65. Clinical trials

Excerpted from the position paper published in September 2006

Background

Introduction

Clinical trials are essential for the advancement of medicine, and without them modern medicine in general, and the development of new drugs in particular, would not be possible. The need for new drugs has increased in recent decades, as scientific knowledge has revealed the genetic and molecular basis of most diseases. New drugs and innovative medical technologies contain great hopes, heretofore unknown, for the healing of incurable illnesses. The good of society dictates that these clinical trials continue to be conducted for the benefit of the human race, its health and increased life expectancy.

Along with the clear hopes they inspire, clinical trials on humans present a risk to the patients participating in them. The researchers' wish to develop innovative methods of treatment is liable to distort and erode the legal and ethical frameworks that protect the method of conducting the trials. Economic interests may also be involved. The law and the ethical code are intended to preserve and protect the health and security of those who risk their health in the hope of finding a cure for their illnesses or even saving their lives. These patients, by their participation in the clinical trials, are likely to also ensure the health and lives of those who follow them.

The rapidly changing reality and the advancement of technology, including the progress of medicine, generally increase the desire of researchers to develop and manufacture innovative treatments and drugs. This intention, whether it derives from the desire of the researcher for self-fulfillment and realization of his professional capabilities or from his desire to promote his name and reputation, may lead to the creation of a conflict of interests, in which the welfare of the patient is liable to be in conflict with that of the physician.

In addition, this changing reality may create new situations in the physician-patient relationship that did not exist even a few years ago. There are physicians who, in addition to their traditional role as healers, have research-economic relationships with the pharmaceuticals industry or startup companies. We, as a society, and especially as a profession, are responsible for preventing improper situations and for protecting the patients.

Articles in the press about clinical trials in Israel have recently attracted considerable public interest. According to these articles, which have not yet been examined in the courts, some physicians have allegedly betrayed the trust of their patients and conducted clinical trials in infringement of the law and of medical ethics. Even if all these allegations

prove to be false, the social damage caused to the image of the physicians and medicine in Israel is tremendous and threatens the future of clinical research in Israel.
The Israeli Medical Association decided, based on deep commitment to the professional and ethical standards of medicine in Israel and to its status in the eyes of the public, to take steps to protect the status of clinical trials, to profess their importance and to minimize, as much as possible, any future deviation from the procedures required for their execution.
This position paper reflects the position of the Israeli Medical Association, as formulated by members of the special committee convened for this purpose.
I would like to thank the members of the committee for the valuable time they devoted to this important subject and for their sensible comments. Special thanks to advocates Gili Shilat and Adva Perry for their significant contribution to the wording of this document, and to Advocate Leah Wapner for initiating this process.

The importance of medical research in Israel

Clinical trials have been conducted in Israel and abroad for decades, and their contribution to the health of patients and to the standard of medicine is clear. The level of clinical research as conducted in Israel ranks us with the most advanced countries in the world regarding the nature and quality of the medical service given to our citizens.
Medical research brings great benefit to all participants:
The patient – The patient undergoes close and continuous medical monitoring and enjoys direct and immediate access to the treating physicians, both junior and senior, without any financial cost or administrative barriers. The treatment given is subject to constant monitoring, both by the inspection committees of the institution – as set forth in the Public Health Regulations (Medical trials on humans), 5740-1980 (hereinafter: "the public health regulations") and in the Procedure for conducting medical trials on humans (2006), published by the Pharmacy Division of the Ministry of Health pursuant to the public health regulations (hereinafter: "procedure for medical trials"), as well as by the pharmaceutical companies who act in accordance with the strict criteria of the FDA in the US and of the EMEA in Europe.
Most patients who participate in clinical trials receive innovative and advanced drugs many years before these drugs appear on the open market, drugs that may significantly improve their quality of life and health, reduce the side effects that accompany existing drugs, reduce the risks involved in the receipt of existing alternative treatment, and frequently even save their lives. All this occurs without any payment on the part of the patients. Furthermore, in Israel there is a unique commitment on the part of the pharmaceutical companies to supply the trial drug free to patients who participate in the trial for an additional three years after the end of the trial or until its inclusion in the national drugs basket.

The physician – The physician is exposed to the most advanced information that exists in the research field, which improves his capability and grants him a prominent advantage in the treatment of similar patients. Meetings of researchers that include the participation of physicians from various countries expose the physician participating in the research to the most advanced global medicine of the time as well as allowing researchers to create valuable professional and personal links with the international professional medical leadership.

