The Helsinki Committee may approve a clinical trial without the requirement to obtain informed consent from all participants if all the following conditions are met:

1. The patient's life is in immediate danger or there is an immediate danger of serious and irreversible disability for the patient.

   Existing treatments do not provide equal or higher probability of saving the patient's life and it is important to determine the safety and efficacy of the treatment for this group of patients; the clinical trial cannot actually be performed without waiving the requirement for the patient's prior informed consent.

2. The patient's participation in the clinical trial offers a direct benefit because:

   2.1. The patient's life is at risk and intervention is necessary.

   2.2. Experiments on laboratory animals and other pre-clinical trials support the possibility that the treatment can benefit the patient.

3. Informed consent cannot be obtained because:

   3.1. It is impossible to communicate with the patient due to his medical condition.

   3.2. The treatment must be given within the window of time defined in the clinical trial plan ("window of time") and there is insufficient time to obtain informed consent from the patient's legal representative (guardian or proxy pursuant to the Patient's Rights Act, 5756-1996).

4. When a patient arrives who is due to participate in a clinical trial, and it is not possible to obtain his written consent:

   4.1. The chief researcher undertakes to make all reasonable efforts to obtain the consent of the patient's legal representative within the window of time. These efforts will be documented and reported to the Helsinki Committee.

      4.1.1. In any case, no treatment will be given as part of the clinical trial if any of the people involved know that the patient or his legal representative is opposed to receiving the treatment.

   4.2. The inclusion of the patient in the clinical trial (according to the rules of inclusion and exclusion specified in the trial protocol) must be approved, apart from the decision of the chief researcher, also by another independent physician[1].

   The researcher will ensure that at the first opportunity, the patient or his legal representative is given detailed information about the treatment, as it would have been given to obtain informed consent, and signs the consent form for continuing participation in the clinical trial. The patient or his legal representative will be told that his participation can be stopped at any time, and this will not affect his rights or his future treatment.

[1] This physician is not part of the trial team, but he is familiar with the trial protocol.

If a patient who is included in a clinical trial without signing the consent form dies before such signature and before his legal representative can be contacted, the researcher must try to locate his legal representative and give him information about the clinical trial.

5. Other protections of participants' rights:

   5.1. The research protocol will indicate an Independent Data Safety Monitoring Board[2] to monitor and assess data collected during the trial.

   5.2. The Institution's Helsinki Committee will determine a mechanism for ongoing checking and review of the conduct of the clinical trial.

Note: the Institutional Committee examines the importance, efficacy and safety of the treatment of trial participants, and can decide to waiver signing the informed consent pursuant to Addendum 1 of this above Procedure when the following conditions are met:

1. The treatment increases the chances of saving life.
2. If there is no other treatment within the window of time and these conditions are met, the following protective measures must be taken:
   - Appoint an independent physician to determine the criteria for inclusion in real time and try to obtain consent, or to determine if the participant is able to give informed consent.
   - For ethical reasons, a family member (previously given power of attorney, according to the Patients' Rights Act) should be informed, and when the patient recovers he should sign the informed consent form.
   - See Appendixes A, B on medical emergencies.

[2] The Independent Board, which can be set up by the initiator and is responsible for regular checks of the trial's progress, safety data and efficacy data, will recommend whether the trial should be continued, or changed, or halted.

Addendum to Form 2A – Waiver of requirement for informed consent for clinical trial in a medical emergency

No. of request to Helsinki Committee (to be completed by Committee secretary): _____

We the undersigned:

Name of patient's legal representative _____

Relationship to patient: _____

Name of first degree next of kin (spouse/ child) _____ if with the patient, or can be located within the window of time for the treatment.

Relationship to patient: _____

Independent physician: 1. _____ License no. _____ Dept. _____

2. _____ License no. _____

hereby declare that the chief researcher/ secondary researcher _____ has explained to us that the patient can participate in the clinical trial without giving consent, based on a decision of the Institution's Helsinki Committee, and that the patient's condition meets the following criteria, as specified in Appendix 1 of the Procedure for Clinical Trials on Humans – Waiver of the requirement of informed consent:

1. The patient's life is in immediate danger or there is an immediate danger of serious and irreversible disability for the patient; existing treatments do not provide equal or higher probability of saving the patient's life and it is important to determine the safety and efficacy of the treatment for this group of patients; the clinical trial cannot actually be performed without waiving the requirement for the patient's prior informed consent.
2. The patient's participation in the clinical trial offers him a direct benefit because:
   - 2.1. The patient's life is at risk and intervention is necessary.
   - 2.2. Experiments on laboratory animals and other pre-clinical trials support the possibility that the treatment can benefit the patient.
3. Informed consent cannot be obtained because:
   - 3.1. It is impossible to communicate with the patient due to his medical condition.
   - 3.2. The treatment must be given within the window of time defined in the clinical trial plan ("window of time") and there is insufficient time to obtain informed consent from the patient's legal representative (guardian or proxy pursuant to the Patient's Rights Act, 5756-1996).
4. When a patient arrives who is due to participate in a clinical trial, and it is not possible to obtain his written consent:
   - 4.1. The chief researcher undertakes to make all reasonable efforts to obtain the consent of the patient's legal representative within the window of time. These efforts will be documented and reported to the Helsinki Committee.
     - 4.1.1. In any case, no treatment will be given as part of the clinical trial if any of the people involved know that the patient or his legal representative is opposed to receiving the treatment.

4.2. The inclusion of the patient in the clinical trial (according to the rules of inclusion and exclusion specified in the trial protocol) must be approved, apart from the decision of the chief researcher, by two other independent physicians.

The researcher will ensure that at the first opportunity, the patient or his legal representative is given detailed information about the treatment, as it would have been given to obtain informed consent, and signs the consent form for continuing participation in the clinical trial. The patient or his legal representative will be told that his participation can be stopped at any time, and this will not affect his rights or his future treatment.

If a patient who is included in a clinical trial without signing the consent form dies before such signature and before his legal representative can be contacted, the researcher must try to locate his legal representative and give him information about the clinical trial.

b. We hereby declare that we have given our above consent of our own free will and that we have understood all the foregoing. In addition, we have received a copy of this informed consent form, dated and legally signed.

c. By signing this consent form, we are allowing the initiator of the clinical trial, the Institutional Helsinki Committee, the Institution's auditor and the Ministry of Health direct access to the patient's medical file in order to verify the clinical trial methods and clinical data. This access to medical information must maintain confidentiality pursuant to the laws and procedures of maintaining confidentiality.

d. If the clinical trial involves the provision of services: medical checks, supply of implements, preparations or implants, we hereby declare that we know and agree that the information about the patient's participation in the clinical trial will be given to his/her family doctor/ the health provider with whom he/she is insured.

We know that the family doctor/ health provider will not use this information in any way except for the purposes of medical treatment and follow up.

And therefore I have set my hand:

Name of legal representative	Signature of legal representative	Relationship to patient	Date
Name of next of kin	Signature of next of kin	Relationship to patient	Date

If with the patient or can be located within the window of time for treatment

Name of independent physician 1	License no. and ID no.	Department and position	Signature
Name of independent physician 2	License no. and ID no.	Department and position	Signature

Declaration and consent of independent physicians

By signing this consent form as independent physicians, we confirm that we have read the consent form and that the patient whose details are given on this form meets the requirements of paras. 1-4 of the form and the criteria for inclusion and exclusion, and we agree to the inclusion of this patient in the clinical trial.

Declaration of Chief Researcher/ Secondary Researcher

I have received the above consent, after explaining all the foregoing to the independent physicians and/or the legal representative and/or next of kin and I have ensured that they understood all my explanations.

I hereby undertake that if and when the patient regains consciousness and is able to give consent for continued participation in the rest of the trial, I shall give him/her a detailed explanation of the trial and his/her continued participation will be as he/she wishes. The patient is free to decide not to participate in the clinical trial and may stop participating in the trial at any time, without affecting his/her rights to receive accepted medical treatment.

Name of researcher/ secondary researcher giving explanation	Signature of researcher	Date

The following steps were taken to obtain the informed consent of the patient/ his legal representative/ next of kin:

1. The measure: _____

   on date: _____
2. The measure: _____

   on date: _____

- Additional next of kin of the same degree of relationship were/ were not located, Names of next of kin who were located: _____
- All next of kin who were located agree to the patient's inclusion in the clinical trial.

Appendix B to Consent Form – Consent to Continue Participation in a Clinical Trial

If the patient becomes fit again and is able to give consent to continued participation in the follow up to the clinical trial, he/she will be given a full explanation of the trial and his/her continued participation will depend on his/her consent and signature to this form.

Trial name:

Patient's declaration:
I hereby declare that I have been told that when I was admitted to the hospital my medical condition made it impossible for me to give informed consent to my participation in a trial before receiving treatment, and that consent for my inclusion in the study was given by three (3) physicians (the chief researcher or secondary researcher and 2 independent physicians) and also by a first-degree relative of mine (if one was available or could be located within the window of time for treatment).
I understand that I can stop my participation in the trial at any time and receive the accepted treatment for my medical condition without loss of any legal rights.
All my questions were answered and I confirm my participation in this trial. I confirm that this consent is given of my own free will and that I have been given a copy of the informed consent form and all its attachments.

Name of participant	Signature	Date

Declaration of Researcher/ Secondary Researcher

I hereby declare that I have explained to the patient the procedure for obtaining informed consent that was done for his/her inclusion in the trial. I explained the medical treatment given to the patient and everything in the informed consent form, and I ensured that the patient understood all my explanations.

Name of researcher/ secondary researcher	Signature	Date

A commercial company making an agreement with a medical institution and/or a researcher regarding execution of a clinical trial, will insure its legal liability pursuant to the laws of the State of Israel against claims submitted by participants in the trial and/or third party claims – all in connection with the clinical trial, whether during or after the actual trial.

The insurance will be extended to cover the legal liability of the medical institution and/or the medical staff and/or the researcher (hereinafter: "the researchers") arising from their involvement in the trial, subject to an exclusion for damage arising from actions and/or omissions by the medical staff of the government hospital due to a deviation from the protocol of the clinical trial, including negligent performance, careless actions or errors in implementing the trial protocol by members of the medical team.

The cover will be based on the incident, and in the case of a policy based on submission of a claim, it will state explicitly that cover is also subject to the Law of Obsolescence of the State of Israel. Nothing in this clause affects the foregoing.

The limit of liability shall be no less than $3,000,000 (three million US dollars). The Ministry of Health shall issue a detailed instruction regarding recommended insurance amounts, by type of trial and degree of risk.

The commercial company shall provide an insurance confirmation suitable for a medical institution.

Purpose of the Procedure

To regulate the process of signing agreements between a commercial company and the Research Foundation of Tel Aviv Medical Center (TAMC), in which a monetary payment is made or a product of equivalent value is received by the Research Foundation.

Definition of Terms

- "Internal Agreements Committee" – an internal committee of TAMC which is appointed by the Ministry of Health and consists of a representative of the Hospital, a representative of the Research Foundation, the committee coordinator and senior members of Hospital staff.
- "Aviv R&D" – a dedicated computer program for entering details of research and budgets. The system at the Research Foundation is linked to the Aviv Finansit system, which follows all financial activity of the research.

Responsibility and Authority

- The Internal Agreements Committee has the power to approve arrangements pursuant to this procedure.
- The Committee's authority is granted by the Ministry of Health.

General

- This procedure also applies to research initiated by the chief researcher and which involves a commercial company, by providing a monetary payment or product of equivalent value.
- Agreements drawn up with non-commercial entities (such as philanthropic organizations, academic, not-for-profit associations, medical centers) are exempt from obtaining the Committee's approval.
- The requirements for the chief researcher and study coordinator are shown on the website of the R&D Division, Contracts & Agreements Unit.

Procedure contents

1. **The Internal Committee for Commercial Engagements – Working process**
   - The Committee will meet once a month, and if necessary – more frequently.
   - The Committee approves the contractual arrangement, the insurance and the research budget. Committee members examine the budget and approve them subject to Ministry of Health procedures.

Written by:	Job:	Date:	Signature:
Approved by:	Job:	Date:	Signature:

1.1. Preparation for Committee

1.1.1. Research budgets totaling less than NIS 450,000 are approved by the Hospital's Internal Committee for Commercial Engagements and notified to the Ministry of Health.

1.1.2. Research budgets totaling more than NIS 450,000 are sent directly to the Ministry of Health's External Committee for Engagements for approval (see section 3).

1.1.3. A study is submitted to the Committee for approval only after all relevant documents have been submitted and approved. The "document package" submitted to the Committee will include the following:

- Legal contract signed by all parties (initiator, chief researcher, general manager of Research Foundation).
- Valid insurance certificate, meeting the requirements of the Ministry of Health and the Medical Center.
- Initiator's form of undertaking (Form 4).
- Details of internal budget
- Form of engagement
- Undertaking of chief researcher
- Form 7 signed by the Hospital Director.

1.1.3.1 The Chief Researcher is responsible for submitting all the documents to the Contracts Unit in the R&D Division.

1.1.3.2 The documents are attached to this procedure and appear on the R&D Division website, under the Contracts & Engagements Unit.

1.1.4. An accompanying letter summarizing all requests and signed by the manager of the R&D Division is attached to every research budget submitted for approval to the Committee.

1.2. <u>Applying to the Internal Committee for Commercial Engagements</u>

1.2.1. The letter to the Committee and relevant forms are submitted for approval to the manager of the R&D Division.

1.2.2. Research documents are scanned and stored in computer directories:

- The first page of Form 7.
- The internal budget form.
- The contract budget.

1.2.3. The letter together with the documents is sent by email to all Committee members by the R&D Division manager, who will reply in the same way.

