaceutical Administration
Jerusalem**

Guidelines for Clinical Trials in Human Subjects

**In accordance with the Public Health Regulations
(Clinical Trials in Human Subjects) 1980**

2006

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General

These guidelines govern the method of submission, approval and inspection of clinical trials and clinical research in human subjects.

These guidelines define the procedure for handling applications for clinical trials and the requirements for the conduct and the supervision thereof.

Any clinical trial, including the planning, approval, conduct, recording, and reporting thereof shall be carried out in due compliance with the principles of the Helsinki Declaration, the Public Health Regulations (Clinical Trials in Human Subjects) 1980, including all subsequent additions and amendments thereto until 1999 (hereinafter "the Regulations"), the Genetic Information Law 2000 (hereinafter: "the Genetic Information Law"), the provisions of these Ministry of Health guidelines, the provisions of the current **Harmonized Tripartite Guideline for Good Clinical Practice (ICH-GCP E6)** and the provisions of the current ISO 14155-1, 14155-2 (2003): **Clinical Investigation of Medical Devices for Human Subjects**, as well as regulations and guidelines published periodically by the Ministry of Health.

Compliance with the requirements of the aforesaid guidelines is designed to protect the trial participants and ensure that their rights, safety and wellbeing are maintained, and that the information obtained from the study is reliable.

In the event of an inconsistency between the aforesaid guidelines, the guidelines of the Ministry of Health shall prevail. In matters not covered by binding provisions in the guidelines of the Ministry of Health, the international guidelines (defined hereinafter) should be followed.

These guidelines, including all appendices and forms, can be found at the website of the Clinical Trials Section of the Pharmaceutical Administration, Ministry of Health, at: <http://www.health.gov.il/drugs>.

Definitions

1. Adverse events during a clinical trial:

(a) **Adverse event (AE):** Any untoward medical occurrence in a clinical trial participant who was given an investigational product, which is not necessarily related to this treatment.

(b) **Serious Adverse Event (SAE):** Any adverse event that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or results in prolongation of existing hospitalization (e.g., need for medical intervention, a risk of disability, or a life-threatening condition)
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly

(c) **Adverse Drug Reaction (ADR) or Adverse Device Effect (ADE):** Any adverse event somehow related to treatment with the investigational product.

(d) **Serious Adverse Drug Reaction (SADR) / Serious Adverse Device Effect (SADE):** Any serious adverse event somehow related to treatment with the investigational product.

2. **Affiliation:** A relationship of paid employment; or commercial or business relationship; or family or personal relationship; or any other relationship, including a subordinate work relationship, which could be construed as a conflict of interest or dependence; except for reimbursement of expenditures or remuneration for participation in committees, subject to these Guidelines.

3. **Amendment to a clinical trial which the Director of the medical institution is authorized to approve:** An amendment to a clinical trial application, which does not require approval by the Ministry of Health in addition to approval by the Institutional Ethics Committee, as set forth in Section 6.4 of these guidelines.
4. **Central Committee for Clinical Trials in Human Subjects:** An advisory committee for clinical trials, appointed by the Director General of the Ministry of Health for any of the following subjects (or any other subjects to be determined in the future):
 - (a) Medicinal products
 - (b) Medical devices and instruments/medical equipment
 - (c) Products containing living human cells and tissues and xenotransplantation
5. **Certified physician/dentist:** A physician or a dentist with an academic degree recognized in Israel (MD, MDD), who is licensed to practice medicine or dentistry in Israel, in accordance with the provisions of the Physicians' Regulations [New Version] -1976, or the Dentists' Regulations [New Version] -1979, respectively.
6. **Clinical trial/study:** A clinical trial in human subjects as defined in the Regulations:
 - (1) Use of a drug, irradiation or a chemical, biological, radiological or pharmacological substance, which is not consistent with the legally authorized use thereof, or where said use is not generally accepted in Israel for the requested indication, or has not yet been tested in Israel, and which may affect or is designed to affect the health, body or mind of a person or a fetus, or part thereof, including their genetic makeup.
 - (2) Performance of any procedure, action or test in human beings which are not generally accepted.

A clinical trial in human subjects also refers to a special clinical trial, as defined in the fourth supplement to the Regulations.

The objectives of a clinical trial in human subjects, as defined in the Helsinki Accords, are to improve the treatment, diagnosis and prevention of diseases, and contribute to the understanding of the etiology and pathogenesis of diseases.
7. **Director General:** Director General of the Ministry of Health, or any other person authorized by the Director General to act in accordance with these Regulations, in whole or in part.
8. **Director of a medical institution:** The medical director or acting medical director of the hospital or medical institution in which the clinical trial is being conducted, for the matter of these Regulations, in whole or in part.
9. **Genetic trial/study:** A study in which biological samples are taken and DNA is produced in order to obtain genetic information, which is governed by the Genetic Information Law, with the following exceptions: clinical genetic tests (location and identification of mutations of a known gene associated with a known disease), and studies of DNA products (RNA, protein expression or enzyme activity).
10. **Good Clinical Practice (GCP):** working and methodology guidelines designed to ensure the wellbeing and rights of the trial participants and the quality and efficacy of the trial.
11. **Hospital or institutional Ethics Committee:** An independent committee whose composition, methods of appointment and legal quorum are defined in the Regulations. Its role is to ensure the rights, safety and wellbeing of the trial participants, inter alia by examining and approving the clinical trial protocol and informed consent form. It is also responsible for the ongoing review of the trial, including amendments to the protocol and informed consent form, and for the supervision of the trial, as set forth in Section 18.1 of these guidelines.
12. **International guidelines:** two international ethical and scientific quality standards for the planning, conduct, recording and reporting of studies involving human subjects.

For investigational products: ICH-GCP – Harmonized Tripartite Guideline for Good Clinical Practice (hereinafter: “**ICH-GCP**”).

For medical equipment/medical devices: Clinical Investigation of Medical Devices for Human Subjects ISO 14155-1, 14155-2 (hereinafter “**ISO 14155**”).

13. **Investigational Product**: A medicinal product (or placebo), medical equipment/medical device, medicinal product containing living cells and tissues, cosmetic product, food, food supplement, homeopathic product or medicinal herb, etc. A product tested or used as a reference in a clinical trial in human subjects, including products approved for marketing if used differently from the registered use or if used for an unregistered indication or if used to obtain further information on a registered indication.
14. **Investigator or Principal Investigator**: A licensed physician or a licensed dentist who acts as an investigator responsible for the conduct of a clinical trial at a trial site, as defined in the trial protocol.
15. **Medical equipment/medical device**: An instrument, device, chemical substance, biological product or biotechnological product used for medical treatment, or required for the operation of an instrument or a device used in treatment, which is not primarily designed to act on the human body as a pharmaceutical agent.
16. **Medicinal product**: A medicinal product as defined in the Pharmacists’ Regulations [New Version] -1981.
17. **Monitor**: A person responsible for monitoring the course of a clinical trial in human subjects who has undergone the relevant professional training.
18. **Monitoring**: The act of overseeing, in real time, the activities of a clinical trial in human subjects, with the intention of ensuring that the study is conducted, recorded, and reported in accordance with the study protocol, the Good Clinical Practice, the approval granted to the study and any applicable legal provisions.
19. **Multicenter trial in Israel**: A clinical trial conducted in more than one medical center in Israel.
20. **National Ethics Committee**: An independent committee whose composition, methods of appointment and legal quorum are defined in the Regulations. Its role is to provide opinions on trials concerning human genetic makeup, IVF, and other matters which the Director General wishes to discuss, including trials governed by the Genetic Information Law.
21. **Non-special clinical trial**: A clinical trial that requires approval by the Ministry of Health following approval by the Institutional Ethics Committee.
22. **Recognized Country**: Any of the following -
 - (a) United States of America;
 - (b) Any member state of the European Union (EU);
 - (c) Switzerland;
 - (d) Norway;
 - (e) Iceland;
 - (f) Australia;
 - (g) New Zealand;
 - (h) Japan;
23. **Recognized medical equipment**: Medical equipment that satisfies any of the following criteria:
 - (a) Found in routine medical use and the Director General has approved its safety;

- (b) Approved for marketing by the US Food and Drug Administration (FDA) and sold in the United States;
 - (c) Approved for marketing and sold in a member state of the European Union (bears the CE mark of approval).
24. **Sponsor:** A person, corporation or institution responsible for the initiation, management, and financing of a clinical trial.
 25. **Sponsor-Investigator:** A person, excluding a corporation or institution, who is both the Sponsor and the Principal Investigator of a clinical trial which is self-financed or financed by a third party, regardless of the source of financing. The duties of the Sponsor-Investigator are both those of the Principal Investigator and of the Sponsor.
 26. **Sub-investigator:** Any member of the clinical trial staff appointed by the Principal Investigator to perform critical trial-related processes and/or make important decisions regarding the trial, under the supervision of the Principal Investigator at the trial site.
 27. **Special clinical trial:** A clinical trial which the Director of the medical institution is authorized to approve. Such a clinical trial does not require approval by the Ministry of Health in addition to approval by the Institutional Ethics Committee, as defined in the fourth supplement to the Regulations, and is included in the list detailed in Section 6 of these guidelines.
 28. **Special population:** Pregnant women, minors¹, patients whose judgment has been impaired by their physical or mental condition and individuals in legal custody.

¹ Pursuant to the Legal Competence and Guardianship Law 1962, minors are individuals under or at the age of 18 years.