Publication of research earns the physician a place of respect among his colleagues, which improves his chances to again serve as a researcher in additional trials, and so on. Furthermore, such a trial obligates strict and methodical recording required for monitoring the patient's clinical condition, the treatment given to him, and the results. This meticulous recording sets proper standards for any medical documentation that the physician may record in his subsequent professional career. This constantly improving process benefits all those concerned.

The State of Israel – The built-in advantages in clinical trials also apply to the State of Israel as an overall framework. Israel's participation in multi-national trials is essential for the creation of foreign relations with countries of the world, for Israel's participation in world medical research and for confirmation of its status throughout the world in the field of medicine.

The health care organizations – These organizations are given the option of granting their patients the most advanced professional medical treatment existing in the world, while at the same time improving the professional knowledge and clinical capabilities of the physicians working for them. This advanced treatment is provided without any financial costs being imposed on the health care organization or on the State.

The pharmaceutical companies – The pharmaceutical companies enjoy clear economic benefits as a result of the development of clinical research in Israel, which leads to the development of innovative drugs and treatments. If more and higher quality clinical research is conducted in Israel, it will constitute an increasingly preferred target for the investment of additional resources for conducting clinical trials.

The general public – It is clear that the public enjoys a variety of advantages inherent in the conduct of clinical research – including more innovative and quality treatment, more advanced technologies, physicians of a higher professional standard, more developed foreign relations between Israel and various countries, and other advantages.

Furthermore, approximate estimates indicate that pharmaceutical companies invest about $300 million in medical research in Israel, and that the lion's share of this money is re-invested in the national medical system, in the expansion and quality of the clinical activities conducted.

Clinical research also permits expanding clinical activities to small hospitals in Israel and to the field of community medicine. In this way, the circle of physicians exposed to the advantages included in these trials expands, and an additional group of physicians is given the opportunity for advancement and improvement, similar to the process existing in the central hospitals.

We can see that there are mutual interests of all the relevant entities regarding the need to conduct and develop the clinical trials conducted in the State of Israel.

The legal framework

The legal framework, pursuant to the Israeli legal system, is derived first and foremost from the primary legislation (laws and ordinances), but may also be deduced from secondary legislation (orders and regulations) as well as from international declarations and conventions and from court rulings.

It is incumbent upon us that the legal framework in Israel for conducting clinical trials conforms to the existing international legal framework, as updated from time to time. This coordination is essential in order to permit the State of Israel to participate in the execution of the clinical trials throughout the world.

Furthermore, in an issue of this magnitude we should strive to reach general world agreement regarding the legal framework that we are using.

Clinical trials on humans contain the hope of a cure for patients who will in the future need new drugs or treatments, and we cannot overstate the importance of their contribution to saving lives and advancing medicine and the medical system.

On the other hand, one should not ignore the risk of misuse involved in these trials, especially given the desire of researchers to develop innovative methods of treatment and to advance at maximum speed through the stages of the clinical trials, sometimes, unintentionally, without strictly observing relevant rules. In the current reality, in which the physician becomes an active partner in medical research with the pharmaceutical industry, there may be economic interests, sometimes covert. For example, the advancement of a new technology or its results may influence the academic or economic status of the physician participating in the research.

In light of this, we have an obligation to formulate clear, fully transparent rules regarding medical trials on humans, that focus first and foremost on the safety and health of the patient while protecting his welfare.

The need to formulate ethical rules for conducting medical trials on humans was recognized for the first time after the end of World War II, with the discovery of the evil experiments conducted by the Nazis on humans. The Japanese Army also conducted depraved experiments on thousands of persons using biological weapons, beginning in 1936 and continuing throughout World War II.

Until World War II, no public, legal, and moral steps were in place for the protection of

patients taking part in research. The judges in the Nuremberg trials called on the nations of the world to create an international procedure for trials on humans, to be based on "natural morality", or as they defined it:

"The principles of the laws of the nations as expressed in accepted behavior between civilized persons, in the laws of humanity and in the public conscience."

The first recognized document to address the regulation of medical trials on humans was the Nuremberg Code, formulated following the trials of the Nazi physicians after World War II.

In 1964, at its 18th General Assembly, held in Helsinki, Finland, the World Medical Association (WMA) adopted recommendations that guide physicians in bio-medical research on humans.

These recommendations were collected into an official document, known as the Helsinki Declaration, which replaced the Nuremberg Code.

The Helsinki Declaration was adopted by many countries throughout the world, and formed the basis for laws, declarations, and national directives in a similar spirit throughout the world. The Declaration itself has been revised seven times since 1964, the last time in 2004, in order to adapt it to the changing reality, and it continues to form the ethical and legal basis for the planning, execution, and recording involved in the execution of clinical trials on humans.