1.2.4. The requirement for approval of the Committee is the approval of at least 4 members of the Committee.

1.2.5. The research documents and approval letters signed by the Division manager are sent to the researchers.

2. **<u>Opening a research budget and distributing documents</u>**

2.1. For each research a fund is opened in the R&D Division, on the Aviv R&D system which is linked to the Research Foundation accounts department. The Foundation manages all research money – income and expenses.

2.2. After Committee approval, an email and fax is sent to the Committee for Commercial Engagements in the Ministry of Health, with the summary report to the chairman of the Committee and a scan of all the Committee documents. Ensure confirmation of receipt from the Ministry of Health.

2.3. The relevant package of documents must be copied and prepared.

2.4. Original documents are filed in the R&D Division:

- If there is a Helsinki number – in the Research file, by consecutive number.
- If there is no Helsinki number – in the researchers' personal files.
- The original letter to the Committee is filed in the Engagements file, in chronological order by Committee date.

2.5. All research details must be updated on a designated Excel file.

3. **<u>Submission to the External Committee for Commercial Engagements</u>**

3.1. The External Committee for Commercial Engagements of the Ministry of Health meets regularly every few weeks. Meeting dates are always shown at the end of letters from the Committee regarding approved researches (sent to us by email from the Ministry of Health).

3.2. Contracts worth more than NIS 450,000 must be submitted separately for approval to the Ministry's External Committee for Commercial Engagements.

3.3. <u>Preparation for the Committee</u>

3.3.1. A study is submitted to the Committee for approval only after all relevant documents have been submitted and approved:

- Contract signed by all parties
- Valid insurance certificate, meeting the Ministry of Health requirements

- Initiator's form of undertaking (Form 4).
- Internal budget form
- Form of engagement
- Undertaking of chief researcher
- Form 7 signed by the Hospital Director.

Responsibility for submitting all the documents to the R&D Division rests with the chief researcher.

For each Committee a letter is prepared summarizing all the researches submitted to that Committee. The letter is sent to the Ministry of Health and a copy is kept in a separate computer folder.

3.3.2. The letter to the Ministry of Health and the forms of undertaking are submitted to the manager of the R&D Division for signature.

3.3.3. For every research, the following documents are scanned and saved in the Committee folder:

- First page of Form 7
- Internal budget form
- Contract budget.

3.3.4. The letter is emailed to the Ministry of Health, together with the scanned copies of all research documents. The letter is also sent by fax.

3.4. Opening funds for research and distributing documents

3.4.1. The replies from the Ministry of Health Committee arrive by email. The letter must be printed out and filed in the Engagements file.

3.4.2. If the Committee has any comments, they must be forwarded to the research coordinator and/or the chief researcher by email, asking for the budget to be amended. The budget amendment must be resubmitted to the Ministry of Health Committee for approval.

3.4.3. When Ministry of Health approval is received, details of the research must be entered into the Aviv system and a printout obtained.

3.4.4. The manager of the Division signs the approval letters for researchers.

3.4.5. The documents are photocopied and distributed in the same way as for the Internal Committee for Commercial Engagements.

4. Updating list of researches with Ministry of Health and reporting

4.1. Each quarter the representatives of the Contracts Unit ask the Ministry of Health for a list of all our researches submitted for agreements.

Written by:	Job:	Date:	Signature:
Approved by:	Job:	Date:	Signature:

4.2. The list must be checked against our Excel file. The Ministry of Health must be notified of any corrections.

4.3. The Contracts Unit copies the quarterly file to the shared driver and sends an email notifying the manager of the Division of the updated report.

Reference to procedures and documents

- Ministry of Health procedure on engagements, 2010
- Letter delegating authority to approve engagements with commercial entities.
- Guidelines for chief researchers and research coordinators.
- Documents to be submitted to the Engagements Committee.

According to the Ministry of Health Procedure to exercise the Initiator's undertaking (Form 4, Section 6.a)

Procedure for submission using Matarot software:

Stage 1: Submit through the mechanism for recording an active research (home page of the application. Enter details of the new research:

- Helsinki number of main research (+ continuation)
- Name of research
- Chief Researcher
- Initiator of trial (chief researcher)
- Latest version of protocol.

Following electronic approval from the Helsinki team:

Stage 2: Submit through the "Addition to Protocol" mechanism, including Form 12. Submit in 3 copies. Under Reasons for Change, enter: "Exercising the initiator's undertaking to continue providing the drug according to Form 4 for continued provision after the trial".

- Submit a continuation protocol pursuant to Min. of Health protocol below.
- The heading is the subject of the research, date and latest version number.
- The protocol must summarize the original protocol plus follow-up protocol.
- Indicate that this is a continuation protocol and the participants will be the patients now participating in the main research, Helsinki no. ____ for whom it has been decided to give them the treatment arm according to the attached protocol, in view of the proven efficacy of the treatment in the main research.
- State that reports of the follow-up protocol will be submitted to the Committee for approval as is normal for clinical trials.
- Attach a letter from the initiator, confirming the protocol of the clinical trial that is now initiated by the chief researcher.

Purpose of the Procedure

Approval of insurance cover for clinical trials. The procedure distinguishes between trials initiated by a commercial company and trials initiated by a hospital researcher.

Procedure Content

1. Trials initiated by a researcher

   1.1. According to Ministry of Health procedures, clinical trials initiated by the chief researcher are covered by the Inbal Insurance Company which insures government hospitals.

   1.2. If it is necessary to increase insurance cover, approval must be requested from the Internal Fund for Government Insurance – Inbal Ltd.

   1.3. Notice of such cases must be sent to the Contracts Unit by the Helsinki Committee or by the chief researcher.

   1.4. Insurance extension is required in the following cases:

   - Use of a drug or medical product that is not approved for use in Israel.
   - Use of a product approved in Israel for a new indication.
   - One or more of the research team has to leave the hospital to give treatment to patients in the trial framework.

   1.5. The Inbal company is contacted by email from the Contracts Unit, to the Underwriter for Property & Obligations (לחתמת רכוש וחבויות?), with the following details, as defined by Inbal:

   - Abstract of the study protocol.
   - Approved consent form.
   - Short description of the trial.
   - Form 6 signed by the chairman of the Helsinki Committee, if Inbal decides to ask for this form.

   The Chief Researcher is responsible for submitting these forms to R&D.

   1.6. Approval is sent by email by the Underwriter for Property & Obligations on behalf of Inbal.

   1.7. If Inbal does not approve the extension, independent purchase of insurance should be considered. Approval for such purchase must be obtained from the manager of the R&D Division.

   1.8. If the purchase of insurance is approved, the Contracts Unit will contact the insurance advisors of the Research Foundation, with the details specified above and the completed signed form, to obtain a minimum of 2 quotes.

2. Trials initiated by a commercial company

   2.1. If a clinical trial is initiated by a commercial company, the initiator must provide the Contracts Unit with an insurance certificate.

   2.2. The insurance certificate must satisfy all the Ministry of Health requirements (attached to the contract) and other requirements of the Medical Center.

2.3. Additional Medical Center requirements:

- Termination clause – notice to the Medical Center if the insurance is terminated, changed or restricted, at least 30 days in advance.
- Additional insured clause – inclusion of the Research Foundation, the Ethics Committee and everyone involved in the trial.

2.4. Checking and approving the insurance certificate:

2.4.1. The initiator must send the insurance certificate to the Contracts Unit.

2.4.2. The certificate will be sent to the insurance advisors of the Research Foundation for checking and approval.

2.4.3. If the insurance advisors have any comments, the Contracts Unit will ask the company to send an amended certificate for checking.

2.4.4. The approved certificate will be filed with the contract in the trial file.

2.4.5. Extending the insurance term is the responsibility of the initiator/ researcher.

2.4.6. The continuity of insurance cover will be reviewed once a year, when a request is submitted to the Helsinki Committee to extend the trial. The Helsinki Committee will send the insurance certificate to the Contracts Unit, for checking and approval.

Reference to procedures and documents

- Internal Insurance Requirements document - Sourasky
- Procedure for Clinical Trials on Humans, Ministry of Health 2006 – Appendix 2

Participation in clinical trials is entirely voluntary. The patient has the right to receive full information about the trial before giving his/her consent to participate.

The patient can refuse to participate or stop participating at any stage.

The medical rights of a patient who decides to stop participating in a trial will not be affected and he/she will receive optimal treatment at all times.

What is a clinical trial (medical research)? (From the Ministry of Health procedure 2006)

A clinical trial on humans is defined in the Regulations as the use of a drug, radiation or chemical, biological, radiological or pharmacological substance, contrary to the approval for its use granted in legislation, or where such use is not usual in Israel for the purposes intended, or that has not yet been tried in Israel, and it is intended to affect the health, body or mind of a person or an embryo, or part thereof, including the genetic system. Also, it is a process, action or test on a person that is not usually accepted. In addition, any action intended to form part of a protocol of a clinical trial on humans even if it includes accepted means. (Public Health Regulations, 5741-1980).

A clinical trial may use a survey or questions to study medical needs, medical problems or various sensations. A clinical trial is research that examines a medical treatment on humans. The treatment may be a drug, device, food additive or procedure.

Who is the Chief Researcher? "A qualified physician or qualified dentist, who is responsible for preparing and conducting a clinical trial at a research site, as defined in the trial protocol" (according to Ministry of Health Procedure 2006).

Any researcher who wishes to obtain approval for a clinical trial on humans must:

- Be trained in managing and conducting clinical trials according to the procedures of Good Clinical Practice (GCP).
- Submit a proposal with any other documents required for approval by the Institutional Helsinki Committee.

What is the Helsinki Committee? (according to Ministry of Health Procedure 2006).

The Institutional Helsinki Committee is an independent committee whose composition, appointment and legal number of members are defined in the Public Health Regulations. Its role is to ensure the rights, safety and welfare of participants recruited for clinical trials, including by examining and approving the trial protocol and informed consent form. The Helsinki Committee also regularly monitors and supervises the conduct of clinical trials, including any changes in the protocol.

The Helsinki Committee operates according to the Procedure for Clinical Trials on Humans, the Public Health Regulations (Clinical trials on humans), 5741-1980) with their additions and amendments, 1999), and implements the principles of the Helsinki Declaration.

The Committee will approve a clinical trial if it is satisfied that the following and other criteria are met, at its discretion:

- The expected benefits to participants and to society justify the risk and discomfort involved in the trial.
- Existing medical and scientific information justifies the trial.
- The clinical trial has been planned scientifically to answer a specific question and has been clearly and accurately defined in detail in the protocol.

- The risk to participants is as small as possible.
- Participants have been selected according to rules of inclusion and exclusion.
- The informed consent form for the trial includes all required information.
- The trial plan includes instructions on maintaining the privacy of participants and the confidentiality of information collected.
- The nature of the commercial arrangement with the researcher and the medical institution does not interfere with proper performance of the trial.

Good Clinical Practice – GDP.

The working procedures and methodology are intended to ensure the wellbeing and rights of participants, the quality and efficacy of the trial.

The procedures define the standard for planning, managing, executing, documenting, monitoring, reviewing and analyzing the data and giving information about the trial.

All collected information ensures that the trial data and results are reliable and accurate, and that the wellbeing, safety, rights and privacy of participants have been maintained.

The principles of the Helsinki Declaration and GCP are specified in the procedure of the International Committee for Guidelines Harmonization: ICH E6 GCP.

A chief researcher at Tel Aviv Medical Center is one who has passed a course on GCP. By July 2013, about 400 of the physicians and researchers at TAMC had taken a special course to qualify them in proper research management and GCP. TAMC continues to provide training and qualification for staff members engaged in research, and each year another 100 staff members successfully complete the training in research management.

In 2013 a refresher course was introduced in order to update procedures and work processes. The first course was attended by 50 senior TAMC physicians and researchers.

Informed consent form

By signing this form, the patient expresses his willingness to participate in the research.

- According to Ministry of Health procedures, the Public Health regulations, and international laws, after the patient has received a detailed explanation of the research, and has read and understood the course of the research, he confirms his understanding and his willingness to participate by signing and dating the form. The physician also signs to confirm that he has explained the research to the patient and believes that the patient understood the nature of the research and its willing to participate.
- The informed consent form includes information on the following:
    - Purposes of the research
    - Approximate number of participants
    - Expected duration of the trial.
    - Research methods including a description of the research product, the processes used during the trial, with a clear distinction between research procedures and medically accepted procedures.
    - The expected benefits of the trial for participants and others.
    - The known risks and/or discomfort that the participant may expect.

  - Circumstances in which the patient's participation in the trial may be stopped by the researcher or the initiator.
  - Explanation for the patient about any alternative treatments available, their benefits and disadvantages.
  - Who to contact with other questions about the research or any medical problems during the research.
  - Compensation (if any) for the patient, including reimbursement of travel costs.
  - Confidentiality of personal and medical information.
- Participation in clinical trials is entirely voluntary. The patient has the right to refuse to participate or stop participation at any stage, and if he decides to stop participating in the trial, his medical rights will not be affected and he will receive optimal treatment at all times.
- By signing the informed consent form, the patient permits the trial initiator, the Institutional Helsinki Committee, the medical institution's auditor and the Ministry of Health direct access to his medical file to verify the trial methods and clinical data.
- After signing the consent form, the patient receives a copy and he can consult the signed form at any time.
- By signing the informed consent form, the patient confirms that information about his participation in the trial can be sent to his family physician and healthcare provider.
- The patient is invited to reviews by the research physician as required by the trial protocol, in addition to his regular treatment.

Research registration site – NIH

According to the guidelines of the Director General of the Ministry of Health of September 2005 and the update of February 2008, all researchers must register their clinical trials in the NIH clinical trials database before starting the trial.