Contents of the Guidelines

1. Conditions for the conduct of a clinical trial in human subjects

- 1.1 A clinical trial in human subjects shall not be conducted unless it complies with the provisions of the Regulations and of these Guidelines.
- 1.2
 - a) A clinical trial in human subjects shall not be conducted unless it has been approved by the institutional Ethics Committee and by the Director of the medical institution, according to the rules set 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 Ethics Committee.
 - c) An application for the approval of a clinical trial in human subjects may only be submitted by a licensed physician or a licensed dentist (depending on the studied subject), who will be the Principal Investigator of the trial.
 - d) The Principal Investigator shall submit an application for a clinical trial in human subjects to the institutional Ethics Committee, as detailed in Section 2 of these Guidelines.
- 1.3 The Ethics Committee shall not approve the conduct of a clinical trial in human subjects unless it has been convinced to its satisfaction that the conditions detailed below, and any other conditions at its discretion, have been met:
 - a) The expected benefits to the trial participant and to society justify the risk and the discomfort to the trial participant;
 - b) Currently available medical and scientific information justifies the conduct of the proposed clinical trial;
 - c) In the event of a clinical trial in a special patient population, the trial is required to improve the health of this population and cannot be conducted in any other population instead;
 - d) The scientific design of the clinical trial allows to answer the test question and is described clearly, accurately and in detail in the study protocol and complies with the principles of the Helsinki Declaration;
 - e) The foreseeable risks to the trial participant are minimized to the greatest extent possible by the use of appropriate research methods, and where possible, the use of procedures already performed in human subjects or tested in animals;
 - f) The trial protocol shall define clear criteria for the selection of trial participants;
 - g) The informed consent form for the clinical trial shall contain a summary of all the required information as detailed in these Guidelines;
 - h) The study plan will contain instructions for protecting the privacy of the participants and the confidentiality of the information collected;
 - i) The study plan will include a structured mechanism for optimal monitoring of the study;
 - 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 relating to the clinical trial, whether during the course of the trial or thereafter. The insurance shall be expanded to include the legal liability of the medical institution and/or the medical staff and/or the Investigator, stemming from their involvement in the conduct of the trial, excluding events of negligence or deliberate deviation from the study protocol;
 - k) Free supply of the investigational product to the trial participants shall be guaranteed

throughout the duration of the trial;

- l) The Sponsor, Principal Investigator and medical institution are capable of and undertake to allocate the resources needed for the proper conduct of the clinical trial, including skilled personnel and necessary equipment;
 - m) The nature of commercial contract with the Principal Investigator and the medical institution in which the trial is being conducted does not prejudice the appropriate conduct of the clinical trial;
 - n) In the event that all or some of the clinical trial participants may be exposed to coercion or undue influence to participate in the clinical trial, appropriate measures have been taken to prevent such coercion or to minimize such influence;
 - o) The rights and safety of the clinical trial participants shall be protected throughout the trial;
 - p) Any decision made and medical treatment given to a participant in the clinical trial shall be the responsibility of a licensed physician or dentist, as applicable;
- 1.4 A clinical trial in human subjects shall be conducted in strict accordance with the provisions of the Regulations, these Guidelines of the Ministry of Health, including the applicable laws set forth therein, the International Guidelines and the requirements of the study protocol as approved by the Ethics Committee and in accordance with the terms of approval;
- 1.5 A Principal Investigator and Sub-investigator (hereinafter: the "Investigator") taking part in a clinical trial in human subjects shall have the appropriate training for conducting clinical trials as well as skills and experience in their field, in respect of clinical trial conduct;
- 1.6 Any information pertinent to a clinical trial in human subjects, which may lead to the disclosure of the identity of trial participants or details of their medical or genetic condition, shall be maintained in confidence and the provisions of Article 19 of the Patient's Rights Law 1996 shall apply, *mutatis mutandis*. In respect of genetic information, the results of genetic tests shall not be included for study purposes in the medical file, pursuant to Article 30 of the Genetic Information Law.

2. Contents of the application for a clinical trial

General comment:

The content of the application documents varies depending on the type of the trial, i.e. trial of a medicinal product, trial of a medical device; trial of a product derived from living cells and tissues; genetic trial; clinical trial not involving the use of investigational or experimental products.

For each type of trial there is a separate application package, as set forth in the table in Section 21 of these Guidelines and forms therein. The application should contain the following documents and data:

2.1 Application form (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).

2.2 Detailed plan for the clinical trial (trial protocol):

2.2.1 Protocol for trials of investigational products:

In general, the protocol shall include the items set forth in the instructions of the international guidelines, particularly:

- ◆ Name, number, date and version of protocol;
- ◆ Name and address of study sponsor and study monitor (if other than the Sponsor);

- ◆ Name and position of the person who signed the protocol;
- ◆ Background and rationale of 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 pertaining to the product. In a trial of a medical device, the name of the manufacturer, the name of the model, accompanying accessories, identification number of the software version and its method of use in the trial shall also be specified;
- ◆ Objectives of the clinical trial;
- ◆ Parameters for evaluation of the results (endpoints);
- ◆ Total number of participants, number of centers scheduled to take part in the study, phase number, and study design e.g. open-label, blind, etc.;
- ◆ Criteria for inclusion, exclusion, and withdrawal from the clinical trial;
- ◆ Investigational product/medical device treatment regimen (including dose, route of administration, duration of treatment and number of doses);
- ◆ Clinical follow-up plan (trial schedule and/or flowchart should also be attached);
- ◆ Laboratory tests and any other relevant test due to be performed during the trial or the follow-up period;
- ◆ Conditions for discontinuation of the clinical trial;
- ◆ Safety evaluation methods and instructions for reporting serious adverse events (the report shall comply with the rules of the guidelines);
- ◆ Methods of analysis and processing of the results;
- ◆ Ethical issues pertinent to the trial;
- ◆ Sample Case Report Forms (if necessary);
- ◆ Method of accountability for the investigational product;
- ◆ Clinical tests, questionnaires.

2.2.2 Protocol for genetic trials

The protocol shall include the subjects listed in Section B (Article 1: the information required in the study proposal) of **The Instructions for Investigators and Application Forms for Approval of Genetic Trials in human Subjects**, 2005.

These instructions can be found at the website mentioned in page 6 above.

2.2.3 Protocol for clinical trials not involving investigational products

- ◆ Name, number and date of the protocol;
- ◆ Name and signature of author of protocol;
- ◆ Background and rationale of the clinical study, including a review of scientific literature;
- ◆ Objectives of the clinical study;
- ◆ Parameters for evaluation of the results (endpoints);
- ◆ Number of participants, and number of centers scheduled to take part in the study;

- ◆ Criteria for inclusion in and exclusion from the study;
- ◆ Study timetable;
- ◆ If applicable: laboratory tests and any other relevant test due to be performed during the study or the follow-up period, site for performance of the tests and handling of samples at the end of the study;
- ◆ Methods of analysis and processing of the results;
- ◆ Ethical issues pertinent to the trial;

2.3 Investigator's Brochure (IB)

2.3.1 Investigator's brochure for a medicinal product:

The **current** investigator's brochure containing information on the investigational product, as detailed in the International Guidelines (ICH-GCP) including:

- ◆ 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 a scientific rationale;
- ◆ Physical, chemical, and pharmaceutical data of the finished product being studied;
- ◆ Preclinical data: pharmacology, pharmacokinetics and toxicology;
- ◆ Current clinical data, including safety and efficacy information;
- ◆ Summary of data, summary of expected risks to the participants and instructions for use of the investigational product.

Notes:

An exemption from the requirement to submit an investigator's brochure may be obtained from the Ministry of Health in the following instances:

- The trial involves a registered product approved in Israel and use thereof for the registered indication.
 - The trial involves a medicinal product previously approved for a clinical trial in Israel, for the same indication and with the same route of administration.
 - The clinical trial involves to an additional indication, dosing form or dosing regimen for a product registered in Israel, provided that the route of administration is the same as that of the registered product and the dose does not exceed the generally accepted dose reported in the literature. Relevant publications, e.g. articles from scientific literature supporting the rationale of the clinical trial, should be attached to the application.
- If the route of administration is different, the specific section of the investigator's brochure relating to the requested route of administration should be submitted.
- A bioavailability trial where one or both of the products are registered in Israel or in a Recognized Country.

2.3.2 Investigator's brochure for a medical device:

The current investigator's brochure containing information on the medical device, as set forth in the International Guidelines (ISO 14155), particularly:

- 2.3.2.1 Cover page, including details of trial Sponsor, name and/or code of the medical device, model number/name, software version, manufacturer details, version date and number;
- 2.3.2.2 Table of contents;
- 2.3.2.3 Introduction, including background and rationale for designated use of the medical device in the trial and for development of the technology;
- 2.3.2.4 General description of the medical device and accompanying accessories, stating the models (including technical description and active components) and number of software version.

This section will include, inter alia:

- ◆ Information on the substances composing the medical device and their suitability for the designated purpose. (All medical devices must comply with biocompatibility requirements in accordance with the ISO 10993 standard);
- ◆ If the medical device transfers energy to or from the body, the type of energy, its description and quantity in physical measurements, and the rate of energy flow should be specified;
- ◆ If substances are transferred to or from the body, a description of the substances, the quantities thereof, and the flow rate should be specified. If isotopes are involved, the dose of radiation received by the clinical trial participant with reference to generally accepted standards;
- ◆ 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 specified, as customary.
- ◆ If the medical device contains a biological substance, a description of the substance, its origin, and method of handling thereof for inclusion in the medical device should be specified;
- ◆ If the medical device is a measuring device, details of the variables measured and the degree of accuracy should be specified;
- ◆ Information about sterilization, if applicable (single or multiple use, sterilization site and method), and compliance with the requirements of Director General circular "Instructions for the Sterilization of Medical Devices and Instruments";
- ◆ If the medical device constitutes a change/modification of "recognized medical equipment" or a medical device previously approved for clinical trial use:
 - Name of original medical device (including model) and name of manufacturer.
 - Regulatory status of the original medical device plus certificates of approval.
 - Description of the change in the medical device.
 - Possible implications of the change on performance of the medical device, its safety, efficacy, method of use and clinical action; references from literature, arithmetical proofs and a report on preclinical trials should be included.
- ◆ If the medical device is a software or a medical device with built-in software, identifying details of the version, a brief description of the algorithm, including a macro flowchart (at the main function and routine level) should be specified. A signed validation certificate should be attached. An explanation should be

provided on how to handle situations, either in software or hardware, where a software malfunction can put the trial participant at risk.

- 2.3.2.5 Explanation on the method of action, performance, and method of use of the device, plus instructions from the manufacturer for use / operation / installation / maintenance (if applicable).

Description of the clinical action (with reference to the intended use in the appropriate patients) and of the indications.

- 2.3.2.6 Description of preclinical studies and results: relevant laboratory and animal trials to demonstrate the safety and efficacy of the medical device in its intended use. Animal trials must have been conducted in accordance with Good Laboratory Practice (GLP) guidelines applicable in the United States or in a member state of the EU.

- 2.3.2.7 Summary of current 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 malfunctions.