The Helsinki Declaration is also the basis for the international guide for the execution of clinical trials formulated in recent years under the name Good Clinical Practice (GCP). These directives are not part of the law, but have been adopted by health authorities in Europe, the US, and Japan.

The Israeli Medical Association was involved in the activities of the WMA and participated in the years 2002 and 2004 in the process of updating the Helsinki Declaration.

The wording of the principles of the Helsinki Declaration, as amended in the 29th World Medical Association Assembly held in Tokyo, Japan, in 1975, was codified and implemented in Israel by virtue of the public health regulations. These regulations constitute the legal basis in Israel for the regulation of medical trials on humans, and they were enacted by virtue of section 33 of the Public Health Ordinance, 1940.

The public health regulations specify that a medical trial on humans is defined by the use of drugs, radiation, or chemical, biological, radiological, or pharmacological material contrary to legislation or to the approval given for such use. It also includes situations when the use in question is not customary in Israel for the needs requested, or has not yet been tried in Israel and that may, or is intended to, influence the health, body, or spirit of a person or fetus or part thereof, including the genetic arrangement, as well as the execution of any process, act, or examination in humans that is not customary.

The principles for conducting a clinical trial as set forth in the Helsinki Declaration and adopted by the public health regulations, place emphasis on the good of the individual

participants, which prevails over the good of society or the good of science. Furthermore, the principles emphasize the obligation to preserve the wholeness of the body, spirit, and personality of the participant and his privacy.

In addition, there is an obligation to receive the comprehensive, designated informed consent of the candidate to participate in the clinical trial, as detailed below, as well as an obligation to conduct trials in accordance with accepted scientific standards and to estimate the risk versus the benefit in the trial.

In accordance with the public health regulations, medical trials are currently being conducted in Israel on humans, in accordance with the provisions of the procedure for medical trials on humans, published as aforesaid by the Pharmacy Division of the Ministry of Health in 1999 and last updated in 2006. This procedure regulates the rules regarding these trials in Israel and describes the procedure for filing an application for a medical trial and the requirements for its approval.

In addition, the ethical basis regulating the execution of medical trials on humans is anchored in the International Convention regarding Civil and Political Rights, which states in section 7, that:

"A person shall not be subject to torture or to cruel, inhumane or humiliating behavior, or punishment; in particular a person shall not be subject to a medical or scientific trial without his free consent."

The State of Israel signed this convention in New York in 1966 and ratified it in 1991, and it took effect in Israel on January 3, 1992.

In addition, a number of laws have been enacted in Israel that have direct and indirect ramifications on the issue of medical trials on humans, such as the Basic Law: Human Dignity and Liberty, the Patient's Rights Law, 5756-1996, and the Genetic Information Law, 5760-2000. The Ministry of Health has also issued several Director-General circulars, as follows:

1. A circular regarding the registration of medical trials in the world database of the NIH (dated 4.9.2005), which states that every clinical trial that meets the criteria set forth in this circular and that is conducted in Israel must be registered by the initiator of the trial in the medical trials database. In the case of a trial initiated by a commercial company, the researcher must ensure the registration of the trial by the company. The Helsinki Committee of the medical institution shall not approve a clinical trial that was not registered, unless it accepts the reasons of the researchers for not doing so. The circular also states that in principle, it is possible to register a medical trial in several sites, but the circular requires that the registration be done on the NIH site, with the aim of uniform registration.
2. A circular regarding the supervision and monitoring of clinical trials in medical institutions in Israel (dated 6.3.2005), aimed at guiding the medical institutions in proper monitoring of medical trials. This circular states, inter alia, that the Helsinki

Committee of the institution is obligated to supervise the clinical trials approved by the committee and by the director of the hospital, and that the researchers responsible for the trial must submit to the committee yearly reports, or more frequently if the degree of risk in the trials is high. They must also submit regular reports regarding adverse events that arise during the trial. The circular also states that the management of the medical institution must appoint a supervisory body for monitoring and checking the clinical trials approved in the institution.

3. A circular regarding guidelines of the Supreme Committee for Medical Trials on Humans, for the setting up and use of banks of genetic samples (dated 2.1.2005). The guidelines are intended for those who wish to set up banks of DNA samples or to make use of existing banks, and are based on the rules employed in the supreme committee for approval of genetic trials on humans and on the relevant law, including the provisions of the Genetic Information Law, 5760-2000, the Law for Protection of Privacy, 5741-1981, and the Privacy Protection Regulations (transfer of information to databases outside the country), 5761-2001.