Registration in a global database, before the first patient is included in the trial, is a condition for publishing the trial results in scientific journals.

<u>According to the guidelines of the Director General of the Ministry of Health of September 2005 and the update of February 2008</u>, all researchers must register their trials in the NIH clinical trials database before starting the trial. Which trials must be registered on the site?

Every clinical trial that meets the criteria in the Ministry of Health guidelines (link above) and planned to take place in Israel must be registered in the NIH database.

<u>The Ministry of Health website</u> has a permanent link to the NIH registration site, with <u>a list of most trials taking place in Israel</u> where there is an intervention (the information is in English). <u>On the NIH registration site</u> it is possible to find out if any trials are taking place on a specific topic anywhere in the world.

<u>FAQ</u>

Is there any clinical research in TAMC or anywhere else in Israel or the world that could be suitable for the patient?

A patient can directly apply to his specialist in the field and ask if there are any clinical trials that could be suitable for him.

Also, the Ministry of Health website has a permanent link to the NIH registration site, with a list of most trials taking place in Israel where there is an intervention (the information is in English). On the NIH registration site it is possible to find out if any trials are taking place on a specific topic anywhere in the world.

What are the benefits and risks of participating in the clinical trial?

A clinical trial may be effective or pose a risk for the reasons specified in the informed consent form. In addition:

- The patient must be an active participant in looking after his own health.
- The participant is exposed to new treatment options before they are generally available.
- The participant is helping others by his contribution to medical knowledge, but as with medical treatments, there are also risks of participating.
- There may be unexpected side effects, some of them unpleasant, difficult and even life-threatening.
- The treatment may not be effective for some participants. Also some participants may receive the comparison preparation and not be exposed to the trial preparation.
- More time may be required before the treatment takes effect than for the standard treatment, and more visits to the hospital may be necessary than for a patient who is not participating in the trial. Additional blood and other tests may be required which are not generally required for patients outside the trial. However, the research team will arrange visits to the Medical Center with consideration for the patient and his needs.
- Some side effects of innovative treatment may be observed throughout the trial. The patient will be informed by the research team of any unusual side effects discovered during the research in Israel and worldwide.

Is it worthwhile participating in a clinical trial?

Participation in a clinical trial is entirely voluntary. People participate in clinical trials for various reasons. Common reasons for participating include:

- Contribution to the scientific effort to promote medicine and find solutions to medical problems for future patients.
- Absence of an accepted and effective treatment, in the hope of finding an optimal treatment for a medical problem affecting the patient or others.
- Help in finding additional treatments which will later become available to the general public, for example improvement to medical procedures, inoculations, drugs and/or medical devices.

Only the patient can decide whether to participate in the trial. He has the right to seek advice from anyone, including the family physician and family members.

Does the researcher have all the approvals necessary for the trial?

An approved clinical trial has been approved by the manager of the Medical Center. The manager's approval (Form 7) indicates the researcher's name, the trial name, and the period of validity. In addition, the informed consent form indicates the name of the approved trial

and the name of the researcher who has received approval for the trial from the manager of the medical institution.

What is required of the participating patient?

- The patient must sign an informed consent form after receiving all the information and replies to all his questions, and understanding the trial's content.
- In order to obtain the best and most effective treatment, the patient must strictly follow all the instructions of the research team.
- The patient must give any letter he receives from the research team to his family physician.
- The patient must inform any other medical services treating him of his participation in the trial (for example, dentist or outpatient clinic).

Who funds the clinical trial?

- Clinical trials initiated by commercial pharmaceutical companies are funded by the companies. They sign a contract which is approved by the Ministry of Health Contracts Committee.
- Trials initiated by physicians and scientists are funded from various sources: competitive research foundations, non-profit associations, universities, commercial companies, international research bodies, national health institutes, and the government.

Insurance: all patients who participate in a clinical trial are insured by the company that initiates the trial or by the medical institution.

What are the rights of a participant?

- A patient can refuse to participate in a trial or stop his participation at any stage, without affecting his medical rights.
- The trial plan includes instructions about maintaining the privacy of participants and the confidentiality of personal and medical information obtained.
- The patient's name and personal details will remain confidential except to the trial initiator, the Helsinki Committee, the auditing body and the Ministry of Health.
- Participation in a clinical trial can be stopped:
    - If the patient wishes.
    - If the research team decides it will be better for the patient.
    - If the patient is not following the instructions of the research team.
    - If the trial is stopped.
- At each stage, the research team will inform the patient of any new information relating to the trial.

What should the patient consider before deciding to participate?

- The patient must receive detailed information about the nature and duration of the trial, from the research team and the chief researcher.
- Answers to the patient's questions are in the informed consent form given to the patient to read. After he has understood it and all his questions have been answered, he signs the form before the trial starts. At the same time the chief researcher also signs the form. Questions that are answered on the consent form are:
    - What is the purpose of the trial?
    - How many people will participate?
    - What treatments will be given to participants?
    - How frequently must participants come to the research center?
    - What side effects can be expected?
    - What is the expected benefit for the patient?
    - How long is the trial expected to last?
    - Does the trial include hospitalization, blood tests or other tests?
    - Will the trial results be accessible to the patient?
    - Are there any alternative treatments for this condition?
    - Will the participant get a refund for travel/ parking costs?
    - What follow up is there after the trial?
    - How will participation in the trial affect the patient's daily life?
    - During the trial, will the patient have to observe restrictions on other drugs? Food?
    - Communication – who can the patient contact if necessary and how – 24 hour response?
    - Will the patient's family physician receive information about the trial?
    - Can the patient stop participating in the trial, and what will happen in this case?

Is there control of clinical trials at the TAMC?

An auditing body for clinical trials was set up in 2005 according to a Ministry of Health procedure. Its purpose is to review and supervise all clinical trials approved by the Institutional Helsinki Committee. This auditing body is independent and appointed by the Hospital management with Ministry of Health approval. The auditing body checks:

- That the actual clinical trial is the same as the approved plan.
- Any unusual events or events that deviate from the procedure.

The auditing body reports directly to the manager of the Medical Center. Every six months it reports its findings to the Ministry of Health.

(באנגלית)

Undertaking to Maintain Confidentiality

I _____ ID no. _____, member of the Committee for Clinical Trials on Humans of Tel Aviv Medical Center, am aware that information about the Committee's discussions and its decisions may only be publicized on the Committee's official documents.

I hereby undertake to maintain the confidentiality of the Committee's discussions and not to pass on information about them to any unauthorized element.

If my membership in the Committee or my presence at any of its discussions creates a conflict of interests, I shall inform the chairman of the Committee and remove myself from the Committee or from participation in such discussion.

Signed:

Name: _____ Signature: _____ Date: _____

- Applications to prepare and conduct clinical trials are submitted using the Matarot software.
- The Matarot software is on the Focus server and only researchers working for Tel Aviv Medical Center are permitted to use it.
- The home page of the software has two links for use by researchers: instructions for using the program and a shortcut to the TAMC/ Helsinki Committee site.
- Only qualified physicians, graduates of a GCP course, are permitted to submit applications for clinical trial, and they will be the chief researcher and responsible for the trial.
- The annual schedule of Helsinki Committee meetings is published on the TAMC/ Institutional Helsinki Committee site.

Physicians wishing to submit a new application for a clinical trial for approval by the Helsinki Committee must be familiar with the requirements of the Ministry of Health procedure and the Institutional Helsinki Committee procedure.

- Details of the application are entered onto the computer after selection of the type of trial – one of 6, according to the subject, as defined in the Ministry of Health procedure.
    - An abstract of the protocol is not a substitute for the full protocol.
    - Section 4 of the Consent Form must be addressed to participants (use of second person) in clear, structured language (see Appendix 9).
- Document files can be attached to the trial file according to the instructions for using the software.
- **Registration of trial on NIH** – according to Ministry of Health procedure 2006, trials must be registered on the ClinicalTrials.gov website.
    - Prospective clinical trials must be registered on the NIH site before the first participant is recruited. If the trial is funded by a commercial company, it must be registered by the company and the chief researcher notified of the number.
    - Trials initiated by a researcher, without involvement of a commercial company, will be registered by the initiator, and the registration number forwarded to the Helsinki Committee.
    - The decision to register the trial on NIH without carrying it out means that the Director will not issue confirmation of the trial.
    - Failure to register in time will prevent publication of the trial.
    - It is not mandatory to register other research.

For NIH registration of trials initiated by a researcher, contact Limor Levy on Tel. 4761 for a site username and password in order to register the protocol.

- When the online application is completed and submitted, the status of the trial in Matarot changes to “Sending Documents to Committee”. A copy should be printed out and signed by all the researchers, and copies prepared for the Committee.

Five copies of applications for clinical trials should be submitted:

4 full copies including Appendices 1,2,4,5,9,11, protocol and researcher's manual, if any.

1 partial copy including Appendices 1-11 (according to the submission package) and the protocol abstract.

When the package is submitted to the Committee, mark on each copy whether it is full or partial.

Applications for non-clinical trials must be submitted in 5 signed copies, including the research tool/ research questionnaire as an attachment to the protocol.

In the case of prospective/ retrospective collection of data, indicate what clinical and demographic data will be collected.

For anonymous retrospective collection of data, specify the mechanism for ensuring anonymity (condition for waiver of informed consent according to Ministry of Health).

The signed application forms must be received by the Committee office no later than the last day for submission shown on the timetable for meetings/ submissions (published a year in advance).

For all new applications for clinical trials initiated by commercial companies and submitted to the Helsinki Committee, the Medical Center will charge a fee of NIS 4,000. The fee for extending a clinical trial or changing its protocol is NIS 800.

To apply for an extension of a trial or report its conclusion, select the tab "Reporting events and applications for changes", then press "Add events and changes". The researcher must submit a signed copy to the Committee.

- Failure to submit an application for approval to extend the trial will automatically block the researcher for all other trials under his responsibility, and the trial will be automatically stopped.

Requests for changes, interim reports, safety reports or anomalous events must be submitted with the software, and a signed copy must also be submitted to the Committee by the chief researcher.

Every researcher and anyone authorized by him can update and track applications and the status of their trials online.

All documents approved by the Committee in the course of the trial are scanned and saved with the research documents.

- The purpose of the consent form is to give participants (ill or healthy) a clear and structured explanation of the nature of the clinical trial in which they are being asked to take part.

For that purpose the Committee asks researchers to describe the purpose of the trial and the logic behind it, and not just leave its name as its purpose.

The trial purposes or its protocol or the protocol abstract must not simply be copied into the form, due to the use of unfamiliar terms.

A long consent form submitted by the company initiating the research also requires an "Explanation for participants", to summarize the main points in no more than 2 pages! Participants must not sign this explanation.

Section D1 – Purposes: The form must address the participant directly ("you"), explaining why he is being asked to participate, and which group he belongs to (ill or healthy). It is important to use the second person form throughout the form and indicate that it is intended equally for both sexes. If the research is only intended for women, it is recommended to use the feminine form of words

- In the case of a new/ familiar preparation or food additive, its action must be described, with detailed information about clinical experience and the number of patients who have tried it – whether healthy or ill, or whether they had other illnesses not part of the study. The participant must also be told whether or not the preparation is registered, and how this treatment differs from standard treatment for the illness.
- In the case of a Phase 1 trial, which tries a new preparation or medical devices, clarify the rationale for testing it and on how many people it is to be tested. It is important to stress that it has not yet been tried on humans and make sure the explanation is full and in everyday language.
- Indicate how many participants are planned for this trial in Israel and elsewhere.

In Section D4 – Methods, explain the research methods in detail.

Describe the process of screening, mentioning the indications and contraindications for participation in the study. Explain randomization, if it is used.

> If the trial uses a placebo, explain the use of placebos in general, the logic behind its use, and what percentage of subjects will receive a placebo.
>
> Describe all visits to the physician, calling them Visit 1, Visit 2 and so on. Describe the procedure at each visit, and the time it takes. Also describe the follow-up period.

If the trial includes various tests, such as blood tests, specify them in simple terms. Indicate how many ml of blood (teaspoons) will be taken in each test, and how much altogether, the total number of imaging tests, etc. needed for the trial. If some of the tests are part of normal treatment, state this explicitly, with a clear distinction between standard procedures and procedures for the trial purposes.

If the intention is to collect data from medical records, state this.

If there is an intention to contact participants by telephone in future, state this.

If data/ samples are to be sent outside TAMC, state this and give details.

Section D5 - Benefits

If a drug is being studied, state that there may or may not be a benefit. No unproven benefit should be promised. If the trial is using a placebo, indicate that if the participant is given a placebo there will be no benefit.

If a medical device is being studied for its accuracy or for comparison with another device, indicate that this is a test of validity, with no benefit for the subject.

If the medical device gives treatment, continue as for a drug, and do not promise any benefit.

In the case of a laboratory trial, which includes taking blood or other body fluids, do not promise any benefit. The researchers can express a hope that the treatments or laboratory trial will help patients in future, but they must not promise any benefit to the participant.

Section D6 - Risks

In the case of a drug or medical device, describe the side effects and their frequency. If the trial involves imaging tests, describe the amount of radiation involved, if any, and side effects associated with contrast substances.

For studies initiated by a company, the Committee does not approve extending the injury clause or the insurance cover in the consent form, except for adding the following "The Hospital maintains sufficient insurance cover for the trial". The accepted insurance clause is described in Section 7 of the MOH standard consent form.

Section D9 – Alternative Treatments

Give details. Do not say "Your doctor will explain alternative treatments to you" but specify all existing alternative treatments.

Section D10 – Relevant Information

Usually, all information relating to the trial must be stated on the consent form. Under this heading, it is recommended to specify any reimbursement for travel expenses or payment to volunteers.