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

- 2.3.2.9 Description of the unique characteristics of the medical device compared with other medical devices that are similar, generally accepted, or approved for use (relevant parameters, uses, risks and benefits).

- 2.3.2.10 Summary of the information and instructions for the Investigator.

- 2.3.2.11 Method of accountability.

- 2.3.2.12 Marketing material (if any)

Notes: An exemption from the requirement to submit material may be obtained from the Ministry of Health in the following instances:

- ◆ Exemption from submission of material as listed in Sections 2.3.2.4 (only a summary is necessary) and 2.3.2.9, for recognized medical equipment or a medical device approved for clinical trial use in Israel.
- ◆ Exemption from submission of material as listed in Section 2.3.2.7, for a medical device previously approved for clinical trial use in Israel for the same indication.
- ◆ In cases of modification to a medical device approved for use, as detailed in Section 25 of the "Definitions", and/or a medical device previously approved for clinical trial use, or use of non-approved devices, a description of the modification and of the devices should be provided, and, if applicable, information should be attached in accordance with the entire Section 2.3.2 above.

- 2.3.3 Investigator's brochure – medicinal products containing human living cells and tissues.

The current Investigator's Brochure in accordance with the 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 shall contain the preclinical information required to demonstrate the efficacy and safety of a medicinal product containing human living cells and tissues (hereinafter: the "Product") intended for clinical trial use, and in particular:

- 2.3.3.1 Cover page, including product name, name of study sponsor, edition date and number.

2.3.3.2 Details of the Manufacturer (where the manufacturer is the Investigator, details of the Investigator shall be included): name, address, telephone number, fax number, name of person to contact with regard to clinical trials.

2.3.3.3 Manufacturing site.

2.3.3.4 Specification of the Product, including:

- Biological description of the end product and its specifications and clinical indication
- Source of cells/tissues:
 - Autologous (from self), allogenic (from non-self human source)
 - Description of the original cells/tissue
- Route of administration
- Mechanism of action

2.3.3.5 The technology – overview:

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 photocopies of supporting literature).

2.3.3.6 Process characterization:

2.3.3.6.1 The donor:

- Description of the donor, including gender and age, medical treatment given prior to extraction
- Donor selection
- Screening and testing for pathogenic elements (specifying the laboratories/examiners). The medical history of the donor should be described.

Note:

The applicants shall relate to the standards and instructions of relevant organizations, in accordance with the source of the tissue.

- Description of donor registration process with reference to the possibility of identifying the donor in the event that the recipient develops an infectious disease.
- Registration and storage process of donor serum with reference to the possibility of testing the serum in the event that the recipient develops an infectious disease.

2.3.3.6.2 Source and characterization of materials in the manufacturing process:

- Description and quality of growth substrates and their components.
- Details of the tests carried out to identify infective agents.
- Human or animal components: growth substrates without the above components are preferable.

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

- a) Director of Medicine Circular 45/97 dated November 10, 1997: "Special Requirements for the Import of Whole Blood and its Components".

- b) Director of Medicine Circular 32/98 dated May 7, 1998: "Food Substrates (media used for the growth of material intended for use in humans) produced from living sources or which contain components produced from living sources – duty of 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 one of the circulars is published, the requirements shall be in accordance with the updated version.

2.3.3.6.3 Manufacture

- Description of the ex vivo manipulation (with emphasis on optimization of the conditions to minimize the risk of infection by infective agents and of infections with other types of cells)
- IPC (In Process Controls)
 - Documentation of the in-process procedures and controls
 - Infection tests (microbiology, virology, mycology)
 - Integrity and function test at each stage
- Characterization of the product during development
- Flowchart

2.3.3.6.4 Characterization of the end product

- The objectives
- **Expected** and **relevant** biological activity
- Absence of long-term risks
- Assessment of identity, purity, and potency using appropriate in vitro methods and, if possible, in vivo tests on a suitable model (validation of the animal model is required)
- Quantitative analysis of the number and proportional percentage of active cells
- Stability: test of the phenotypic and genetic characteristics of the cells over time
- Toxicity – upper permissible limit of residues from materials used in the manufacturing process and tissue culture and animal trials, if possible.

2.3.3.6.5 Results of in-vitro model trials

2.3.3.6.6 Results of animal model trials

2.3.3.6.7 Results of previous human trials

2.3.3.6.8 Description of the quality assurance system

Note:

The brochure shall refer to the laws / regulations / director's circulars / standards / guidelines / directives generally accepted in Israel and worldwide, compatibility therewith, and appropriate certificates of compliance therewith shall be attached.

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2.3.4 Investigator's brochure – xenotransplantation:

Instructions for the Investigator's Brochure are detailed in the document "Instructions for the Performance of Xenotransplantation", which can be found at the website specified on page 6 above. Owing to the length of the instructions, they are not specified in these Guidelines.

2.3.5 Investigator's brochure – gene therapy:

The instructions concerning gene therapy medicinal products are described in the EMEA document Note for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products, CPMP/BWP/3088/99.

Owing to the length of the instructions, they are not specified in these Guidelines.

2.4 Certificate of analysis from a recognized laboratory

This certificate is required for clinical trials of non-medicinal products (cosmetic products, food, food supplements, homeopathic products or medicinal herbs) which are not marketed in Israel.

2.5 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 not involving an investigational product; Form 3, a parent/guardian informed consent form for clinical trials in which participants are minors/wards/legal incompetents. Form 3A, 3B and 3C for trials of investigational products, genetic trials and trials not involving investigational products, respectively. In an application for a trial that involves 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 given to the participant about the clinical trial, pursuant to Sections 3.4 and 3.5 below, provided that all the information considered declarative is recorded in detail. The form should be written in standard language which is clear, lucid and understandable to any person and in the language of the participant, where possible.

2.6 Sponsor's statement of commitment (Form 4A for clinical trials of investigational products; Form 4B for genetic trials; Form 4C for clinical trials not involving investigational products):

2.6.1 This statement of commitment shall be signed by the Sponsor and approved by the signature of the Principal Investigator. This statement of commitment shall also be attached to the contract between the Sponsor and the Principal Investigator/medical institution.

2.6.2 In the event of a Sponsor-Investigator, this statement of commitment shall be signed by the Sponsor-Investigator and approved by the signature of the director of the hospital or designee.

- 2.7 Declaration of Sponsor or Sponsor's representative in Israel (Form 5)
- 2.8 Document checklist: before submission of the application to the institutional Ethics Committee, the Principal Investigator shall complete and sign the document checklist (Form 9A, 9B or 9C, depending on the type of trial).
- 2.9 Notice for enrollment of participants (Form 10): if necessary, the Principal Investigator shall attach to the application documents the text of the enrollment notice for clinical trial participants.
- If the Investigator wishes to deviate from this text, he/she must request approval from the Ministry of Health.
- 2.10 Letter to the attending HMO physician (Form 11): if the clinical trial involves the administration of medical tests or provision of devices, products or implants, the Investigator shall complete this form.

General note:

The Ministry of Health / institutional Ethics Committee may each request further documents or data in addition to those stipulated above, if applicable.

3. Informed consent procedure

- 3.1 A clinical trial involving human subjects shall not be conducted unless the Investigator¹ has received informed consent from the clinical trial participant, after the Investigator has given the trial participant an appropriate verbal explanation and the participant has read the informed consent form for the clinical trial. Consent to participate in the clinical trial shall be given in writing, on the informed consent form approved by the Ethics Committee for the specific trial. The informed consent form shall be signed by both the participant and the Investigator. A copy of the signed form shall be given to the participant.
- 3.2 If the participant is a minor, legal incompetent, ward, or cannot provide informed consent for medical treatment and has a legally appointed guardian, or if the participant duly appointed a representative in accordance with Article 16 of the Patient's Rights Law 1996² (hereinafter: the "Legally authorized Representative"), the Investigator shall obtain the consent of the Legally authorized Representative, in addition to, or in place of, the participant's consent. In this case, wherever the word "participant" appears in this section, it shall also refer to such Legally authorized Representative. A family member not appointed as Legally authorized Representative may not consent in place of the participant.
- If the Investigator has any doubt regarding the competence of the participant to provide informed consent and knows that no Legally authorized Representative has been appointed for the participant, the Investigator must obtain an assessment from a psychiatrist/geriatrician who is independent of the study. The populations listed in this section shall not be included in a clinical trial unless their inclusion is essential for improving their health and the trial cannot be conducted in an alternative legally competent population.
- 3.3 In order to obtain informed consent, the Investigator shall provide the participant with information about the clinical trial, in clear language which is understandable to the participant; the Investigator shall take all possible measures to allow the participant to understand the information to the maximum extent, with the aim of obtaining a voluntary independent decision, after due consideration and without coercion or undue influence.

¹ The investigator is the Principal Investigator or a Sub-investigator.

² In certain cases, a power of attorney for medical treatments, in the context of the Patient's Rights Law, may not be sufficient, and a power of attorney for participation in clinical trials may be required.

3.3.1 In the event that the participant is a minor, the Investigator shall also provide the participant with explanations of the clinical trial appropriate to the participant's level of understanding. The minor can sign a form which states that he/she has received an explanation of the trial. The Investigator must take into consideration the wish 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 shall sign an informed consent form. The participant may withdraw, modify or qualify the consent which was previously given by or for him/her when he/she was a minor.

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

3.3.2 In the event that the participant and/or his/her Legally authorized Representative are unable to read the consent form, an independent witness shall be present while the Investigator provides the participant with explanation and shall read to the participant the text of the informed consent form and any other accompanying material. The trial participant and/or his/her Legally authorized Representative shall give verbal confirmation that he/she has understood what has been said and that his/her signature constitutes consent to participate in the trial. Only then will the independent witness sign the consent form, and this signature will confirm that the explanation and reading of the material were done voluntarily by the participant, without coercion or undue influence.