   It should be noted that these instructions expressly state that the setting up of a DNA bank does not grant exemption from the filing of an application for approval of genetic research on humans, if the execution of such research is requested after approval of the DNA bank. In addition, the application for research will be determined separately, in accordance with the rules and procedures customary in the committee.

4. A circular jointly issued by the Ministry of Health and the Clalit Health Services, that addresses agreements with commercial entities (dated 19.4.2004) and is aimed at formulating rules for agreements between institutions of the Ministry of Health and Clalit Health Services with commercial entities for the purpose of conducting clinical trials, research, participation in conferences and study days in Israel and abroad, and other connections, within the context of accepted ethical rules. This circular anchors the demand unique to the State of Israel, that the initiator of the research must supply to a patient who participates in the research the drug or treatment that he received during the research, for a period of up to three years, without payment, after the end of the trial, as long as it cannot be received from the health care organization in which the patient is insured, or as long as it has not yet been approved for marketing in Israel and when no suitable alternative treatment exists.

Nonetheless, and notwithstanding the aforesaid, rules for conducting medical trials on humans have not yet been codified in primary legislation in Israel. The Ministry of Health has been drafting a bill on the subject of medical trials on humans since 1997, but no government bill has been submitted.

On December 21, 2005, a (private) bill was published, entitled Medical Trials on Humans, 5765-2005, submitted by members of the Science and Technology Committee of the Knesset. The aims of this bill are to formulate the principles according to which medical

trials on humans are to be conducted. For example, the bill states that a medical trial on humans shall be conducted while maintaining the dignity, freedom, and rights of the person. Furthermore, the bill specifies the conditions for conducting medical trials on humans, the definition of the committees for human trials and the method of their functioning, the setting up of a supervision and monitoring committee, consent for participation in the medical trials, and definition of the obligations and rights of all those involved in those trials.

In June 2005 the Israeli Medical Association sent its comments regarding the draft of the proposed law and suggested the addition of sections contained in the revised Helsinki Declaration, since that is the most advanced document in the field of medical trials on humans that is binding on physicians throughout the world. For example, the IMA proposed adding a reference to considerations relating to distributive justice (it shall be justified to conduct medical trials on humans only when there is a reasonable chance that the population on whom the trial was conducted will benefit from its results). The IMA also suggested extended obligations of disclosure regarding informed consent (see details in the part addressing this subject), extended obligations in connection with publication of the findings of the trial including negative results, sources of financing, conflict of interests, etc.

The private bill passed in its first reading on December 14, 2005, before the dissolution of the 16th Knesset. If the rule of continuity will apply to it in the current Knesset (the 17th) it will be sent for a second and third reading.

The position of the Israeli Medical Association is that there is an urgent need for primary legislation on the subject of medical trials on humans, both from a declarative aspect, since it is important for the Israeli Knesset to be the one to address the issue, and from a practical aspect, since the power of primary legislation is greater than that of secondary legislation, is more difficult to change, and reflects a more intensive public debate.

It is ironic that in contrast to humans, trials on animals have been secured for several years in various laws. Until completion of the legislation, it is necessary to preserve a balance between giving maximum protection to participants in a trial on the one hand, and the essential need to conduct the medical trials, on the other hand.

Informed consent

The obligation to receive a person's informed consent for every activity related to his body and health, including the use of parts of his body such as organs, tissues and blood samples, is derived from the fundamental principles of a person's right to his body and the obligation to respect his dignity, rights and freedom. It also stems from the obligation to conduct medical trials on humans in the spirit of the Helsinki Declaration and in accordance with proper clinical practice.

This obligation applies even more strictly to medical trials on humans, since these trials

have extensive potential to reveal information concerning the participants in the trial, perhaps his family and offspring and even large populations. In addition, although we are speaking of an action that contains numerous and significant advantages for the patient, we are dealing with a new and experimental drug that also involves an unknown risk that cannot be ignored.

In Israel, the obligation to receive informed consent is codified in the Patient's Rights Law, 5756-1996, in the public health regulations, and in the procedure for medical trials.

The obligation to obtain informed consent, as set forth in the procedure for medical trials, also includes the obligation of the researcher to give the participants information about the medical trials in a clear comprehensible way. Information about the trial includes, inter alia, an explanation of the nature and process of the research, its aim and duration, the average number of participants in the trial, a description of the various processes, and indication of the chances to receive each of the treatments proposed in the trial, including a placebo, if any. It also includes a description of the advantages expected as a result of participation in the trial, a description of the expected risks, and an explanation of alternative treatments, if any. Furthermore, the researcher must inform the participant that he has the right to absolute confidentiality and that his documents will be examined by authorized entities only., In a genetic trial, this right, as well as the participants' right to privacy, must be emphasized even more.