(באנגלית)

Nevertheless, if you have any questions concerning your rights in the study, or ethical issues you would like to raise, or in any case of inconvenience discussing your questions with the study team or the primary investigator, do not hesitate to apply in writing to the Public Inquiries Unit in the medical center and your questions will be responded as best we can.

Form 2: Informed consent by telephone to participate in a clinical trial on humans

First name and surname:	
ID number:	
Address:	ZIP:

a) Hereby declare that I agree to participate in the trial specified in this document.

b) Hereby declare that I have received an explanation from:

Name of researcher/ secondary researcher giving the explanation:

(1) That the chief researcher _____ has received from the manager of the medical institution approval to carry out the trial.

(2) That the subject of the trial is _____

(3) That I am free to decide not to participate in the trial and that I am free to stop my participation at any time, without affecting my rights to receive standard treatment.

(4) That I have been promised that my personal identity will be kept confidential by everyone involved in the trial and will not be published, including in scientific publications.

(5) That if I am asked to complete a questionnaire, I can refuse to answer all or some of the questions.

c) I hereby declare that I have been given detailed information about the trial, and in particular the following details, specified below/ on an attached information sheet[1]

(1) Purposes of the research.

(2) What is required of the patient.

(3) Any discomfort that may be caused.

d) I hereby declare that I have given my above consent of my own free will and that I have understood all the foregoing. I have also received a copy of the informed consent form and the attached information sheet (if any).

Name of person interviewed	ID no.	Time	Date

Declaration of researcher/ secondary researcher:

The above consent was received by me after I had explained to the participant in the trial everything stated above and ensured that he/she had understood all my explanations.

Name of researcher/ secondary researcher giving explanation	Signature	Date

[1] The information in this section can be given on a separate sheet attached to this form.

Version and date: _____

Form 3: Informed consent by telephone given by the parents/ guardian for the participation of a minor/ ward in a trial

We the undersigned parents/ guardians of the following minor/ ward* (hereinafter: the Patient):

Mother's name	ID no.
Father's name:	ID no.
Guardian's name:	ID no.

* Delete as appropriate

Patient's name	ID number	Date of birth
Address:		

a) Hereby declare that we consent to the patient participating in the trial, as specified in this document.

b) Hereby declare that we have received an explanation from:

Name of researcher/ secondary researcher giving the explanation:

(1) That the chief researcher _____ has received from the manager of the medical institution approval to carry out the trial.

(2) That the subject of the trial is _____

(3) That we are free to decide that the patient will not participate in the trial and that we are free to stop his participation at any time, without affecting his rights to receive standard treatment.

(4) That we have been promised that the patient's identity and the identify of his parents/ guardians[1] will be kept confidential by everyone involved in the trial and will not be published, including in scientific publications.

(5) That if there is a questionnaire, we can refuse to answer all or some of the questions.

c) We hereby declare that we have been given detailed information about the trial, and in particular the following details, specified below/ on an attached information sheet[2]

(1) Purposes of the research.

(2) What is required of the patient in the trial.

(3) Any discomfort that may be caused.

[1] Delete as necessary

[2] The information in this section can be given on a separate sheet attached to this form.

d) We hereby declare that we have given our above consent of our own free will and that we have understood all the foregoing. We have also received a copy of the informed consent form and the attached information sheet (if any).

Name of person interviewed (father/ mother)	Guardian's name	Time	Date

Declaration of researcher/ secondary researcher:

The above consent was received by me after I had explained to the parents/ guardian of the participant in the trial everything stated above and ensured that they had understood all my explanations.

Name of researcher/ secondary researcher giving explanation	Signature	Date

Version and date: _____

Introduction

The body that audits clinical trials was set up in 2005 pursuant to the Ministry of Health procedure. Its purpose is to review and supervise clinical trials at the hospital.

1. Definitions

1.1. Audit: "The Audit is an integral part of the requirements for proper conduct of clinical trials, according to local and international guidelines which are intended to ensure the safety, well being and rights on the participant."

1.2. Ministry of Health Procedure:

Supervision and audit of clinical trials (within the meaning of the Public Health Regulations, (Clinical Trials on Humans),5741-1980 in medical institutions in Israel.

Addendum to the Procedure for Clinical Trials on Humans, 1999.

Procedure for clinical trials on humans – 2006.

1.3. The Auditing body

A body funded by the Hospital management or whoever is delegated by it to check and monitor approved clinical trials in the institution.

The auditing body is independent.

1.3.1. Members of the Auditing body

The auditing body has 5 members:

Chairman of the Committee, Adv. Ruth Perry, Legal Advisor of Tel Aviv Medical Center.

Representative of the public – Adv. Dr. Avi Weintrot

Member of the auditing body – Prof. S. Kaviti, Manager of the Clinical and Allergic Immunology Unit.

Member of the auditing body – Prof. G. Keren, manager of Cardiology Arrangements. the R&D Division.

Management representative – Dr. Michal Roll, manager of R&D Division.

Committee coordinator – Ms. Michal Shneider, responsible for quality control in the R&D Division.

Guest member, chairman of the Helsinki Committee, Prof. M. Topilasky.

1.3.2. Reporting to: the Manager of the Medical Center.

Members of the Auditing Body are appointed by the Manager of the Medical Center.

1.3.3. Duration of appointment – 3 years

2. Duties of the Auditing Body

To check that actual performance of the clinical trial matches the approved plan.

The unusual events and examine events that deviate from the procedure.

3. Reporting

The Auditing Body will report to:

- The chairman of the Helsinki Committee
- The Director of the Medical Center
- The Chief Researcher
- The Manager of the Division/ Department where the review takes place
- The Ministry of Health.

4. Reporting period

- To members of the Auditing body – the results of every review.
- To the chairman of the Helsinki Committee – the results of every review.
- To the Chief Researcher – the results of every review.
- To the manager of the Division/ Department – results of every review.
- To the Director of the Hospital – every 6 months*
- To the Ministry of Health – every six months.

* Any review whose results deviate from the procedure.

4.1. **Confirmation of reporting review**: Confirming of the audit report will be given in writing:

- By the Chief Researcher
- By the manager of the Division/ Department
- By the chairman of the Auditing Body
- By the chairman of the Helsinki Committee
- By the Ministry of Health

The review process

5. Criteria for examining trials

5.1. Meeting timetables.

5.2. Validity.

5.3. Interim reporting.

5.4. Request for extension.

5.5. Reporting completion.

6. Selection of sample trial for checking

6.1. Scope of departmental activity.

6.2. Activity of the chief researcher.

7. Types of trials

7.1. Drug/ preparation + initiator

7.2. Drug/ preparation without initiator

7.3. Medical device

7.4. Genetic

7.5. Human samples

7.6. No research product.

8. What is checked?

8.1. The protocol against implementation.

8.2. Validity

8.3. Approvals

8.4. Reports

8.5. Patient file

8.6. Illness file

8.7. Conduct of the pharmacy

8.8. Genetic trials – storage, documentation

8.9. Database

9. Scope of review

9.1. About 40 reviews are planned each year.

9.2. There are also unplanned reviews.

10. Process of summarizing reporting and approving

10.1. Review summary: On conclusion of the review, a written summary is submitted to auditing body members, to the Helsinki Committee chairman, to the chief researcher, the manager of the Division/ Department, and the Hospital Director.

10.2. Six-monthly report – summary of all reviews during the period.

The annual reports and six monthly reports are signed by the Hospital Director and sent to the Ministry of Health.

11. Working process of the Auditing Body

11.1. After every review a written report is prepared for members of the auditing body, the chief researcher and the Helsinki Committee. Members of the auditing body can make comments and suggestions for amendments.

If there is a deviation from the procedure, the Auditing Body invites the chief researcher to give an explanation which is discussed and decisions are made about the continued conduct of the trial.

In exceptional cases, the Director of the Medical Center is notified.

11.2. The Committee meets regularly once a year.

11.3. Extraordinary meetings take place following anomalous events and audits whose reviews deviate from the procedure.

Appendix 12 – Procedure of the Helsinki Sub-Committee for Research that is not a Clinical Trial

According to a directive from the DG of the Ministry of Health (No. 15/06) dated 6.6.2006 (attached), a research that is not a clinical trial on humans will be defined as one of the following two types of research:

a. Research in which information is gathered from people, by interacting with them.

b. Research in which information is gathered from the records of physicians, nurses, social workers and other paramedics about patients, without involving the patients.

Providing that the research does not involve any processes, action or physical tests, or makes use of a drug, radiation, or any chemical, biological, radiological or pharmacological substance on the participant.

In such research the chief researcher is not required to have an MD or DMD degree, but must have at least a Master's degree and have the professional knowledge and experience that qualify to carry out the research specified in the application.

Application forms for research that is not a clinical trial on humans are different from the forms specified above, and can be found on the website of the Hospital's Helsinki Committee and the website of the Ministry of Health.

The Helsinki Committee in its current format will serve as a sub-committee for this purpose, to discuss and approve such research, since its composition and activity do not conflict with the DG's guidelines for approving research of this type.

The Committee's approval is issued on Form 4 and the Director's approval on Form 5.

The researcher may start conducting the research only after receiving the Director's approval.

State of Israel, Ministry of Health

Circular from the Director General

No. 15/06 Date: 10th Sivan 5766 (6.6.06)

Subject: Helsinki Sub-Committee to Approve Research that is not a Clinical Trial on Humans

1. Background

The Public Health Regulations (Clinical trials on humans), 5741-1980 (hereinafter: the Clinical Trial Regulations) have adopted the Helsinki Declaration of 1964 (Amended version 1975) on the subject of approvals for biomedical research involving humans.

By virtue of these regulations, Helsinki Committees are currently operating in hospitals, to discuss applications to approve clinical trials on humans, with the definition of the Clinical Trial Regulations.

In fact, medical institutions carry out two kinds of research:

a. Clinical trials on humans, within the definition of the Clinical Trial Regulations.

b. Research that is one of the following

   i) Research in which information is gathered from people, by interacting with them.

   ii) Research in which information is gathered from the records of physicians, nurses, social workers and other paramedics about patients, without involving the patients.

   Providing that the research does not involve any processes, action or physical tests, or makes use of a drug, radiation, or any chemical, biological, radiological or pharmacological substance on the participant.

At present, applications to conduct research of the types specified in paragraph (b) are also submitted to the Helsinki Committee for professional and ethical review, even though they do not involve clinical trials on humans.

A clinical trial on humans must be under the responsibility of a physician. **However**, research of the **types specified in paragraph (b) can be conducted under the responsibility** of a range of health professionals who are not necessarily physicians.

Research of this type could make a significant contribution to promoting and improving the quality of care of patients but in this case there is no need to comply with all the requirements in the Regulations and Procedures of the Pharmacy Division with respect to clinical trials on humans.

Below are the rules for submitting applications for researches that are not clinical trials on humans and for their checking and approval by a sub-committee of the Helsinki Committee.

Note: The director of a medical institution may decide that at the institution he manages, applications under this procedure for researches that are not clinical trials of humans can be examined by the institution's regular Helsinki Committee.

2. <u>Track for approving research that is not a clinical trial on humans</u>

a. Applications for research that is not a clinical trial on humans will be submitted to the relevant sub-committee of the Institutional Helsinki Committee.

b. The sub-committee will examine the application according to the criteria given in section 5 below, and decide whether to approve the research, reject it, or ask for additional details.

c. The sub-committee may determine that this is a clinical trial that does not meet the criteria of this procedure, and the application will be returned to the researcher for re-submission as a clinical trial.

d. The director of the medical institution will approve the sub-committee's decision in the normal way for a special clinical trial.

e. Notice of approval of the research will be send to the Pharmaceutical Division, Clinical Trials Department, **as part of the annual report** (submitted pursuant to section 15.4 of the Procedure for Clinical Trials on Humans, 2006 edition), for information and review.

3. <u>Composition of the sub-committee</u>

a. The chairman of the Helsinki Committee will appoint a sub-committee with at least 3 members, of whom at least 2 will be members of the Institutional Helsinki Committee. The Committee will include:

i) A management representative – physician.

ii) Representative of the public.

iii) Senior professional with a PhD degree in one of the following: Nursing, Pharmacy, Social Work, Psychology, Physiotherapy, Occupational Therapy, Communication Disturbances, Natural Sciences.

b. The chairman of the Institutional Helsinki Committee will appoint one of the sub-committee members to be its chairman.

c. The legal quorum of the sub-committee will be at least the three members given in paragraph (a) above.

4. <u>Submitting an application for approval of research</u>

An application to approve a research that is not a clinical trial on humans must be submitted in writing by the chief researcher to the chairman of the Institutional Helsinki Committee where the research is to take place.

The application must include the following documents:

a. Request to approve research that is not a clinical trial on humans (Form 1).

b. Detailed plan of the research, including an explanation sheet for completing forms and submitting the plan:

i) Background to the research, with reference to the literature.

ii) Purposes.

iii) Hypotheses or research questions.

iv) Details of the research method, including research tools in full.

c. Format of the consent form for participants (Form 2 or 3).

The consent form for participants includes:

- An explanation of the purposes of the research
- An explanation of what is required from participants in the research and for the purpose of participation.
- An explanation of possible discomfort involved in participation.
- Assurance that a refusal to participate in the research will not affect the patient's relationship with the medical team or his rights regarding treatment.
- Assurance of confidentiality, and an undertaking to use the results for the purposes of that research only.
- Name of the chief researcher, responsible for the research.
- Place for the participant to sign, to confirm his consent to participate in the research, and the date.

d. CV of the chief researcher.

e. If the research is carried out in the framework of academic studies, appropriate confirmation from the academic institution will be attached. This confirmation will include the name of the research tutor.