3.4 **Information about the clinical trial, including:**

1. Explanation of the investigational nature of the procedure, the study objective, notification of the anticipated duration of participation in the trial and approximate number of participants in the clinical trial;
2. Description of the various procedures due to be performed during the trial period (treatment and follow-up) with a clear distinction between investigational and standard treatment procedures; statement of the participant's chances of receiving each of the treatments offered in the trial (including placebo, if any).
3. Description of the expected benefits to the participant or to others, as a result of the trial;
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 an unforeseeable risk to the participant;
5. If the clinical trial involves a risk to the participant, an explanation of the medical treatment given if the participant's health condition is adversely affected and of the responsibility for providing such a treatment;
6. Circumstances under which his/her participation in the clinical trial could be discontinued at the decision of the Investigator or Sponsor.
7. In a study involving the administration of medical treatment to the participant:
 - 7.1 Declaration that participation in the clinical trial shall not entail any additional financial cost to the participant beyond the cost of necessary regular treatment;
 - 7.2 Explanation of alternative treatments, their advantages and disadvantages, if any, to the participant.

3.5 In addition, the Investigator shall give the participant the following information:

1. Explanation that participation in the clinical trial is completely voluntary, declaration of the participant's right to refuse to participate in the trial or to discontinue at any stage of the trial, and a declaration that the medical rights of the participants shall not be jeopardized by refusal to participate in or withdrawal from the clinical trial.
2. Where applicable, information on possible medical consequences of the participant's decision to withdraw from the clinical trial before completion thereof.
3. Details on whom to contact at any time of day with any question about the clinical trial, participant rights, and in the event of any health injury as a result of participation in the trial.
4. Explanation to the patient that the information in the patient file, including medical records, will be reviewed only by authorized individuals (e.g. the Ethics Committee, the audit panel of the hospital, the Ministry of Health, representatives of the company responsible for the trial and trial monitoring), while maintaining absolute confidence, and that the patient's identity shall not be disclosed to non-authorized individuals either verbally or in scientific / medical publications.
5. If the clinical trial involves the administration of medical tests or the provision of devices, products or implants, the Investigator shall obtain consent from the participant to send information about his/her participation in the trial to his/her attending physician at the HMO with which he/she is insured.

3.6 The participant shall be advised of any new information that becomes available during the clinical trial which could affect his/her decision to continue in the trial. The trial participants shall sign an updated consent form at the earliest possible opportunity. If new participants are still being enrolled, they shall sign the updated version of the consent form.

3.7 The consent form for genetic trials should particularly address the specific subjects related to genetic trials:

1. How DNA samples will be handled, kept and stored at the end of the trial.
2. Confidentiality of genetic information: personal details and results received from trial participants are information protected by the right of privacy, and it shall be protected in accordance with the provisions of all laws. The investigators shall restrict access to places where medical information and genetic test results of the participant are kept.
No genetic test results will be filed in the medical records of participants.
3. Risks involved in genetic trials: consequences for the participants and his/her family or community of learning of the participant's genetic information, use of the genetic information to the detriment of the participant and/or his/her family.

3.8 Information about the trial, request for informed consent and consent form for participation in the trial shall not contain any instructions or requirements which constitute any kind of waiver by the participant of his/her rights pursuant to any law, or which could exempt the Investigator, Sponsor, medical institution or representatives thereof, from the duty or responsibility imposed on them pursuant to any law or agreement.

3.9 Under special conditions, as set forth below, the Ethics Committee may approve a waiver of the requirement for informed consent:

1. Retrospective study based on unidentified data collected from medical records of patients.
2. In accordance with the Genetic Information Law, in trials using unidentified DNA samples or existing DNA samples from which identifying details have been removed as

to render it impossible to identify them in any way, there is no requirement for completing an informed consent form.

3. Regarding a clinical trial designed to include only participants in medical emergencies, as defined in the Patient's Rights Law 1996, where it is impossible to obtain informed consent from the participant, his/her guardian or legally authorized representative (hereinafter: "Legally Authorized Representative"), and it is reasonable to expect that participation in the proposed trial is more likely to improve the participant's medical condition than other standard treatments, and outweighs the harmful consequences to the participant rights and wellbeing.

In such cases, the Ethics Committee may approve the conduct of clinical study without the requirement for obtaining prior informed consent from the participant or his/her Legally Authorized Representative, provided that all the provisions detailed in the appendix to these Guidelines are met.

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

- ◆ The patient is in a life-threatening condition and currently available treatments do not provide equal or better chances for saving the 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.

- 3.10 In special cases, as set forth below, the Ethics Committee may approve a waiver of the requirement for obtaining a written informed consent:

If the only risk to the clinical trial participant is the disclosure of 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 shall always have the option of choosing to provide informed consent in writing. In any event, the Investigator must document receipt of the patient's verbal consent.

4. Rules for the approval of clinical trial applications

The final approval of any clinical trial shall be granted in accordance with the definitions set forth in the Regulations.

- 4.1 Special clinical trial: The Director of the medical institution shall issue said approval after the Institutional Ethics Committee has approved the clinical trial and determined that it is a special clinical trial.
- 4.2 Non-special clinical trial: The Director of the medical institution shall issue said approval after the institutional Ethics Committee has approved the clinical trial and determined that it is a non-special clinical trial that requires approval by the Ministry of Health, provided that such approval has been granted.

5. Authorities of the Director of a medical institution

The authority of the Director of a medical institution to approve clinical trials is delegated by the Director General of the Ministry of Health. This authority is conditional on full compliance with the requirements set forth in the Guidelines and Regulations, and it may be revoked in the event of failure to comply with these requirements.

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

Special clinical trials:

6.1 Medicinal products (including biological products)

6.1.1 A clinical trial using a medicinal product registered in Israel or authorized for marketing in recognized countries for an approved indication and at the generally accepted dose.

6.1.2 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 to evaluate the safety and efficacy of the product have been completed in a Recognized Country, and their results are reported in the study protocol and its appendices.
- ◆ The clinical trial involves an indication, a dosing form and a route of administration used in previous trials.
- ◆ The clinical trial is not planned to involve a special population.

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

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

6.1.4 A clinical trial, the objective of which is to evaluate the comparative bioavailability of a generic product as opposed to a registered product, or a product approved for marketing in a Recognized Country.

6.2 Medical devices and instruments/medical equipment

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

6.2.2 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 applicable to a device of the same type;
- Previous clinical trials to assess safety in human subjects have been completed in a Recognized Country and their results are reported in the trial protocol and its appendices;
- The clinical trial involves a method of use applied in previous trials;
- The clinical trial does not involve a special population;

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

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

- 6.2.4 The collection of data from adults using recognized non-invasive medical equipment, including weighing, electrocardiography, electroencephalography, thermography, identification of naturally occurring radioactivity, diagnostic echography, electroretinography, ultrasound, MRI test, except for collection of data that requires exposure to ionic radiation.

6.3 Miscellaneous: trials not involving medicinal products or medical devices/medical equipment

- 6.3.1 A clinical trial of a non-medicinal product such as a cosmetic product, food, food supplement, homeopathic product, or medicinal herb, which is approved for marketing in Israel.
- 6.3.2 Collection of blood from a vein in a volume not exceeding 450 ml over a period of 8 weeks, no more than twice a week, from healthy adults (not including pregnant women), except for blood sampling for genetic research.
- 6.3.3 Collection of body fluids, secretions, or non-viable tissues (except hair, nails, teeth) from adults, in the usual way, except those intended for genetic research.
- 6.3.4 Voice recording as generally accepted in speech impairment studies.
- 6.3.5 Mild physical exercise performed by healthy volunteers.
- 6.3.6 A clinical trial performed using existing data, documents, recordings, notes, radiology (e.g. X-rays, ultrasound, etc.) pathological samples or diagnostic samples taken for medical purposes.
- 6.3.7 Collection of information using questionnaires (information directly relating to the state of health, physical or mental, of the participant/patient or to his/her medical treatment).

Special Amendments

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

- 6.4.1 Amendments in clinical trials with valid approvals.
- 6.4.1.1 Amendments which do not significantly increase the probability of risk to the clinical trial participants, do not detract from the scientific value of the study, and do not derogate from the rights, safety, health and wellbeing of study participants, including:
- ◆ Administrative amendments;
 - ◆ Increase in the number of clinical trial participants, if not initially limited by the Ministry of Health (e.g. due to a high rate of withdrawal from the clinical trial which is not the result of the investigational product).
- 6.4.2 Extension of approval validity
- 6.4.2.1 The validity period will be extended after receipt of the requisite report, for example, in the following cases:
- ◆ Clinical trial was initially planned for a period exceeding the validity period of the approval;
 - ◆ Clinical trial initiation date was delayed for technical or logistical reasons;

- ◆ Enrollment of trial participants was slower than expected.

7. Process of handling clinical trial applications or requests for amendments therein

The Principal Investigator shall submit the clinical trial application or request for amendments therein to the institutional Ethics Committee.

The Ethics Committee shall review the clinical trial application or request for amendments therein and decide whether to approve or reject the application. The Ethics Committee shall also decide, based on the criteria and definitions set forth in Section 6 above, whether the Director of the medical institution is authorized to approve the clinical trial or amendment therein, or whether additional approval by the Ministry of Health is required.

As a rule, Ethics Committees must follow a written work procedure. Specifically, all decisions (approvals and rejections) made by the committee shall be reasoned and recorded in writing in the minutes of the meeting. The minutes shall record the decisions concerning both new applications and existing applications with valid approvals (amendments, validity extensions and reports). In respect of applications for trials of investigational products, the minutes should state the name of the investigational product and the name of the manufacturer.

7.1 Handling new applications for special clinical trials by the medical institution

7.1.1 The Ethics Committee shall forward to the director of the medical institution (hereinafter: the "Director") its decisions regarding applications for clinical trials which it has approved and which the Director is authorized to approve without additional approval by the Ministry of Health. The approvals of the institutional Ethics Committee (Form 6) shall be sent to the Director with a copy to the Principal Investigator.

The Director shall issue an approval for the clinical trial to the Principal Investigator, detailing the terms and conditions (Form 7). A copy of the Director's approval shall be sent to the director of the institutional pharmacy (if necessary). The Investigator shall send a copy of the approval to the Sponsor of the trial.

The Investigator may initiate the clinical trial only after receipt of said approval.

7.2 Handling applications for special amendments in clinical trials by the medical institution

7.2.1 The work procedure of the Ethics Committee shall determine which amendments require approval by both the Ethics Committee and the Director of the medical institution, which amendments require approval by the Ethics Committee only, and which amendments should be only reported for information. Furthermore, the committee shall determine which amendments may be approved only by the chairman of the committee and then submitted to the committee for information at its next meeting.