5. Criteria for approval of a research that is not a clinical trial of humans

Members of the sub-committee will approve research that is not a clinical trial of humans if it believes that all the following conditions are met:

a. The purpose of the research is to study, improve and promote scientific knowledge and processes in the professional field it deals with;

b. Existing scientific knowledge in the field of the research justifies the proposed research.

c. The research has been planned in a scientific way that will enable it to answer the research question, and is described in a clear, detailed and accurate way in the research plan.

d. The expected benefits for participants or society justify any discomfort that might be caused to participants.

e. The nuisance involved in the interaction with the participant is being kept to a minimum, and data will be collected about him in a way that minimizes any possible damage to his privacy.

f. The chief researcher has a Master's degree at least (if he is not an MD or DMD), with professional knowledge and experience that qualify him to carry out the research as specified.

g. Participants in the trial will be selected without discrimination and according to the rules of inclusion and exclusion defined in the research plan.

h. The informed consent form includes all the items required as specified in clause 4 above.

i. Details are given of how privacy will be maintained.

j. Nothing in the research procedure or conduct amounts to injury to the participant or his rights under any law.

k. If the participants in the research could be exposed to unfair pressure or influence to participate in the research – suitable steps will be taken to prevent such pressure or minimize such influence.

6. Exemption from informed consent: if the research wishes to gather information from medical, nursing and social records only, without involved patients, and maintaining full anonymity of the data, the sub-committee may exempt the researcher from obtaining the patients' informed consent, providing that the chief researcher is a member of a university hospital attached to a recognized Faculty of Medicine pursuant to the Council for Higher Education Act, 5718-1958.

7. This procedure does not exempt the research from approval pursuant to the Procedure on Agreements with Commercial Companies, as appropriate.

Please bring the contents of this Directive to the information of everyone concerned in your institution.

Yours sincerely,

Prof. Avi Israeli

Copy: MK Yaakov Ben Izri, Minister of Health

File 96042/SB

Explanatory Sheet for Completing Forms and Submitting Research Plan

The forms can be downloaded from the website of the Ministry of Health on http://www.health.gov.il/download/drugs/mk15_06_tofes.doc

1. All forms must be completed by typing only.
2. Extra rows/ pages can be added as necessary to expand the information.
3. The checklist of documents (Form 6) must be completed and signed and linked to the main application.
4. The application form (Form) must be completed in detail and accurately, and the chief researcher must sign the declaration. An unsigned application will not be processed and will be returned to the sender.
5. Instead of completed Section (c) on the consent form (in Form 2 or 3), a separate explanation sheet for participants can be attached. This sheet will give all the information about the research, under the headings given in Section (c), in simple, clear language, so that anyone can understand it.
6. Before starting the research, the participant or his legal representative will receive a full copy of the consent form, signed and dated as required by law.
7. Approval of the Helsinki Sub-Committee (Form 4) and approval of the medical institution (Form 5) will be printed on the official headed paper of each.
8. The research plan will include:
    a. Heading of the research.
    b. Background of the research, including review of literature.
    c. Purposes of the research.
    d. Hypotheses/ research questions.
    e. Details of research methodology (including: population, size of sample, criteria for inclusion, research procedure, estimated duration).
    f. Details of research tools (attach in full).
    g. List of sources.

Part B: Instructions for completing the file

This file is modular; that is, the researcher must enter the appropriate details in the spaces provided. Any parts that are not relevant to the proposed study must be deleted.

For example, if no minors are involved in the study, the informed consent form for minors is not required. If the samples are not identified (according to the above definition from the Genetic Information Act) note in the appropriate space below, in the informed consent and the explanation for participants that the study uses unidentified samples. For study where there is no risk of stigmatization, the section discussing this will be removed from the file, and so on, to the extent that it affects the whole study proposal. The form must be completed using Arial Bold, font size 12.

1. Information required in an application to approve the study protocol

a. Basic information

1) Name of study and date of proposal.
2) Names of chief researcher and secondary researchers, including the address and name of the institution to which each belongs (with telephone, fax and email).
3) For multi-center study, names of centers and researchers at other centers.
4) Name, address and description of study initiator. "Initiator" – the commercial company or other entity, excluding the chief researcher, that is initiating and funding the study.
5) Approval of the Institutional Helsinki Committee dated _____ (must be attached).
6) Approval of the Institutional and/or Supreme Helsinki Committee for all previous study for which the requested study is a continuation.
7) Please indicate if the study includes:
   - Collection of DNA/ RNA samples.
   - Storage of DNA/ RNA samples.
   - Testing of DNA/ RNA samples.
8) Purposes of the study.
9) The scientific background, the rational for the study, and a review of the scientific literature (in brief); reasons why the study is needed, including the collection and/or storage and/or testing of DNA.
10) Please indicate a specific timetable for the study, including the following:
   - Time required to collect samples.
   - Time required to analyze results.
   - Time for which samples will be stored.
   - Time for which samples will remain identified.

b. Information about participants in the study

11) Number of participants, including power analysis or statistical justification for the sample size, if necessary.

12) Description of the method of recruiting participants (including members of the control group). If family members of subjects are included in the study, they must be contacted through the subject, and not directly by the researchers, in order to avoid infringing on their privacy and medical confidentiality.

13) The criteria for including participants.

14) The criteria for not including participants.

15) Please indicate the source of samples.

Specify if the samples were collected by the researchers for the current study or were supplied from another source. If samples were received from another source, please indicate whether the people who provided the samples gave informed consent for their use in the current study. If the source is an archive, please indicate whether the donors are alive or not, and if the researcher has received approval to use the sample. This approval must be attached to the application for approval of the current study from the Institutional Helsinki Committee. Whenever samples taken from a source for diagnostic purposes are used for study, it is important to ensure that the use of the sample for study does not affect the possibility of using it for diagnosis, treatment, or any other use pursuant to the law.

16) Please indicate if the participants in the study include minors, wards or the legally incompetent, with reasons for the necessity of their participation. Specify how their informed consent has been obtained, and the separation of their identifying details (see Article E of the Genetic Information Act).

c. Collection, storage and testing of DNA samples.

17) a. For study including the collection of DNA please indicate the source:

- Blood
- Biopsy of _____
- Cell culture
- Mucus from the mouth
- Samples from the pathology archive
- Other _____

b. Indicate if blood lines have will be prepared from the blood samples and the exact type (such as lymphoblastoid blood lines, fibroblasts culture, etc.).

c. Please indicate the location of collection (town, name of laboratory and hospital). If the samples are collected from other sources at other sites, all such collection sites must be indicated.

d. Indicate the name and address of the researcher responsible for collection (at each site if there is more than one).

18) DNA testing:

a. Please indicate where the DNA will be tested (country, city, name of laboratory or institute). If the DNA is to be sent to an overseas laboratory, attach a letter confirming this from the researcher responsible for this laboratory, including reference to the commitment of this researcher to the terms of the Committee's approval and compliance with the provisions of the relevant laws in Israel and the overseas country where the study is taking place.

b. Please indicate the name and address of the researcher responsible for the test.

c. Please indicate the test or tests to be performed on the sample.

d. Indicate whether additional/ repeat use of the DNA is planned for other study, and what it is. For each such use, separate approval is required and obtaining informed consent accordingly.

19) Storage of DNA

a. Please indicate where DNA samples will be stored (country, city, name of laboratory or institution). If samples will be stored in more than one location, indicate all the locations.

b. Please give the name and address of the researcher responsible for such storage (in each location if there is more than one).

c. Please indicate for how long the samples will be stored and the storage method.

d. Genetic information

20) Please describe the manner of handling samples on conclusion of the study, including specific timetable (for example, deletion of identifying details, destruction of samples, transfer of samples to other researchers, etc.).

21) Please indicate who is responsible for protecting genetic information (name, position, institution, address, telephone, fax and email).

22) Will the study make use of identified or unidentified samples? (Remember: a coded sample is an identified sample)

23) Please indicate the following details regarding identified genetic information:

a. Where will the genetic information be stored and kept (country, city, name of laboratory and institution)?

b. What is the method of storing genetic information?

c. Please indicate the means to be used to protect the identified genetic information of participants, and who will have access to this identified information.

24) Please indicate the following details regarding the unidentified genetic information:

a. Where will the genetic information be stored and kept (country, city, name of laboratory and institution)

b. What is the method of storing genetic information?

c. Please indicate the means to be used to protect the unidentified genetic information, and how it will be separated from the identified genetic information of participants. Will there be any link between the unidentified genetic information and the identifying details of participants, and if so, how?

e. Rights of participants

25) Specify the risks and benefits for participants.

26) Specify the rights of participants to stop their participation in the study. Pursuant to the law, if a participant wishes to withdraw from the study, no more use will be made of samples obtained for him and any details about him will become unidentified, unless he specifically agrees to their remaining identified.

27) Will participants be given the opportunity of receiving genetic information and results of identified genetic tests if there are any significant findings? If relevant, genetic counseling without payment must be promised to a participant and his family regarding information obtained during the study.

28) Will participants be able to obtain a summary of the study findings in clear language following scientific publication?

29) If participants are being asked to agree to identified scientific publication pursuant to Section 23(2) of the Genetic Information Act, 5761-2000, please emphasize this.

30) Declare your intentions regarding the rights of participants with respect to patents and intellectual rights.

31) Declare and specify whether there is any possible or actual conflict of interest between researchers and whether there is a link between the initiator and the researchers ("link" - any connection involving paid employment, as a contractor or in any other way, or commercial or business link, or family or personal link, and any other connection that could arouse a suspicion of conflict of interest or lack of independence, and excluding reimbursement of expenses or payment for participation in committees pursuant to this procedure. If the chief researcher is the initiator, please state this explicitly).

32) Please attach an explanation sheet for participants in the study.

33) Please attach an informed consent form for participants.

34) Please refer to any additional question or ethical matter that may arise in the study.

The informed consent form must be completed according to the instructions given at the end.

Informed Consent for Participation in Whole Genome Genetic Study

(Consent to participate in a trial that involves collection, storage or analysis of genetic material)

Shalom, you are being asked to participate in a genetic study. The purposes and details of the study will be explained later, so that you will have all the information necessary to give your i**nformed consent** to participation.

1. **General**

Clinical trials on human beings, including genetic study, which includes analysis of genetic material (DNA), are permitted pursuant to the law only if they protect the rights and privacy of all participants. The study in which you are being asked to participate has received such permission. It is important that you understand the details and purpose of the study, so that your consent to participate is based on knowledge and understanding. Please carefully read the attached information sheet and the informed consent form. Don't hesitate to ask the team member for explanations and clarifications. Take your time to consider your participation and discuss it with other people. If you decide to participate, complete the form as requested and sign at the end where indicated.

2. **The Study**

2.1. Study name and subject: study on _____ including whole exome/ whole genome sequencing.

2.2. Description of study (background to study) _____

This study uses laboratory methods to examine all your genetic material (DNA) using methods called "whole genome". A human being's genetic material can be compared to a book written in various combinations of 4 letters: A, T, G, C, with a total of about 3 billion combinations, of which only about 1% (the genetic sequence) represents body proteins. The remaining genetic sequences have various functions, most of which are still unknown. "Writing errors" in the total genetic sequence, also known as mutations or genetic changes/variants, are common and every individual has several million such changes. Some of these changes are linked to diseases or various physical conditions, some have no medical significance, and in the vast majority of cases – their significance is not year clear. Previously, only short sections of the genetic sequence could be tested. Today, using whole-genome new technologies, it is possible to read the whole genetic sequence, including that 1% coded to physical proteins (this part is called by professionals the "exome"), and well as all 3 billion letters, i.e. the whole of the genetic material, or the genome.

The purpose of this study is to understand _____. This will be done by comparing the genetic sequence of the study group with a control group. Changes differentiating the two groups could be linked to the condition being studied.

Whole genome study has several unique aspects:

c. The purpose of this study is to examine the genetic factors of _____ (*disease/ condition being studied*). In this whole genome study, many genetic changes will be found in your genetic sequence that are not linked to _____ (*disease/ condition being studied*), but the researchers will only report to you

changes that are definitely linked to _____ (*disease/ condition being studied*) and which have medical significance. The report will be given as part of genetic counseling. **The reason is that the study will gather vast amounts of data, but the researchers will only analyze findings relating to _____** (*disease/ condition being studied*) and are only permitted to examine in depth aspects relating to the current study. The genetic sequence of every person contains million of changes that are not related to _____ and the researchers are unable to examine them all and find possible links between them and diseases or other conditions unrelated to the present study. Moreover, such links may change as genetic knowledge advances. You are advised to ask your family physician about genetic tests recommended for everyone in your group.

d. The total genetic sequence is a kind of unique "fingerprint" that identifies each individual. As part of this study, your genetic sequence may be included in databases intended only for researchers. The researchers are committed to making every effort to maintain the confidentiality of information derived from your genetic sequence, although even if the sample *is not identified/ coded*, there is a theoretical possibility of linking you to your genetic data, if another person has information about part of your genetic sequence. In the case of study on identified samples, you can ask for your genetic data to be removed from the database at any time.

2.3. Purpose and processes: the purpose any medical study is to expand and develop current knowledge with the aim of preventing disease, finding cures or relieving the suffering of patients. You inherited your genes from your parents. These genes determine, for example, your eye color, your appearance, whether you will develop certain diseases and how you will react to certain drugs. The genes you inherited from your parents may be different to their genes. They can also change over time. We will take a sample of _____ and analyze the genes in the sample, in order to study the following:

- ○
- ○
- ○

2.4. The study is being conducted at _____.

2.5. The chief researcher is _____.

2.6. The study is initiated by: _____

2.7. If the initiator of the study also has commercial aims: the researcher/s **is/are linked/ is/are not linked** to the initiator.

2.8. For your information, there is a possibility that your sample may be sent to a laboratory/ joint researcher [*delete as applicable*] overseas. See section 4.5 below, where you are asked to consent to this.

3. **Participants**

3.1. You have been chosen to participate in this study as a member of the _____ group.

3.2. Your participation in this study is entirely voluntary, and you will not receive any monetary or other benefit for consenting to participate.

3.3. Your consent or refusal to participate in the study will not in any way affect your right to receive medical treatment, its quality, or the attitude of your medical healthcare providers.

3.4. Your personal details and details of the sample you gave will be kept confidential in order to maintain your privacy, and will only be used by the authorized researchers.

3.5. You have the right to decide not to participate in the study, or to withdraw at any time, so long as the identifying details of your DNA sample have not been destroyed.

3.6. If you have any questions or problems about the study, you can contact the physician in charge, Dr. _____, telephone _____.

4. **Samples**

4.1. Your participation in the study involves giving a sample of blood (a skilled professional will take ____ cc of your blood, about ____ spoonfuls)/ saliva/ skin/ biopsy, in order to produce your DNA.

4.2. The study also involves a personal interview. A member of the study team will ask about your state of health, medical treatments you have received, your origins and medical history, or that of your family. This is personal medical information, and the study team are obliged to keep it fully confidential.

4.3. The researchers may use your genetic material and genetic information derived from it **solely for the purposes of this study.**

4.4. You can agree to have your genetic material used in additional study relating to the disease from which you suffer, or in future study on another subject. If you consented to the use of your sample solely for this study, and the researchers wish to use it for other study purposes, they must contact you again (providing that your sample remains identified) and ask for your additional consent.

4.5. I consent to have my DNA sample sent to a laboratory overseas, in coded form (identifiable only to the researcher in Israel, who has the key to the code, but anonymous to the overseas laboratory). [Signature: _____].

4.6. It is stressed that any further study on the sample requires approval from the Ministry of Health, just as it applies to this study, according to the explanation you will receive about possible other uses of your blood sample. Please sign to indicate your consent to **<u>one of the following options only</u>**:

☐ I consent to the use of my DNA sample **for the current study only**. [Signature: _____].

☐ I consent to the use of my DNA sample **for the current study and for any other legally approved study dealing with _____ (disease)** [Signature: _____].

☐ I consent to the use of my DNA sample f**or any legally approved study** [Signature: _____].

4.7. If you consent to the researchers using your blood sample to prepare **permanent blood lines** (that is, cultivating some of your blood cells in the laboratory so that they can continue to use them for other study, as necessary), sign here: _____.

4.8. How will the samples be preserved and what will be done with them?

4.8.1. The samples will be kept as identified*/ identified (encoded) unidentified samples for a period of _____ years from the date of approval of the study, at _____ (place) under the responsibility of _____.

4.8.2. On conclusion of the study, **your samples will be destroyed/ your identifying details will be removed from your samples** and the genetic information obtained from testing them, unless you give consent as follows to keeping the sample identified.

☐ When the study is finished, I consent to my DNA material being kept as an **identified sample***, which can be linked to the results of the study [Signature: _____].

☐ When the study is finished, I do not consent to my DNA material being kept as an **identified sample***, and **ask for it to be kept as an unidentified sample**, which cannot be linked to the results of the study [Signature: _____].

* An **identified sample**, as defined by law, is a sample whose donor can be identified, even if it is marked with a code and does not bear any identifying details of the participant, such as name, ID number and so on.

5. The Right to withdraw from the Study

If you decide to participate in the study, you can cancel your consent at any time and for any reason. It is important that you notify your study physician of your decision. You do not have to give a reason, and this will not affect the treatment to which you are entitled. You can withdraw from the study as long as the sample you gave can be identified, can be linked to you and can be located. Your sample and any identified genetic information relating to it will be destroyed. Any tests will be stopped. Any results obtained from the samples will become unidentified. The researcher will only be permitted to make use of unidentified information obtained from tests done on your sample before you withdrew.

6. Benefits and risks

6.1. **Are there any benefits to participating in the study**? At this stage, it is not possible to promise that the study results will have any direct significance or benefit for you. However, the results could advance medical knowledge, contribute to the diagnosis and treatment of people with the same or similar conditions to you.

6.2. **Are there any risks of participating**? In this genetic study there is no direct medical risk for participants. When the blood sample is taken you may feel a slight discomfort from the puncture and there may be slight bleeding.

Regarding your privacy and confidentiality of information – all information collected in this study, particularly your personal information, is confidential and protected by law. The researchers are obliged to maintain this confidentiality, to prevent access to the information by anyone except the study team and/or study initiators and/or responsible elements in the Ministry of Health (who have access to your medical file for purposes of the study and verifying study methods and clinical data).

6.2.1. The results of this study will not be included in your medical file. In the event of any identified clinical genetic test or other medical test which could have medical significance for you, or if you receive medical treatment as part of the study – in accordance with the law, only information about **the fact of doing the test** (and not its results) or giving the treatment will be sent to your family doctor in the healthcare provider where you are insured. It is clarified, that by consenting to participate in this study and by signing this form, you are also consenting to the fact that the above information will be sent to your family physician.

6.2.2. If you do not wish this information to be forwarded to your physician, please sign here: _____.

6.3. Genetic counseling

6.3.1. If during the study the researchers discover any information of medical significance for you or your family, you will be informed (if the study is using identified samples), if necessary as part of genetic counseling.

6.3.2. **You have the right not to know the results of your genetic testing.** If you do not wish to receive **personal** genetic information that may be discovered during the study, please sign here: _____.

7. **Consent to participate in the study**

By signing you are confirming that you have read the informed consent form and you are prepared to participate in this study, after understanding its details and significance.

Participant's details and signature:

Forename:	Surname:
ID number:	Date:
Signature:	

Details of person receiving the informed consent:

The foregoing consent was received by me, after I had explained all the above to the participant and ensured that my explanations had been understood.

Forename:	Surname:
Job title:	Date:

Signature and stamp:

Declaration of Chief Researcher

I undertake to comply with all legal provisions relating to medical study on humans and to meticulous about all the ethical reservations, including the principles stated in the Helsinki Declaration and the physician's oath.

Signature:	Date:

The following will be attached to an informed consent form intended for a minor/ ward/ legally incompetent individual:

Addressed to parents*

As the parents of a child who is being asked to participate in the proposed study, you are responsible for giving consent in his name and for him. Genetic study does not in general pose any risk to the participant (except for the discomfort when giving blood) and could advance medical knowledge. However, it is important to remember that genetic information is very important, particularly in a personal and family context. As the people responsible for the wellbeing of your child, it is important that you know that the proposed study is subject to the guidelines of the Supreme Committee for Approval of Clinical Trials on Humans and has been approved by it in accordance with the law, and that you are permitted to decide that your child will not participate in the study, without affecting his/her right to receive the standard treatment.

Minors over the age of 16

If your child is aged over 16 years, he must receive from the researcher or his representative a clear and full explanation of the nature of the study **in your presence**. After he has received the explanation, you must ensure that, if your child consents to participate in the study, he confirms this by signing the form (in addition to your signature).

It is important to clarify to your child that, **when he reaches the age of 18** he may, according to the law, cancel, express reservations or change his participation in the study, by contacting the researchers.

Results of study using identified samples

If the study uses identified samples and results or obtained, or findings are discovered that have clinical significance for your child, you may ask for these results in the framework of genetic counseling, as usual. According to the law, the results will only be given if it emerges that your child **is not** carrying the gene for a disease, or if the existence of a disease or a carrier gene for a disease is discovered, that can prevent the disease or delay its appearance, or treat it, as long as no health or mental injury is caused to your child as a result of exposure to this information.

* The above refers also to the legal guardians of a minor/ ward/ legally incompetent person.

We the undersigned, parents/ guardians of the minor/ ward/ legally incompetent person ("the participant")

Mother's name	ID no.	Signature	Date
Father's name	ID no.	Signature	Date
Guardian's name**	ID no.	Signature	Date

** Attach a copy of the order of guardianship

Participant's name	ID no.	Date of birth (in the case of a minor)	Address

Hereby declare that we consent to the participant's participation in this study, as specified in the informed consent form.

If necessary[6]:

Name of independent witness:	ID no.	Signature	Date

It is clarified that any treatment, experimental and other, of the minor must be in the spirit of Clause 17 of the Legal Competence and Guardianship Act, 5722-1962 (compatible with the obligation of the parents):

"In their guardianship of a minor, the parents must act for the benefit of the minor as devoted parents would do in the circumstances."

The chief researcher in a clinical trial has the obligation to bring the contents of this clause to the attention of parents and to explain the nature of the treatment to them, included any expected benefit, the risks involved and possible discomfort to the minor, and to ensure that the parents have understood all these meanings.

After the parents have understood the foregoing, they are **both** asked to sign the consent form. Nevertheless, in the following circumstances it is possible to be satisfied with the signature of **one parent:**

- At the decision of the Supreme Helsinki Committee*;
- Participants with single parents (only when the father's identity is unknown);
- In special cases, when a child is in the custody of one parent and it is impossible to obtain the consent of both – the Supreme Helsinki Committee must be asked to give approval.

If the minor is able to understand the explanation, the minor must give his consent and sign the form.

In relevant cases (such as someone who is legally incompetent), the guardians appointed by order of the court must be treated as parents.

[6] If the participant in a clinical trial or his legal representative is unable to read the informed consent form, an independent witness must be present during the explanation of the nature of the trial, and after the participant or his legal representative has expressed his verbal consent to participation in the trial, the witness will sign and date the consent form.

* in special cases where the treatment cannot be delayed and it is not possible to obtain the consent of both parents, the signature of one parent can be sufficient, according to Clause 18 of the Legal Competence and Guardianship Act, 5722-1962. The clause is conditional on obtaining prior written approval from the chairman of the Medical Institution's Helsinki Committee regarding its consent that the signature of only one parent is sufficient for the aforesaid clinical trial.

Guidelines for the Researcher on Drawing Up the Informed Consent Form and Adapting it to the Study

(The paragraph numbers refer to the sections in the Informed Consent Form)

2.2 Description of the study – describe the purpose of the study and the manner of conducting it (in a general way) using simple, everyday language.

2.7 There is/ is not a link to the initiator of the study – delete as necessary. Also, **if the study is funded by a commercial company**, indicate this on the informed consent form.

3.1 A **separate** informed consent form must be prepared for each group of participants: the group of patients suffering from the disease being investigated/ the participants who are carriers of the gene being investigated/ the control group of healthy people/ other.

3.2 If the participant is due to receive payment for participation, amend this section accordingly, specifying what payment is promised.

4.1 Adapt this section to the type of sample taken as a source of DNA – blood, internal tissue, skin tissue, cheek mucous tissue, or any other option. Specify how the sample is to be taken and the risks involved. If the samples have already been taken as part of a clinical process, indicate that their use for study purposes will not affect the possibility of using the pathological material for the patient's future benefit (which is a condition for approval of the study).

4.2 If the study does not involve completing a questionnaire, delete this section. If there is a questionnaire, indicate this and clarify the nature of the questionnaire, its purpose, how it is completed, the time required to complete it and the significance of its findings.

4.8.1 Samples will be stored as **identified/ identified (coded)/ unidentified** samples – delete as appropriate. Indicate where the samples will be kept and the name of the person responsible for them.

4.8.2 **Identifying details will be separated from the samples / the samples will be destroyed** – choose one option and delete the other.

6.2 If there is an expected direct risk associated with participation in the study – indicate this.

6.2.1 If the study does not involve a clinical genetic test to produce identified genetic information about the participant, or other medical test, or if treatment is given – delete the sentences that are irrelevant in this section. It is clarified that if the study involves an identified clinical genetic test, other medical test, or the provision of medical treatment – the participant's refusal to permit forwarding information about the fact of his participation to his family physician will of necessity prevent his participation in the study.

7. The informed consent form referring to the participation of a minor/ ward/ legally incompetent person in a study must be addressed to the participant's parents/ guardian.

3. Explanation for Participants from the Physician/ Researcher

[To researchers: this text must be adapted for the specific study you propose to conduct.]

The purpose of this sheet is to explain to you the various aspects of the study in which you are asked to participate.

1. **Purpose of the study**
2. **What is required of participants?**
3. In this study we will use **identified/ coded (identified)/ unidentified** samples [delete as necessary]:
    - **Identified/ coded (identified) samples** – a sample which bears information that enable it to be linked to you, such as your name, ID number or a code number given to the sample.
    - **Unidentified sample** – a sample which has no link to any details that identify you, and therefore there is no way of linking the results of your DNA test to you in future. There is no way of linking unidentified DNA samples with your personal medical information. Your sample is given a random number for medical information and genetic results. This number has no connection to your participant number or your name.
4. **Discomfort when the sample is taken**

    you might feel a slight pain when blood is taken, including a slight subcutaneous bleeding – bruising. In rare cases there may be a local infection. If so, contact your physician. [*Researcher: adapt to suit the type of sample taken for this study, e.g. skin, cheek tissue, hair, other*]
5. **Keeping some of the DNA sample in Israel**:

    For your information, some of the DNA sample taken from you will be kept in Israel for the purpose of future medical treatment, or for the purposes of future medical study (subject to legal approval).
6. **Risks**:

    The risks involved in genetic study derive mainly from the fact that the results of your test could give you some genetic information about yourself, your family or your community, which could have personal, psychological or social implications. Such information obtained as part of a study cannot yet lead to a diagnosis or better treatment of any medical condition that may be discovered.

    In many cases the information is based on probability, that is, the test results show that you have a greater than average chance (more than most people) of contracting a particular disease, but this is not definite. Apart from the results of this test, the information obtained depends on many other factors, such as: the effect of other genes, lifestyle (diet, physical activity) and environmental influences.