Approval of the chairman of the committee shall be sent to the Investigator on an application form for amendments to a clinical trial (Form 12). The Investigator shall send a copy of the approval to the Sponsor.

7.2.2 The chairman of the Ethics Committee shall send to the Director of the medical institution the committee's decisions regarding trial validity extensions which the director is authorized to approve pursuant to Section 6.4.2. Approval of trial validity extensions shall be granted on Form 6A, which shall state the current versions and dates of the application documents.

Pursuant to this approval, the Director shall send the Principle Investigator a validity extension approval for the clinical trial, detailing the terms and conditions (Form 7A). A copy of the director's approval shall be sent to the Director of the institutional pharmacy (if necessary). The Investigator shall send a copy of the approval to the Sponsor.

- 7.2.3 The Chairman of the Ethics Committee shall inform the Ministry of Health of any validity extension / study completion. The Investigator's report to the Ethics Committee shall be attached to such notifications.

The report is a control tool for the Ethics Committee and the Ministry of Health. The reports received by the Ministry of Health are updated in the computer records of valid clinical trials.

7.3 Handling new applications for non-special clinical trials and non-special amendments by the medical institution:

After each meeting of the Ethics Committee the committee secretariat shall send the following documents to the Ministry of Health:

- a) Full minutes of the meeting

The minutes shall be sent to the Clinical Trials Section and to the National Coordinator for Clinical Trials of Medical Devices in the Pharmaceutical Administration.

- b) Applications for clinical trials that require additional approval by the Ministry of Health, including Ethics Committee approvals (Form 6) for these applications:

- **Applications** for clinical trials of **medical devices** and clinical procedures as well as applications for trials of products containing **living cells and tissues** shall be sent in **5 copies** to the National Coordinator for Clinical Trials of Medical Devices.
- **Applications** for **genetic** trials and **in vitro fertilization** trials shall be sent in **13 copies** to the Clinical Trials Section.
- **All other applications** for clinical trials shall be sent in **1 copy** to the Clinical Trials Section in the Pharmaceutical Administration.

- c) Non-special amendments.

- d) Reports listed in Section 7.2.3 above.*

*The amendments and reports shall be sent to the relevant sections, depending on trial type.

7.4 Handling new applications for non-special clinical trials by the Ministry of Health

7.4.1 Receipt of minutes of the Ethics Committee meeting

The Ministry of Health shall inform the chairman of the Ethics Committee in writing about the date of receipt of minutes. All applications included in the minutes and approved by the committee are entered into a computer and assigned an application number. A list of these applications is sent to the Ethics Committee secretariat.

All future communications with the Ministry of Health (in respect of protocol amendments, extension of approval validity, reports, etc.) must state this number. Reports, amendments and validity extensions included in the minutes are entered into the computerized clinical trial database but no separate notice is sent.

7.4.2 Process of handling new applications

The Ministry of Health reviews the applications and decides to handle the applications in one of three ways:

7.4.2.1 Granting approval for the clinical trial

The Ministry of Health will send an approval (Form 8) to the chairman of the Ethics Committee and a copy will be sent to the Director of the medical institution. The Director shall send the Principle Investigator an approval for the clinical trial, detailing the terms and conditions (Form 7). The Investigator shall send a copy of the approval to the Sponsor and to the director of the institutional pharmacy (if necessary).

The Investigator may initiate the clinical trial only after receipt of said approval.

7.4.2.2 Sending the application for expert opinion:

A notice shall be sent to the chairman of the Ethics Committee who shall inform the Investigator. The notice shall include details of the documents or data required for continued processing of the application.

If the experts recommend approval of the application, the Ministry of Health shall send an approval as set forth in Section 7.4.2.1 above. If a recommendation to approve the trial is not made, the application shall be sent for discussion at the Central Committee for Clinical Trials.

7.4.2.3 Sending the application for discussion at the Central Committee for Clinical Trials or at the National Ethics Committee¹:

A notice shall be sent to the chairman of the Ethics Committee who shall inform the Investigator. The notice shall include details of the documents or data required for continued processing of the application.

The Central Committee for Clinical Trials and the National Ethics Committee of the Ministry of Health convene every 6-8 weeks to discuss applications for which all the applicable material was received up to 2-3 weeks before the discussion date.

After the discussion in the committee and receipt of its recommendations and decisions, the Ministry of Health shall send the decision to the chairman of the Ethics Committee who shall inform the Investigator.

- If it is decided to approve the application, approval shall be granted pursuant to Section 7.4.2.1 above.
- If additional information is required for a further discussion of the application, the process described in Section 7.4.2.3 shall be repeated.
- If it is decided not to approve the application, a reasoned reply shall be sent. In the event of an appeal of the decision of the Central Committee or the National Committee, an opportunity shall be granted to the Investigator to make his/her arguments to the committee. This shall be after the Investigator sends them in writing to the Ministry of Health.

7.4.3 Timetable for handling applications

¹ In addition to the subjects discussed by the National Committee (as set forth in Section 6 of the Definitions), the committee advises the Minister of Health on subjects included in the Prohibition of Genetic Intervention Law (Human Cloning and Genetic Modification of Reproductive Cells), 1999. Pursuant to Article 5 of this law, the Minister may, under certain conditions, permit in the regulations implementation of actions using reproductive cells which have deliberately undergone permanent genetic modification with the aim of creating a human being, such actions being prohibited under Article 3 (2) of the law. This was recommended by the National Committee.

The timetables are currently being reviewed by the Ministry of Health. A detailed notice regarding this matter shall be sent separately within 90 days of release of these Guidelines.

7.5 Handling applications for non-special amendments by the Ministry of Health

The chairman of the Ethics Committee shall send to the Ministry of Health any applications for amendments in a clinical trial which are not specified in Section 6.4 above. The time to process the request for amendment shall be determined as applicable, but shall not exceed the timetable for handling new applications, as set forth in Section 7.4.3 above.

7.6 Multicenter trials in Israel

The trial Sponsor shall inform the Ministry of Health of its intention to conduct a multicenter clinical trial in Israel, upon receipt of approval for the trial from the Ethics Committee in at least one of the medical centers planned to participate in the trial.

The notice shall include the following details:

- Study title
- Protocol number and date
- Names of the medical institutions (planned to participate in the study)
- Names of the Principal Investigators (planned to participate in the study)
- Date of approval by the Institutional Ethics Committee (of the first institution, at least) plus the committee's decision in respect of classification of the trial as a special/non-special trial.

After an application for a multicenter trial has been approved in one of the above processes, and after the approval has been sent to the Ethics Committee of one medical center and to the Sponsor, the Sponsor shall inform the other medical centers planned to participate in the trial that approval was granted by the Ministry of Health.

The Ethics Committee in each of the remaining centers shall discuss the application. If the application is approved by the Ethics Committee, there is no need to resend it for approval by the Ministry of Health, and the Director of the medical institution may issue an approval for the trial.

8. Single-patient access to investigational treatment

Single-patient access to investigational treatment refers to the administration of an innovative investigational product not yet registered in any country worldwide, regardless of whether data on such investigational product have been published in the professional literature based on previous clinical trials. This is in the settings of emergency life-saving or compassionate use.

The content of an application for a single-patient access to investigational treatment is set forth in the table in Section 21 of these Guidelines.

The application shall be submitted to the chairman of the Ethics Committee, who shall determine whether such an application shall be approved by him/her in an expedited process or handled by the committee. Then the application shall be sent for final approval to the Pharmaceutical Administration of the Ministry of Health, to the pharmacist responsible for approval pursuant to Regulation 29 A (3) of the Pharmaceutical Regulations.

At the completion of the investigational treatment, in accordance with the treatment protocol, the Investigator shall send a report to the institutional Ethics Committee which shall forward it to the Pharmaceutical Administration.

9. Clinical trial agreement

Every contractual agreement between a Sponsor and a Principal Investigator conducting a clinical trial requires approval by the Committee for Contracts with Commercial Companies and by the Director of the medical institution in which the trial is conducted or designee thereof appointed for this purpose, such as the director of the institutional research fund. Approval by the director of the institution, as mentioned above, is also required for any contract between a Sponsor or representative thereof and a Principal Investigator or any other Investigator who is taking part in and affiliated (as defined above) with the clinical trial.

The Principal Investigator and any other Investigator taking part in a clinical trial conducted in a medical institution must be granted prior approval by the Director of the medical institution or designee appointed for this purpose, for any remuneration to be received either directly or indirectly related to the clinical trial. Failure to obtain such approval constitutes a deviation from these Guidelines.

All the instructions of the Service Regulations in respect of contracts with commercial companies apply to such an agreement.

9.1 The agreement shall include, inter alia, the following details:

- 9.1.1 Names of all the parties signing the agreement, including the Principal Investigator, the Sponsor and/or representative thereof and the medical institution or the institutional research fund;
- 9.1.2 The clinical trial protocol, number and date of the protocol, and dates of any protocol amendments;
- 9.1.3 Statement of commitment by the Principal Investigator to conduct the clinical trial in compliance with the ICH-GCP (and/or ISO 14155 for trials of medical devices) and the requirements of the Ministry of Health Guidelines;
- 9.1.4 Approximate number of participants, budget of the clinical trial and payment dates;
- 9.1.5 Name of the medical institution's business unit or research fund to which the payments should be made;
- 9.1.6 Statement of commitment by the Sponsor of the clinical trial to take out the appropriate medical insurance, including insurance against third-party claims resulting from the clinical trial (see Appendix 2 – section entitled "Insurance in contracts with commercial entities to conduct clinical trials in government hospitals");
- 9.1.7 Statement of commitment by the Principal Investigator and the medical institution to cooperate fairly and appropriately with the Sponsor in the event of a legal claim relating to the conduct of the trial;
- 9.1.8 Statement of commitment by the Sponsor not to refer directly and/or indirectly in commercial publications to the name of the institution conducting the clinical trial and/or to the name of any employee of the institution conducting the clinical trial and/or to the trial results, and not to use their names as recommendations for the quality of the investigational product and/or medical device;
- 9.1.9 Each agreement shall be accompanied by a Sponsor's statement of commitment (Form 4); the text of the statement shall comply with the requirements of the guidelines for contracts with commercial companies.

9.2 The Director of the medical institution must ensure that there is no conflict of interest in conducting the trial at the medical institution between the commercial company and the Investigator, employee of the medical institution.

Note:

In trials where the Sponsor is a Sponsor-Investigator, he/she must present to the Director of the medical institution or designee appointed for this purpose, an estimate of the cost of the trial and information regarding the sources of finance, and must obtain consent from the medical institution to insure the trial participants and the study staff involved in the clinical trial.

10. Advertisement publications

No information about the clinical trial shall be published in the media or in any other way (except for professional scientific journals, with consent of the parties involved) for purposes other than enrollment of participants. The text of a standard advertisement for enrolment of healthy volunteers and patients can be found in Form 10. Where a different text is required, approval must be obtained from the Ministry of Health. Under the directive set forth in Director General Circular 32/05 dated September 4, 2005, controlled prospective clinical trials must be registered at the NIH website, <http://www.clinicaltrials.gov>.

11. Labeling of investigational products for clinical trials

The principles of labeling investigational products are stated in the instructions of the international guidelines. Packages of investigational products given to patients in clinical trials must also be labeled with the following:

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

Note:

Medicinal products registered in Israel and used in studies shall be labeled “For clinical trial use only” featuring some identification details for the trial. This is all in addition to the standard labeling according to the Pharmacist's Regulations (Medicinal Products) 1986.

12. Import of an investigational product for a clinical trial

12.1 Every application to the Ministry of Health for approval of import of an investigational product shipment for a clinical trial should include the import documents (order/proforma invoice/supplier's invoice), and approval by the Director of the medical institution for the trial (Form 7).

* In trials where the informed consent form is written in languages other than Hebrew and English, the indication “For investigational treatment only” or “For clinical trial use only” must also be added in the other languages.

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- 12.2 If the approval has expired before the clinical trial has been completed, the Investigator shall endeavor to provide the agencies handling the import of the investigational product with a valid approval by the Director of the medical institution for the trial.
- 12.3 In special cases, the importer may obtain an import permit before all the conditions mentioned in Sections 12.1 and 12.2 have been met. To this end, the importer must contact the Ministry of Health in writing, attach a valid approval by the Ethics Committee, and undertake that:
- a) Medicinal products for the trial shall be stored in the importer's pharmaceutical point of sale or in the institutional pharmacy. Other non-medicinal devices / investigational products shall be kept by the importer.
 - b) Investigational products shall not be distributed and shall not be used before the Director of the medical institution has approved the study.
 - c) The importer is aware that these actions do not guarantee that the Ministry of Health will approve the clinical trial;
 - d) In the event that the trial is not approved, the importer shall be responsible for returning the investigational products to the overseas supplier or destroy them.

13. Supply of an investigational product for a 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 / medical institution are responsible for storing and dispensing the investigational product to the patients.

Medicinal products shall be supplied, stored and dispensed by the institutional pharmacy unless otherwise decided by the Ethics Committee.

14. Amendments to application documents

Any modification to the content of the clinical trial application documents shall be submitted by the Investigator to the institutional Ethics Committee with indication of the date of amendment and with the amended documents attached.

Amendments are handled by the Ethics Committee as set forth in Section 7.2 above.

Applications for amendments to clinical trials should be submitted on Form 12.

15. Reports

Reports are intended to enable ongoing control of the course of the trial until completion by all the parties involved in trial conduct and approval.

15.1 Safety reports on serious adverse events (SAEs) occurring during a clinical trial

15.1.1 At the responsibility of the Investigator:

Note:

The requirements set forth below are added to the obligation of reporting to the trial Sponsor, as stipulated in the clinical trial protocol and in accordance with international guidelines.

15.1.1.1 Death:

The Principal Investigator shall report immediately, within 48 hours of actual knowledge of the event, to the chairman of the Institutional Ethics Committee and to the Director of the medical institution.

The Investigator shall issue the report on the Sponsor's report form or on Form 13.

(The note at the end of Section 15.1.2.1 is also applicable to the Investigator's liability).

15.1.1.2 Other SAEs

The Investigator shall report immediately, within 48 hours of actual knowledge of the event, to the chairman of the Institutional Ethics Committee, provided that the SAE is unexpected and that a connection between the event and use of the investigational product cannot be excluded.

The Investigator shall issue the report on the Sponsor's report form or on Form 13.

15.1.1.3 Malfunction in the investigational medical device:

The Investigator shall report immediately, within 48 hours of actual knowledge of the event, to the chairman of the Institutional Ethics Committee regarding any malfunction in a medical device/instrument that can compromise the safety and efficacy of the medical device.

The Investigator shall issue the report on the Sponsor's report form or on Form 13.

15.1.1.4 Safety reports received from the Sponsor:

Upon receipt of reports from the Sponsor, the Investigator shall send them to the Ethics Committee. The reports shall contain information on any unexpected SAEs that occurred at the Investigator's site or at other sites in Israel or overseas, where a connection between these events and use of the investigational product cannot be excluded.

15.1.2 At the responsibility of the medical institution / Institutional Ethics Committee

15.1.2.1 Death:

Once informed of a death, the chairman of the Ethics Committee shall immediately investigate the event. If the chairman concludes that the death is not at all related to use of the investigational product and/or the patient's participation in the trial, he/she shall report the event and his/her conclusion to the Ethics Committee and to the Ministry of Health, within 30 days of actual knowledge of the event.

If the chairman concludes that it is impossible to exclude a connection between the death and use of the investigational product and/or the patient's participation in the trial, he/she shall immediately inform the Director of the medical institution that an enquiry team must be established. The team shall discuss the occurrence within 14 days of the Director's actual knowledge of the event, and shall decide whether there is a connection between the event and use of the investigational product and/or participation in the trial.

If it is decided that there is a connection, the team shall also decide whether it is possible to continue with the trial, whether it should be

discontinued (no enrollment of new patients), or whether a recommendation should be made to the Ethics Committee to discontinue the trial.

The team shall report its conclusions and decisions to the Director of the medical institution, the Investigator and the Ethics Committee.

If it is decided to discontinue or to recommend discontinuation of the trial, the chairman of the Ethics Committee (or designee) shall send the Investigator a written instruction to discontinue the trial. This decision of the enquiry team shall be discussed by the institutional Ethics Committee at its next meeting, and the committee shall decide whether or not to accept this decision.

The discussion and decision of the Ethics Committee shall be documented in the minutes of the meeting, as customary.

The Ethics Committee shall report to the Director of the medical institution and to the Ministry of Health on the results of the discussion of the enquiry team and the committee's decisions on Form 14. Appropriate notice shall also be sent to the Investigator.

Note:

This requirement is applicable to clinical trials sponsored by a Principal Investigator at a medical institution or sponsored by another Sponsor, such as a commercial company, corporation, institution, etc.

15.1.2.2 Other SAEs

The Ethics Committee shall receive follow-up reports from the Investigator concerning the continued treatment given to the patient following the SAE, and discuss the case.

The Ethics Committee shall discuss the reports and their implications on the safety of the trial participants and shall note them in the minutes of the committee's meeting.

The Ethics Committee shall send the reports, updates and its conclusions to the Ministry of Health, including conclusions on possible connection between the event and the person's participation in the clinical trial, within 30 days or with the minutes of its next meeting.

15.1.2.3 Safety reports received from the Sponsor:

The Ethics Committee is exempt from sending these reports to the Ministry of Health since it is the responsibility of the Sponsor, as set forth in Section 15.1.3 below.

15.1.2.4 Any notice of discontinuation of a study at a medical institution shall be sent by the Ethics Committee to the Ministry of Health within 7 days of the committee's decision to discontinue the study or of receipt of discontinuation notice from the Investigator, with a statement of the reason for discontinuation.

Note:

When a special clinical trial which did not require approval by the Ministry of Health is discontinued because of an SAE, the Ethics Committee shall also send all clinical trial application documents to the Ministry of Health. This information shall be used to draw conclusions.

15.1.3 At the responsibility of Sponsor

- 15.1.3.1 The Sponsor is responsible for the ongoing safety assessment of the investigational products.
- 15.1.3.2 The Sponsor shall inform all the parties involved in the conduct and approval of the trial, i.e. the Investigators, Ethics Committees and the Ministry of Health, of findings that may affect the safety of trial participants, or findings which have implications on the method of trial conduct, or findings that may affect the decision of the parties that approved the trial.
- 15.1.3.3 As a rule, the Sponsor shall report to the Ministry of Health, the Investigators and all the parties involved in the trial in accordance with the ICH-GCP directives, and in particular of:

Unexpected SADR or SADE occurring in sites in Israel, according to the following timetable:

- A. Cases of death or life-threatening events shall be reported within 7 days of the Sponsor's actual knowledge of the event.
- B. All other events shall be reported within 15 days of the Sponsor's actual knowledge of the event.
- Investigator's Brochure Safety Addenda. The addenda shall be sent to the Ministry of Health once included in the Investigator's Brochure.
 - Conclusions of the Independent Data Safety Monitoring Board concerning protocol amendments and continuation or discontinuation of a trial. The conclusions shall be sent to the Ministry of Health within 7 days of the Sponsor's actual knowledge of the conclusions.
 - Any notice of discontinuation of the clinical trial for any reason must be sent within 7 days of the decision.

- 15.1.3.4 The Sponsor is **exempt** from sending the Ministry of Health reports of unexpected SADRs or SADEs occurring at **overseas sites** participating in a trial protocol also being conducted in Israel, or in other trial protocols with the same investigational product, which are only being conducted at overseas sites.

15.2 Interim report / extension of trial validity

Two months prior to the end of the period approved for a clinical trial, the Principal Investigator shall act to extend the validity of the approval, if necessary, as follows:

The Investigator shall submit to the institutional Ethics Committee a **progress report** of the clinical trial, to include the following:

- Date of report;
- Date and validity of approval by Director of the medical institution for the clinical trial;
- Application number or approval number in the Ministry of Health;
- Investigator name and department;
- Names of the additional investigators taking part in the trial;
- Subject of the clinical trial;

- Protocol number and date;
- Version and date of informed consent form;
- Number of participants enrolled in the clinical trial;
- Number of participants withdrawn from the clinical trial, and the reasons therefor;
- Number of participants who discontinued from the clinical trial, and the reasons therefor;
- Details of adverse events observed;
- Treatment outcomes (if possible);
- Approximate date of completion of patient enrollment and/or trial completion;
- Reason for request to extend validity of the clinical trial;

In addition, if necessary, the Investigator shall note the amendments made in the application documents throughout the year. After the Ethics Committee approves the extension of validity for a clinical trial (on Form 6A), the approval shall be sent to the Director of the medical institution for approval pursuant to Section 7.2.2, or to the Ministry of Health for additional approval, in cases other than those mentioned above.