    The test results may tell you that some of your family members have a higher than average risk of contracting a particular disease. This knowledge could cause you concern and change your relationship with your extended family.

    You should know that, according to the law, an employer cannot ask an employee or applicant for work for genetic information or ask him to take a genetic test, and he is forbidden to harm the employee in any way because of the refusal to give genetic

information or have such a test, with respect to acceptance for work, promotion, working conditions or dismissal. Exceptions could apply to certain places of work where concern for employee health requires genetic testing, as determined by the Minister of Health in the regulations.

According to the law, an insurer may not ask an insured person or applicant for insurance if he has had genetic testing and may not ask for the results of any genetic testing or require him to have genetic testing, and cannot make insurance cover conditional on genetic information or refuse to provide insurance while using identified genetic information.

7. **Patents and future rights**:

the results of genetic studies could have value and form part of a patent or the development of drugs, medical preparations and so on. In general, participants in the study have no rights regarding such patents, drugs or preparations developed as a result of the study in which they participated.

Institutional Procedure for Safety Reports of Serious Adverse Events (SAEs) in the Course of a Clinical Trial

(Specified in detail in Section 26: Managing reports of safety information)

1. Reporting a death

   - The chief researcher is responsible for the immediate reporting, within 48 hours of learning of the event, to the chairman of the Institutional Helsinki Committee, who will report to the person authorized by the director of the Medical Institution, any death of a participant in a clinical trial for which he is responsible.
   - The chief researcher will report the death on Form 13, including his opinion regarding the existence/ non-existence of any link to the trial drug (attaching any available relevant documents, such as: disease summary, summary of the death etc.).
   - On the basis of the findings, the Committee chairman will examine the possible consequences of any link to the trial drug and if he believes there is no link to the trial drug, he may authorize continuation of the trial. When the hospital has completed its investigation and the Helsinki Committee has made a decision regarding the trial, the report will be submitted to the Ministry of Health on Form 14, with a copy to the chief researcher, who is responsible for submitting a copy to the study initiator.

2. Reporting SAEs

   - The chief researcher is responsible for reporting to the chairman of the Institutional Helsinki Committee of any SAE that occurs in the course of the study for which he is responsible. The report must be immediately after the event comes to his attention, according to the schedule determined by the initiator in the study protocol. The researcher must report to the initiator on any new information relevant to the event by means of follow-up reports.
   - The initiator who receives the SAE reports from the chief researcher or the secondary researcher, makes an initial assessment and updates all researchers taking part in the study with safety reports including information on unexpected SAEs in cases where a connection between the SAEs and the use of the study product cannot be ruled out (Suspected Unexpected Serious Adverse Reactions – SUSAR). The time specified for the report is 7 days in the case of a death, and up to 15 days in other cases.

3. Safety reports (SUSARs) received from the initiator:

   - On receipt of the reports from the initiator, the chief researcher is responsible for forwarding them to the Helsinki Committee chairman. The reports will include information about all unexpected SAEs and those where a connection with the study product cannot be ruled out, that occur at the center and in other centers in Israel and overseas.
   - The chief researcher will decide whether the reports from other centers should be reported to the Helsinki Committee based on any possible connection with the study product and their severity, and will submit individual reports to the Committee.

- The chief researcher will submit the periodic reports (quarterly/ six monthly) received from the initiator to the Helsinki Committee, signed by him, confirming that after reading the reports he believes there should/ should not be a change to the protocol and the consent form. This report will include a list of all events and a summary of the main points that have arisen on the subject of the safety of the study product.
- On the basis of the findings, including the opinion of the Independent Safety Committee, the chairman of the Committee examines the possible consequences of a link with the study product, and if he believes that there is no such connection, he confirms continuation of the study.
- In cases where there is doubt about the existence of a possible connection with the study product, the chairman of the Committee summons an investigation committee that includes 2 extra members (usually experts in the field or deputy chairmen) and if necessary, the chief researcher is invited to attend.
- Depending on the severity of the events, the chairman decides whether a further debate is required with the full Committee, or informs members of the Committee of the decision to approve the continuation/ termination of the study.
- The Committee's decisions are reported to the Ministry of Health and the chief researcher, who is responsible for reporting them to the study initiator.

The guidelines of the DG of the Ministry of Health dated September 2005 and the update to the guidelines dated February 2008, refer to the obligation on all researchers to register their clinical trials before they begin in the clinical trial register of the NIH. Below are detailed guidelines on this subject.

1. Background

   After two years of registering clinical trials in global databases, the International Committee of Medical Journal Editors (ICMJE) published an editorial on the criteria for registration of clinical trials. Registration in a global database, before recruitment of the first participant, must be a condition for publishing the trial results in scientific journals.

   This policy applies to all trials that start recruiting subjects after 1.7.08.

2. What to register

   a. **A clinical trial** is defined according to the WHO definition: any research in which human participants or groups of participants are subject to one or more prospective medical interventions, to examine the effect on health outcomes.

   b. **Medical interventions** may include drugs, surgical procedures, medical devices and instruments, behavioral treatments, dietary intervention, changes in the course of standard treatment. The purpose of the intervention is a change in biomedical or health outcomes.

   c. **Health outcomes** include all changes in biomedical or health parameters obtained in patients or participants in the trial, including pharmacokinetic measures and side effects – registries.

   d. Phase 1 trials whose purpose is to examine the safety of a new drug and trials whose purpose is to determine pharmacokinetics, **are exempt from the obligation for registration**.

3. Obligation to register

   The Ministry of Health has adopted the ICMJE policy and requires registration of clinical trials taking place in Israel.

   Every clinical trial that meets the above criteria and is planned to take place in Israel must be registered in the NIH database of clinical trials. Dr. Michal Roll, the manager of the R&D Division, is responsible for managing registration at the Medical Center.

4. Registration procedure

   The researcher registers the trial immediately after submitting the application to the Helsinki Committee and receiving an application number. The researcher registers the trial on the website: http://register.clinicaltrials.gov/. The name of the organization (as shown in the site records) is: TelAvivSMC. (TelAvivSMO?)

   a. Researchers registering for the first time should go to Quick Start Guide.

   b. Researchers who know the procedure should go to Create and follow the process.

c. Numbering – the trial protocol ID number is composed as follows:

TASMC -	08 -	XX -	000 -	CTIL
	Year	Chief researcher's initials	Helsinki number	

(CTIL and TASMC are mandatory fields, to allow us to locate the registration.)

d. As the trial progresses, the information on the site must be updated.

e. Researchers who have a problem registering are asked to contact the R&D Division on tel. 4761 or email mop@tasmc.health.gov.il.

When registration is complete, (with a few days), the record is transferred to a database that can be accessed by anyone. The researcher must send a copy of the registration by fax (on 6973974) to the **Helsinki Committee coordinator**, in order to obtain the Committee's approval for the trial.

5. Responsibility for Registration

The initiator of the clinical trial is responsible for ensuring it is registered in the database.

a. If the initiator is the researcher, he is responsible for registration.

b. For a multi-center trial taking place in Israel, and initiated by a researcher (and not a company), the person responsible for the trial must register it once in the database, indicating all the centers as required.

c. For trials initiated by commercial companies, the researcher must ensure the company registers the trial on the NIH site and obtain a copy of the confirmation.

d. If the researcher has not registered the trial in the database, he must indicate this and give the reason.

If the researcher is not sure whether he has to register the clinical trial in the international database in order to publish an article about it, he should consult Dr. Roll (tel. 4761) or Liora Etgar (tel. 4924).

A researcher who fails to register a clinical trial in the database will not receive approval for the trail, and as stated will not be able to publish his work in the international scientific literature.

Appendix B – Application to set up, or approval of a stockpile of DNA samples for medical or research purposes

(According to the guidelines of the Supreme Helsinki Committee for Genetic Research on Humans on setting up and using stockpiles of genetic samples and according to Directive 01/05 from the DG of the Ministry of Health).

8. **Title:** _____

The applicants and their job titles:

Ministry of Health Procedure:

1. Names of the applicants and their departments: _____
   _____
   _____
   1.1 Chief Researcher: _____
   1.2 Secondary Researchers: _____
   _____
2. The applicant's institution and its address: _____
3. Identity of the stockpile owner (in the case of a corporation – its owners of control and directors): _____
   _____
4. Management of the stockpile:
   4.1 Manager of the institutional stockpile: _____
   4.2 Members of the accompanying committee: _____
   _____
5. Purpose of setting up the stockpile: _____
   _____
   _____
   5.1 To permit the following types of research: _____
   _____
   _____
   5.2 Sample storage location, conditions of storage and means of security: _____
   _____
   _____
   _____
   5.3 Planned number of samples to be collected for the stockpile (if possible, by type of source, from sick and healthy people): _____
   _____
   _____
   5.4 Nature of the samples: _____
   _____
   _____
   _____

6. Sources of collecting samples (types of populations – sick and healthy, minors, wards, legally incompetent): _____
   _____
   _____
7. Details of the method of collecting samples: _____
   _____
   _____
8. Details of the method of compensating donors and/or collectors of samples: _____
   _____
   _____
9. Terms of use for samples from the stockpile: _____
   _____
   _____
10. Means for securing the genetic information linked to the samples: _____
    _____
    _____
11. Boundaries for use of samples (in Israel, or if overseas – which countries): _____
    _____
    _____
12. Sources of funding to set up and maintain the stockpile: _____
    _____
    _____
    _____

I/we the undersigned confirm that the details we have given above are correct, true, full and to the best of our knowledge. I/we undertake to comply with the instructions of the relevant instructions and laws in everything relating to the requested/ existing stockpile.

Signatures and details (of at least the applicant, the intended manager and a representative of the owners of the stockpile):

_____

_____

_____

1. Applications will be submitted to the Helsinki Committee according to the existing instructions.
2. All applications on this subject will be handled by Prof. Yehuda Carmeli, who has been authorized by the Hospital management.
3. Every application to the Helsinki Committee concerning a study of any disease precursors must be submitted on the attached form together with the submission documents. This form can also be downloaded from the Helsinki Committee website and the Hospital website.
4. The chairman of the Committee for Regulating Studies of Biological Disease Precursors will give the researcher instructions based on the provisions of Section 15 of the Law:
   a. An institutional committee will approve the keeping of disease precursors or studies on them if it is persuaded that all the following criteria are met:
      1) Nothing in the study will endanger national security or the welfare, health or security of the public; among other things, the Committee will consider the following aspects of the study:
         a) Increasing the damage that the disease precursors could cause;
         b) Increasing the resistance of disease precursors to drugs, means of sterilization or other physical conditions;
         c) Making the disease precursors harder to discover or identify.
      2) The research complies with the requirements and procedures, including the rules of safety in any law, regarding the keeping of disease precursors or conducting research on them, including the equipment required and the research team and its qualifications.
   b. The Institutional Committee will not approve the keeping of disease precursors or conducting research on them unless:
      1) The Institution where the disease precursors will be kept or where the research will take place has a stockpile of written procedures regarding the rules for keeping disease precursors or conducting research on them pursuant to this law;
      2) The researcher submits an affidavit, legally drawn up and signed and according to the provisions determined by the Minister, declaring that he has not been convicted of any security offense.
   c. For the purpose of issuing the approval pursuant to this Section, the Institutional Committee may ask the applicant for any additional item of information it requires in order to consider the application.
   d. The Institutional Committee shall not refuse to approve an application if it can be approved conditionally, or with regard to an application to approve research, the research can be restricted and instructions given on its conduct.
   e. If the Institutional Committee finds that an approval it has issued could endanger national security or the welfare, health or security of the public, or that it has issued such approval in error, or based on mistaken information, or that the research is not

being conducted according to the conditions and restrictions it defined, it may determine new conditions or restrictions for the approval, or cancel such approval.

f. The decision of the Institutional Committee pursuant to Sub-section (e) shall be given after the researcher has been given an opportunity to state his case, but the Institutional Committee may hear such arguments after canceling the approval if it finds that a delay in cancelation could damage national security or the welfare, health or security of the public.

5. If the research involves collecting and creating an archive of disease precursor or the products of disease precursors or any other product of dealing with disease precursors, the chairman of the Committee shall consult the Hospital's qualified Data Security Manager on the subject of securing this stockpile.

6. After examining the matters relating to the subject of the research, the research will be approved by the chairman of the Helsinki Committee and the manager of the Hospital in the accepted manner.

Form to accompany an application to conduct research on biological disease precursors

The researcher should circle the appropriate answers, sign and attach this form to the documents submitted to the Helsinki Committee.

A list of disease precursors is attached.

- ✓ I have checked and the disease precursors that I am studying do not appear in the above list of disease precursors. If they are not included in the list, please sign and submit this document to the Helsinki Committee. Yes / No
- ✓ If the research deals with disease precursors defined in the attached list, the researcher must submit the following information for approval by the Committee:

a. Will the research increase the damage the disease precursors could cause? Yes No

b. Will the research increase the resistance of the disease precursors to drugs, sterilization means or other physical means? Yes No

c. Will the research make these disease precursors harder to discover and identify? Yes No

If one of the answers to the above questions is affirmative, you must contact the Helsinki Committee coordinator for instructions on how to proceed.