Approval by the Director of the medical institution to extend the validity of the trial (Form 7A) shall be sent to the Principal Investigator. The Investigator shall send a copy of the approval to the Sponsor.

If approval by the Ministry of Health is required to extend the validity of the trial, the approval (Form 8A) shall be sent to the chairman of the Institutional Ethics Committee, with a copy to the Director of the medical institution, who shall issue an approval to extend the validity of the trial (Form 7A), as set forth above.

An investigator who does not fulfill his/her obligation to submit a progress report on the above-mentioned date, where the trial has not yet concluded, shall be obliged to submit an application to renew the trial in the form of a new application.

15.3 Report on the completion of a clinical trial

Upon completion of a clinical trial, the Investigator shall submit to the institutional Ethics Committee a trial **completion report**, to include the following:

- Date of report;
- Date of approval of the clinical trial by the Director of the medical institution (if the validity period of the trial has previously been extended, the extension dates should be stated);
- Application number or approval number in the Ministry of Health;
- Name and department of Investigator;
- Subject of the clinical trial;
- Number and date of protocol (if available)
- Version and date of informed consent form;
- Number of participants enrolled in the clinical trial;
- Number of participants withdrawn from the clinical trial, and reasons therefor;
- Number of participants who discontinued from the clinical trial, and reasons therefor;
- Details of adverse events observed;

- Results of the clinical trial to date (if available);
- Date of completion of the clinical trial;
- Report on the collection / destruction of all investigational products (as applicable);
- Details about the duration and site of trial document retention.

15.3.1 The Ethics Committee shall forward the reports to the Ministry of Health together with the minutes of the meeting, as set forth in Section 7.2.3 above.

After final processing of the clinical trial results, the trial Sponsor shall send the results or a copy of the article (if published) to the Ministry of Health. This applies to applications requiring approval by the Ministry of Health.

15.4 Annual report

The Director of the medical institution shall send an annual report to the Ministry of Health describing completed/ongoing clinical trials conducted at his/her institution. The report shall be made on a report form (Form 15). Report date: last date of the fiscal year, and no later than three months after this date.

At the request of the Ministry of Health, the Ethics Committee shall send information and/or documents pertaining to certain trials specified on Form 15.

The reports shall be used as a control tool for the Ministry of Health to evaluate the extent to which the decisions of the Ethics Committee and the application approval process comply with the rules set forth in the Guidelines.

Note:

The Director of the medical institution may be exempted from sending an annual report to the Ministry of Health if the Ethics Committee has sent the full minutes of all the meetings which have taken place throughout the year, as they occurred. The exemption shall be granted by the Ministry of Health at the Director's request.

16. Completion or discontinuation of a clinical trial

16.1 Notice of completion/discontinuation of a clinical trial shall include:

- ◆ Name of the investigational product;
- ◆ Name of the manufacturer;
- ◆ Name of the Investigator and medical institution;
- ◆ Subject of the study and protocol number;
- ◆ Date of approval by the Director;
- ◆ Reason for discontinuation of the clinical trial;
- ◆ Method of discontinuation and recall of the investigational product;
- ◆ Patient follow-up plan.

16.2 Notification procedure

Notice of completion/discontinuation of a clinical trial shall be sent to all the parties involved in the approval and management of the trial.

For the discontinuation of a special clinical trial, there is no need to inform the Ministry of Health, except in those cases where the trial is discontinued for special safety reasons, such as SAEs.

16.2.1 Discontinuation by the Sponsor or planned termination:

The Sponsor shall inform the Investigator and the Ministry of Health, the section for clinical trials of drugs or medical devices, as appropriate. The Investigator shall inform the chairman of the Ethics Committee at his/her institution.

The Ethics Committee shall inform the management of the medical institution and the institutional pharmacy (if necessary, in trials of medicinal products).

16.2.2 Discontinuation by the Investigator:

The Investigator shall inform the Sponsor and the Ethics Committee.

The Ethics Committee shall inform the management of the medical institution, the institutional pharmacy (if necessary, in trials of medicinal products) and the Ministry of Health.

16.2.3 Discontinuation by the institutional Ethics Committee:

The chairman of the Ethics committee shall inform the Investigator, the Sponsor, the management of the medical institution, the institutional pharmacy if necessary, and the Ministry of Health.

16.2.4 Discontinuation by the Ministry of Health:

The Ministry of Health shall inform the Director of the medical institution, the chairman of the institutional Ethics Committee, the Sponsor, the Investigator, and, if necessary, the institutional pharmacy.

16.3 Collection/recall/destruction of investigational products (for medical devices – only if relevant) used in a clinical trial which was completed or discontinued:

The study Sponsor must ensure that investigational products are discontinued and collected/recalled/destroyed, when a clinical trial is completed or discontinued. Investigational products shall be collected/recalled/destroyed in accordance with the Sponsor's Standard Operating Procedures (SOP).

16.4 Reporting:

Following the collection/recall/destruction of the investigational product, the Sponsor shall report to the institutional Ethics Committee, with a copy to the Ministry of Health.

The report shall include:

- Identifying details of the clinical trial as per Section 16.1, including trial initiation date.
- Date of notice of discontinuation of the clinical trial, and the reasons therefor.
- Details of the quantities of the investigational product/medical device (as applicable) distributed in said medical institution; how many were used in the clinical trial and how many were returned. In the case of a medical device intended for repeated use – number of times used.
- Summary report of the course of the clinical trial up to discontinuation thereof as set forth in Section 15.3.

17. Continued provision of investigational product after completion of the clinical trial

- 17.1 If it transpires after completion of a clinical trial and is recommended by the Principal Investigator that the wellbeing of the patient participating in the trial requires continued treatment with the investigational product and no other alternative treatment is appropriate for him/her, the patient shall continue to receive the investigational product free of charge in accordance with a written structured follow-up protocol, even after completion of the clinical trial, for a period not exceeding 3 years, except in one of the following instances:
- 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 insured¹.
 - B. Development of the product was discontinued or the clinical trials of the product were not successful.
 - C. Administration of the investigational product for such a prolonged period of time may jeopardize the patient's health due to insufficient information about the long-term safety of the product.
 - D. When the investigational product is not a medicinal product, such as a cosmetic product / food / food supplement / medicinal herb.
- 17.2 The decision on continued provision of the investigational product is made by the institutional Ethics Committee, which may reconsider its decision periodically. The Principal Investigator and Sponsor have the right to appeal this decision to the Director General of the Ministry of Health or designee appointed for this purpose.

Note:

If the trial is sponsored by the Principal Investigator and is not at all financed by a commercial company, the Ethics Committee may exempt the Investigator from the obligation to continue providing the investigational product after completion of the trial. This is provided that the Investigator will contact the Ethics Committee in writing and explain his/her reasons for requesting an exemption. The committee shall report its decision to the Ministry of Health in the minutes of the meeting.

- 17.3 Continued provision of investigational product after completion of the clinical trial is subject to the following conditions:
- 17.3.1 Continued treatment shall be governed by a structured follow-up protocol to be written by the Principal Investigator and approved by the Sponsor and the Institutional Ethics Committee.
 - 17.3.2 Continued treatment shall be provided to the participant after approval by the Director of the medical institution, as is customary with clinical trial applications.
 - 17.3.3 The Principal Investigator is responsible for the ongoing monitoring of the patient's health condition and for reporting to the Ethics Committee on any

¹ Clarification: this is either under the National List of Health Services ("the Health Basket) or the supplementary insurance, provided that excess insurance does not exceed the sums approved in the HMO collection plans.

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adverse events occurring during the follow-up treatment, as generally accepted in clinical trials.

17.3.4 The Principal Investigator shall report to the Ethics Committee at least once a year on the progress of the patient's treatment.

17.3.5 The medical institution in which continued treatment is being provided shall take out appropriate insurance to cover the liability of the medical institution and the Principal Investigator towards the patient in the settings of continued provision of the investigational product after completion of the clinical trial.

18. Supervision of clinical trials

18.1 Supervision by the Ethics Committee:

The institutional Ethics Committee is responsible for supervising the clinical trials approved by it and by the director of the hospital. The committee shall receive periodic reports from the investigators responsible for the trials, at least once a year. In trials where the committee believes that participants are at high risk, the committee shall require more frequent reports, as applicable.

The committee shall also receive regular reports of adverse events occurring during the trial and shall discuss these events.

The committee shall follow-up on the investigators' reports, contact the Investigator about 2 months before completion of the trial, and remind the investigator that he/she must submit a progress report or a trial completion report to the committee, as applicable. The Ethics Committee shall discuss the findings of the reviews performed by the audit panel, as set forth in Section 18.2 hereunder, and shall report on them to the Ministry of Health once every 6 months.

18.2 Supervision by the medical institution:

The management of the medical institution or designee thereof must appoint an audit panel to review and monitor the clinical trials approved at the institution. The composition of the audit panel and validity of the appointment are detailed in Director General Circular 7/05 dated March 6, 2005. The duty of the audit panel is to review actual compliance with the approved trial plan. The audit panel shall report every 6 months on its activities and findings to the management of the medical institution and to the Ethics Committee.

18.3 Supervision by the Ministry of Health:

The Ministry of Health shall supervise the medical institutions (by carrying out sample reviews) and evaluate, inter alia, the actual compliance of clinical trials with the approved protocols, the provisions of the law and the Guidelines of the Ministry of Health.

19. Document retention

All entities involved in the sponsoring, approval, conduct, and control of a clinical trial are required to keep the trial documents, as detailed hereunder

19.1 The institutional Ethics Committee/Director of the medical institution shall keep the following documents for at least 7 years from the completion of the clinical trial:

- Standard operating procedures (regulations) of the committee;
- List of committee members who reviewed the application for approval of the clinical trial;

- Documents submitted for review;
- Minutes of the meetings;
- Correspondence;
- Decisions of the Director;

19.2 The Sponsor/Principal Investigator shall keep all the application documents, including the documents submitted to the Ethics Committee for approval, and all the documents obtained during the clinical trial, for at least 15 years from the completion of the trial.