Date: _____ Name & signature of chief researcher: _____

Questionnaire for setting up a stockpile – Appendix B

1. The application indicates that its purpose is to set up a stockpile of samples. Therefore the researchers must complete the following details:

   1.1. The applicants and their job titles:

      1.1.1. Name of person submitting application.

      1.1.2. The institution he belongs to and its address.

      1.1.3. Identity of the stockpile owner (if a corporation – its owners of control and directors)

      1.1.4. Details of the stockpile manager

   1.2. The stockpile

      1.2.1. Description of the required or existing stockpile.

      1.2.2. Purpose of setting up the stockpile (type of research/ diseases)

      1.2.3. Sample storage location, conditions of storage and means of security

      1.2.4. Planned number of samples to be collected for the stockpile (if possible, by type of source, from sick and healthy people)

      1.2.5. Nature of the samples (identified or unidentified, note: coded samples are deemed identified pursuant to the law)

      1.2.6. Sources of collecting samples (types of populations – sick and healthy, minors, wards, legally incompetent)

      1.2.7. Details of the method of collecting samples

      1.2.8. Details of the method of compensating donors and/or collectors of samples

      1.2.9. Terms of use for samples from the stockpile

      1.2.10. Means for securing the genetic information linked to the samples

      1.2.11. Boundaries for use of samples (in Israel, or if overseas – which countries)

   1.3. Add a reference to ethical aspects and the risks of donating to the aforesaid stockpile of samples.

   1.4. Add a declaration: "I/we the undersigned confirm that the details we have given above are correct, true, full and to the best of our knowledge. I/we undertake to comply with the instructions of the relevant instructions and laws in everything relating to the requested/ existing stockpile.

   1.5. Add signatures and details (of at least the applicant, the intended manager and a representative of the owners of the stockpile)

Date: _____

1. **Details of the Clinical Trial**

   Confirmation of the Hospital director (Form 7): No. _____ Date: _____

   Validity of approval: _____

   Helsinki Committee clinical trial no. _____

   Ministry of Health clinical trial no. _____

   Chief researcher (name and department): _____

   Subject of the clinical trial: _____

   _____

   _____

   _____

   _____

   Name of the trial product: _____

   Name and address of the initiator/ his representative in Israel: _____

   _____

2. **The clinical trial documents (last approved version, including all amendments)**

   Protocol: no. _____ dated _____

   Researcher's manual, version: _____ dated _____

   Informed consent form, version: _____ dated _____

3. **List of requested changes (indicating bookmarks in the trial documents)**

   _____

   _____

   _____

   _____

4. **Reasons for the changes**

   _____

   _____

   _____

   _____

5. If the request refers to changes in the <u>medical device itself</u> (including changes in auxiliary equipment or software), for each change give the following details:

a. Identifying details (model name, number etc.) of the medical device that was previously approved for a clinical trial.

b. Identifying details of the new medical device in which changes will be made.

c. Description of the changes.

d. Rationale for the changes.

e. Possible implications of the changes for the safety of the medical device, its performance, the manner of using it, and its clinical action.

f. The pre-clinical tests done on the medical device after the changes were made (attach a summary of the tests and their results).

_____	_____	_____
Name of researcher	Signature	Date

6. <u>Approval of the changes by the chairman of the Helsinki Committee</u>

I hereby approve the changes requested above.

Name of chairman of Helsinki Committee	Signature	Date

Copy: Initiator/ representative in Israel (via the researcher)

Date:_____

To:

Chairman of Helsinki Committee
Lic. No. _____

To:

Director of the Hospital
Lic. No. _____

(*) Only in cases of death

Notice of an SAE affecting a participant in a clinical trial

1. **General**

No. of application in Ministry of Health _____ / HT

No. of trial in Helsinki Committee _____

Date of Hospital Director's approval (Appendix 7) _____

Subject of the Trial _____

Number and date of the protocol _____

Name of research product (medical preparation, medical device, cells, etc.) _____

Name of manufacturer: _____

Name of chief researcher at _____ Department: _____

2. **Details of participant**

2.1 Initials of his name _____

2.2 Participant code _____

2.3 Age _____

2.4 Sex (Male/ Female) _____

3. **Trial treatment - timetable**

3.1 Start date _____

3.2 Date when treatment was stopped _____

3.3 Date when treatment was renewed, if renewed _____

3.4 Date when treatment ended, if ended _____

4. **The incident**

4.1 Type of incident (mark as appropriate):

- ☐ Death
- ☐ Danger to the trial participant's life

- ☐ The incident led to the participant's hospitalization, or the duration of existing hospitalization was extended (possible reasons – need for medical intervention, or risk of disability or risk to life).
- ☐ The incident caused disability or severe and/or lengthy restrictions, or there was a congenital defect.
- ☐ Massive medical intervention was required due to the incident.
- ☐ A fault in the trial instrument which has implications for safety and efficacy.

4.2 Date when incident began: _____

The incident occurred in the course of giving treatment/ carrying out a procedure/ during treatment period/ during follow-up period/ other – specify: _____

_____

_____

_____

4.3 Detailed description of the incident:

_____

_____

_____

_____

_____

5. Treatment given to the trial participant following the incident

_____

_____

_____

_____

_____

6. Participant's condition on the date of reporting

_____

_____

_____

_____

7. **Possible link between the incident and the trial product and/or participation in the trial**

_____

_____

_____

_____

8. **Was the incident expected? (Explain on the basis of the trial protocol, the literature, existing knowledge and experience)**

_____

_____

_____

_____

9. **Comments:**

_____

_____

_____

_____

10. **Accompanying documents – as necessary**

_____

_____

_____

_____

_____	_____	_____
Name of researcher in charge	Signature	Date

Copy: Clinical trial file

Date:_____

To:
Director of Hospital
_____

National Coordinator of Clinical Trials
Ministry of Health

Death of a participant in a clinical trial – Report of the investigation and the conclusions of the Helsinki Committee

Reference: Researcher's report of the participant's death (Form 13) dated _____

Attached is the notification from the Researcher (name) _____ dated _____ (report date).

1. **General**

No. of trial in Ministry of Health _____ / HT _____

No. of trial in Helsinki Committee _____

Subject of the Trial _____

Research product (medical preparation, medical device, etc.) _____

Name of product: _____ Name of manufacturer: _____

2. Results of the investigation by the Team

2.1 The patient was selected according to the criteria for inclusion and exclusion in the protocol Yes / No (circle as appropriate).

If not -

a. Describe the deviation: _____

_____

b. Possible link between the deviation and the incident: _____

_____

2.2 Treatment of the patient was according to the approved protocol Yes / No

If not -

a. Describe the deviation: _____

_____

b. Possible link between the deviation and the incident: _____

_____

2.3 There was a fault in the trial product / manner of delivering/ using/ operating it (circle as appropriate): Yes / No

If yes -

a. Describe the fault: _____

_____

b. Link between the fault and the incident: _____

_____

2.4 Monitoring and follow-up of the patient were as defined in the trial protocol and the criteria for removing a participant from the trial were observed: Yes / No

If not -

a. Describe the deviation: _____

_____

b. Possible link between the deviation and the incident: _____

_____

2.5 The incident was expected/ unexpected (refer also to the frequency of this type of incident in patients with similar conditions who receive the standard treatment):

_____

_____

_____

_____

2.6 The protocol indicates death as an expected SAE: Yes / No

2.7 The informed consent form mentions the possibility of death: Yes / No

2.8 Possible link between use of the trial product and death: Yes / No / Cannot be ruled out.

2.9 Possible link between participation in the clinical trial and death: Yes / No / Cannot be ruled out.

2.10 Summary and conclusions:

_____

_____

_____

_____

2.11 Recommendations:

_____

_____

_____

_____

Should the trial be stopped?

_____

Should the trial protocol be changed?

_____

Should the informed consent form be changed?

_____

Should there be a reassessment of the product used in the trial?

_____

3. <u>Discussion in the Helsinki Committee</u>

The death was discussed on _____

3.1 The Committee's decision:

_____

_____

_____

_____

_____ _____

Name of chairman of Helsinki Committee | Signature

Enc: Patient's record
Report on any surgery performed
Form 13

Copy: Physician responsible for the trial

Form 2

(Sections 3b(1)(a), (2)(b) and 9a(1)(a))

Form for Approving the Use of an Unregistered Medical Preparation in a Medical Institution (Group Approval)

Name of medical institution: _____ Department: _____

Name of preparation, its format and method of delivery:

Composition (quantity/ concentration of active ingredients): _____

Name of manufacturer and country of manufacture: _____

Requested indication: _____

Reasons: _____

_____

_____

(Attach medical references – literature, articles etc.)

Total quantity required (per year) _____

I the undersigned hereby declare that:

- The preparation is essential and there is no suitable registered alternative preparation that is marketed in Israel for the same purpose.
- The benefit of using the preparation is greater than the risk involved.
- Instructions for the use of the above preparation and for the requested indication are from the treating physician and are his responsibility.

Please mark as appropriate:

☐ The preparation is included in the basket of health services pursuant to the National Health Act, but is not registered in the Register of Medical Preparations in Israel.

☐ The preparation is registered in the Register of Medical Preparations in Israel but not for the requested indication, Off-Label.

☐ The preparation is registered by the Ministry of Health of one of the recognized countries listed below and accepted in it for the requested indication:

☐ Western Europe (name of country: _____) ☐ USA ☐ Canada ☐ Australia ☐ Japan

Name and signature of the chairman of the Drugs Committee of the Medical Institution: _____

Approvals from the Medical Institution:

	Director or his authorized representative	Manager of pharmaceutical services
Name and signature of person giving approval		
Date:		

The approval is valid for no more than 12 months.

Copy: Pharmaceutical Division, Ministry of Health, Fax: 02-5655969

Form 3

(Sections 3b(2)(a), f(4) and 9a(2)(a))

Physician's prescription for use of an unregistered preparation in a medical institution for an individual patient

Patient's name and ID no: _____ Age____ Sex: _____

Name of Medical Institution: _____ Department: _____

Name of preparation, its format and method of delivery:

Composition (quantity/ concentration of active ingredients): _____

Name of manufacturer and country of manufacture: _____

Requested indication: _____

Reasons: _____

_____

(Attach medical references – literature, articles etc.)

Daily dose: _____ Duration of treatment: _____

Total quantity required (no more than the quantity required for 6 months) _____

Physician's declaration (please mark as appropriate)

1. I the undersigned am aware that:

- The preparation is essential and there is no suitable registered alternative preparation that is marketed in Israel for the same purpose.

☐ The preparation is not registered in the Register of Medical Preparations in Israel.

☐ The preparation is registered in the Register of Medical Preparations in Israel but not for the requested indication, Off-Label.

☐ The preparation is registered by the Ministry of Health of one of the recognized countries listed below and accepted in it for the requested indication:

☐ Western Europe (name of country: _____) ☐ USA ☐ Canada ☐ Australia ☐ Japan

2. I declare that

2.1 The benefit of using the preparation is greater than the risk involved.

2.2 I have explained to the patient the significance of treatment with the preparation for an indication that is not registered and he has given his informed consent to the treatment of his own free will.

2.3 Instructions for the use of the above preparation for the requested indication are my medical responsibility.

Physician's name: _____ Tel. no. for clarifications: _____

License no. _____ Specialist field: _____

Physician's signature: _____ Date: _____

Approvals from the Medical Institution:

	Chairman of Drugs Committee	Director or his authorized representative	Manager of pharmaceutical services
Name and signature of person giving approval			
Date:			

This prescription is valid for no more than 6 months.

Form 4

(Section 3b(3)(b))

Physician's instruction for urgent mercy trial use or treatment of an individual patient

Patient's name and ID no: _____ Age____ Sex: _____

Name of Medical Institution: _____ Department: _____

Name of preparation, its format and method of delivery:

Composition (quantity/ concentration of active ingredients): _____

Name of manufacturer and country of manufacture: _____

Requested indication: _____

Reasons: _____

_____

(Attach medical references – literature, articles etc.)

Daily dose: _____ Duration of treatment: _____ Total qty required _____

Physician's declaration

1. I the undersigned am aware that the preparation is essential and there is no suitable registered alternative preparation that is marketed in Israel for the same purpose.

2. I declare that

2.1 The benefit of using the preparation is greater than the risk involved.

2.2 I have explained to the patient the significance of treatment with the preparation for an unregistered indication and he has given his informed consent in writing.

2.3 Instructions for the use of the above preparation for the requested indication are my medical responsibility.

Physician's name: _____ Tel. no. for clarifications: _____

License no. _____ Specialist field: _____

Physician's signature: _____ Date: _____

Approvals from the Medical Institution:

	Chairman of Helsinki Committee	Chairman of Drugs Committee	Director or his authorized representative	Manager of pharmaceutical services	Ministry of Health*
Name and signature of person giving approval					
Date:					

* For urgent mercy treatment, Ministry of Health approval is not required. A copy is sent to the Pharmaceutical Division on fax 02-5655060.

This prescription is valid for no more than 6 months.

Consent Form: Use of a drug not in the "Basket of Hospitalization Services"

I the undersigned _____ (patient's name), ID no. _____ am supposed to receive a drug of type _____ ("the drug") to treat my condition.

It has been explained to me and I understand that this drug is not included in the "Basket of Hospitalization Services", within the meaning of the National Health Insurance Act, 5754-1994, and therefore it is also not funded by the health service providers and not approved for use by them.

It has been explained to me that in the medical literature support can be found for use of the drug to treat my condition and on this basis I am being offered this treatment. This is/ these are not a research/ trial drug/s but a known drug that is currently used for other indications.

However, it has been explained to me and I fully understand that neither Tel Aviv Medical Center nor my healthcare provider nor any other entity are obliged to treat me with the aforesaid drug. Also, it is clear to me that after receiving the initial treatment of the drug as specified, and even if I respond well to the treatment, I cannot ask for further doses or supply of the drug from any source and all expenses will be paid by me alone.

_____	_____	_____
Patient's name	Signature	Date

I hereby confirm that I gave the patient a detailed verbal explanation of all the above as required and he/she signed this consent form in my presence after I was convinced that he/she understood all my explanations.

_____	_____	_____	_____
Physician's name	Signature	License no.	Date