19.3 The pharmacy shall keep the approval for the clinical trial, the import permits (if the pharmacy is an importer), or the acknowledgment of receipt of goods, as well as documents relevant to the dispensing of drugs in a certain trial, for at least 7 years from the completion of the trial.

Note:

At the end of the retention period, the medical institution can arrange with the Sponsors for continued retention at the Sponsors' facilities. Clinical trial documents in possession of the medical institution shall not be destroyed without prior arrangement with the Sponsor.

20. Service fees

The Director of the medical institution shall collect from the Sponsor, as defined in these Guidelines, service fees for the handling of applications for approval of clinical trials in human subjects in his/her center. The medical institution shall collect a sum that shall not exceed \$1,000, where the service fees for the handling of non-special trials using an investigational product are shared equally by the medical institution and the Ministry of Health. For any change or addition to the approval for the clinical trial, a fee of \$200 shall be collected accordingly.

21. Required submission package for clinical trial applications

Trial type \ Documents	Trial of an investigational product – medicinal product	Trial of an investigational product – medical device	Trial of an investigational product – cells and tissues	Genetic trial ¹	Trial not involving an investigational product	Single-patient access to investigational treatment
Application form	1A	1 B	1C	1D	1E	Letter to the committee ²
Trial protocol	√	√	√	√	√	√
Investigator's brochure ³	√	√	√			
Relevant literature ⁴	√	√	√	√	√	√

¹ More details on the information required for genetic trials can be found in the **Instructions for investigators and forms for submitting applications for the approval of genetic studies in human subjects, 2005**. These instructions can be found at the website of the Pharmaceutical Administration

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

³ Cases where the requirement for submission of an 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 an Investigator's Brochure is not required, relevant current articles regarding the study subject must be submitted.

Trial type \ Documents	Trial of an investigational product – medicinal product	Trial of an investigational product – medical device	Trial of an investigational product – cells and tissues	Genetic trial ¹	Trial not involving an investigational product	Single-patient access to investigational treatment
Consent form - Participant - Guardian	- 2A - 3A	- 2A - 3A	- 2A - 3A	- 2B - 3B	- 2C - 3C	√
Sponsor's statement of commitment	4A	4A	4A	4B	4C	
Sponsor's declaration regarding authenticity of the documents	5	5	5	5	5	
Letter to attending HMO physician	11	11	11			
Document checklist	9	9	9	9	9	
Notice for enrolment of participants ⁵	10	10	10	10	10	

Note:

Please read the explanations before completing the forms.

22. Additional forms for use after approval of the trial

Form 6 - Approval of the institutional Ethics Committee to conduct a clinical trial in human subjects

Form 6A - Approval of the institutional Ethics Committee to extend the validity of approval 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 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 a notice for the enrollment of clinical trial participants, for publication in the mass media

Form 12 - Application form for amendments to a clinical trial in human subjects

Form 13 - Investigator form for notification of an SAE that occurred to a clinical trial participant

Form 14 - Form for notification of death of a clinical trial participant – event enquiry report and conclusions of the Ethics Committee

Form 15 - Annual report of clinical trials in human subjects approved by the Director of the medical institution

Note:

Please read the explanations before completing the forms.

⁵ This form shall be submitted if necessary.

23. Applicability

These Guidelines are valid from April 1, 2006.

24. Update

These Guidelines cancel and supersede the previous guidelines from September 1999.

25. Applicable documents

- 25.1 Public Health Regulations (Clinical Trials in human Subjects) 1980, including amendments and additions thereto until 1999.
- 25.2 ICH-GCP (E6): Harmonized Tripartite Guideline for Good Clinical Practice, 1996.
- 25.3 ISO 14155-1, 14155-2: Clinical Investigation of Medical Devices for Human Subjects (2003)
- 25.4 Notes for Guidance on the Quality, Preclinical and Clinical Aspects of Gene Transfer Medicinal Products, CPMP/BWP/3088/99
- 25.5 Points to Consider on the Manufacture and Quality Control of Human Somatic Cell Therapy Medicinal Products published by published by the EMEA CPMP on 31.5.2001. (<http://www.emea.eu.int/>)
- 25.6 Genetic Information Law, 1999.
- 25.7 Ethics Committee Instructions for Genetic Trials, 2005.
- 25.8 Prohibition of Genetic Intervention Law – (Human Cloning and Genetic Modification of Reproductive Cells), 1999.
- 25.9 Patient's Rights Law, 1996.
- 25.10 Pharmaceutical Regulations (Medicinal Products), 1986.
- 25.11 Director General Circular (Instructions for the Sterilization of Medical Devices and Instruments), 1999.
- 25.12 Director General Circular “Xenotransplantation”, 2000.
- 25.13 Director General Circular on living cells and tissues, 2001.
- 25.14 Ministry of Health guidelines governing contracts with commercial companies, 2004
- 25.15 Director General Circular “Supervision and Control of Clinical Trials in Medical Institutions in Israel”, 2005
- 25.16 Director Consent Conditions, Publications Gazette, 1999, Page 1.
- 25.17 Director General Circular “Registration of Clinical Trials in the NIH Database”, 2005.

26. Circulation

- Director General
- Medical Deputy Director General and Director of the Medical Division
- Head of the Medical Technologies and Infrastructures Administration
- Legal Advisor

- Head of the Medical Administration
- Director of the Pharmaceutical Administration
- Director of the Medical Device Unit
- Directors of the Medical Institutions
- Chairmen of the Ethics Committees
- Members of the Central Committees for Clinical Trials and members of the National Ethics Committee

Written by: Dr Mina Arinos Mgr. Hannah Billig Ester Kats, M.Sc.	Positions: National Coordinators for Clinical Trials	Signatures: Date:
Reviewed by: Mgr. Batya Haran	Position: Head of Pharmaceutical Administration	Signature: Date:
Approved by: Prof Avi Israeli	Position: Director General	Signature: Date:

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Appendix 1 – Waiver of requirement for informed consent for a clinical trial in a medical emergency

The Ethics Committee is authorized to approve the conduct of a clinical trial without the requirement to obtain informed consent from each study participant, provided that all the following conditions are met:

1. The patient has an immediate life-threatening condition or is at immediate risk of severe, irreversible disability;

Currently available treatments do not provide an equal or better chances for saving the life of the patient and it is important to determine the safety and efficacy of the treatment in this patient population; the clinical trial may not be conducted without a waiver of the requirement to obtain prior informed consent from each participant.
2. Participation in the clinical trial guarantees direct benefit to the patient because:
 - 2.1 The patient has a life-threatening condition which requires intervention.
 - 2.2 Trials in laboratory animals and other preclinical trials support the possibility that the drug will improve the patient's condition.
3. It is impossible to obtain informed consent for the following reasons:
 - 3.1 It is impossible to communicate with the patient because of his/her medical condition.
 - 3.2 The treatment must be given within a certain time frame defined in the clinical trial protocol (hereinafter: the "Time Frame"), and there is not enough time to obtain informed consent from the patient's legally authorized representative (guardian or representative pursuant to the Patient's Rights Law, 1996).
4. When a potential trial participant is admitted, and it is impossible to obtain his/her written consent:
 - 4.1 The Principal Investigator must take all reasonable measures to obtain consent from the patient's legally authorized representative within the given Time Frame. The Investigator shall document these steps and report it to the Ethics Committee.
 - 4.1.1 In any event, treatment will not be given in a study if any of the caregivers knows that the patient or his/her legally authorized representative objects to the administration of medical treatment.
 - 4.2 Inclusion of the patient in the clinical trial (in accordance with the inclusion and exclusion criteria set forth in the trial protocol) shall also be approved, in addition to the Principal Investigator, by another independent physician¹.

The Investigator shall ensure that, at the first opportunity, the patient or his/her legally authorized representative shall receive detailed information about the treatment administered, in the manner in which it would have been given in order to obtain his/her informed consent, and shall sign the consent form in order to continue in the clinical trial. The patient or his/her legally authorized representative shall be told that he/she may discontinue any time, without prejudice to his/her treatment or loss of rights.

If a patient who was included in the clinical trial without signing the consent form dies before such signature could be obtained and before contact could be established with his/her legally authorized representative, the Investigator must endeavor to locate the patient's legally authorized representative and provide him/her with information about the clinical trial.

¹ A physician not part of the study staff but acquainted with the trial protocol.

5. Additional protection of participant rights

- 5.1 The study protocol shall state an Independent Data Safety Monitoring Board¹ for monitoring and evaluation of the information assembled during the study.
- 5.2 The institutional Ethics Committee shall determine a continued review mechanism to oversee the conduct of the study.

¹ An Independent Data Monitoring Board can be established by the sponsor with the role of periodically evaluating the progress of the clinical trial and the safety and efficacy data, and recommending the continuation, modification of the protocol or discontinuation of the clinical trial to the sponsor.

Appendix 2 – Insurance clause in contracts with commercial organizations for conducting clinical trials in government hospitals

A commercial company entering into an agreement with a medical institution and/or Investigator to conduct a clinical trial shall insure its legal liability pursuant to the laws of Israel against claims filed by clinical trial participants and/or third-party claims in connection with the clinical trial, whether during the course of the trial or thereafter.

The insurance shall be expanded to include the legal liability of the medical institution and/or medical team and/or Investigator (hereinafter: the “Individuals conducting the Trial”) resulting from their involvement in the conduct of the trial, subject to an exclusion of damages resulting from acts and/or faults made by the medical staff of the government hospital owing to deviation from the clinical trial protocol, including negligence, carelessness or error originating from the implementation of the clinical trial protocol by the medical staff.

The coverage shall be on an event basis and in the event of a policy based on the filing of claims, it shall explicitly state that the coverage is also subject to the statute of limitations in the State of Israel. This is without any prejudice to the aforesaid.

The limit of liability shall be set at no less than \$3,000,000 (three million US dollars). The Ministry of Health shall issue an explicit directive regarding the recommended insurance amounts, in accordance with trial type and degree of risk.

The commercial company shall present appropriate insurance confirmation to the medical institution.