In the absence of primary legislation that addresses medical trials on humans, the issue of informed consent specific to this matter has not yet been secured by law. The bill includes the demand to receive the informed consent of every participant in a medical trial conducted on humans, and even describes the type of consent required, the method of furnishing the information to the participant in the trial, the way in which the informed consent is given, and the conditions permitting deviation from receipt of the informed consent.

The principle regarding the receipt of informed consent for participation in a clinical trial as specified in the Helsinki Declaration, last revised in 2004, obligates broader disclosure regarding the method of obtaining the informed consent than is included in the bill. The Israeli Medical Association proposes that the Helsinki Declaration, including its integrated system of checks and balances, be adopted as a single unit. In addition, its position is that the principles appearing in the revised wording of the Helsinki Declaration, including the broadened obligations for disclosure in connection with informed consent, and the increased stringency of the requirements for formulating informed consent, should be codified in primary legislation.

For example, the IMA feels that the law should include the principle as set forth in section 22 of the revised Helsinki Declaration, according to which every participant in the trial shall be given information regarding the sources of financing of the trial, the connections between the researcher and the company managing the medical research,

the researcher's involvement in the proposed research and any potential conflict of interests. In addition, the trial participant must be informed, in language comprehensible to him, that research in which a commercial company is involved contains a chance for a profit by said company. He should also be informed whether the physician involved is a research agent who receives financial remuneration for his services from the commercial company conducting the research.

The law should include the principles of section 23 of the revised Helsinki Declaration, which mandates extreme caution regarding the informed consent of the patient when there are relations of dependency with the practitioner, in which case it must be verified that the consent is not given in any way under any pressure or threat whatsoever. In such cases, a practitioner who is not involved in the research and who has no connection with the relationship between the physician and the patient, must be the one to obtain informed consent.

Finally, section 11 of the Helsinki Declaration from 1975 (which is codified in the public health regulations) states that in the case of a legally incompetent participant, the medical treatment shall be requested and received from the legal guardian, in accordance with the national legislation. When physical or mental incompetence makes it impossible to obtain informed consent, or when the person used for the research is a minor, the responsible relative shall grant permission instead of the person used for the research.

The Israeli Medical Association also advises including reference to section 24 of the revised Helsinki Declaration, which gives broader protection to participants who are unable to give their consent. The section states that research on these groups shall only be conducted if the research is vital for the advancement of the health of this specific population, and only if it is impossible to conduct the research with participants who are legally competent to give informed consent.

The Israeli Medical Association believes that primary legislation should also include the rule currently found in the procedure for medical trials referring to populations in special conditions. According to this rule, whenever the researcher has doubt regarding the competence of the participant to give informed consent, and the researcher knows that a legal guardian has not been appointed for the participant, the researcher must obtain the evaluation of a psychiatrist or geriatrist who are independent of the research. Furthermore, when speaking of a participant who is a minor, the researcher must give an explanation of the trial in accordance with the minor's understanding.

The Helsinki Committees

The execution of medical trials on humans in Israel comes under the supervision of the Ministry of Health by means of the Helsinki committees in the hospitals. In every hospital the Helsinki committee comprises the most senior physicians and researchers in the institution, representatives of the public (clergy or lawyers), and representatives of

the hospital. In 1990, a requirement of the Director-General was added to include in the committee a senior pharmacist, so that the considerations of the committee would also include his/her professional skills and considerations.

The members of the committee serve on a voluntary basis and receive training in the rules of management of clinical research. The members of the committee are appointed by the management of the hospital and approved by the Director-General of the Ministry of Health. The Helsinki committees act in accordance with the procedure for medical trials of the State of Israel. This procedure corresponds to the rules for clinical research of the European Union and the rules for research of the American FDA.

Every proposal for research on humans is submitted to the Helsinki committee of the institution for approval. The committee focuses mainly on the good of the patient and on the potential risks and benefit to the patient as a result of participation in the research. Special emphasis is placed on giving a detailed explanation to the participant in the trial and to his signing an informed consent form, in which all the details are given of the trial and its ramifications. In addition, every participant in the trial is insured with special insurance.

When dealing with a trial that includes administering an experimental drug, the initiator of the trial must undertake to supply the drug to the patient for up to three years after the end of the trial or until the drug is included in the national drugs basket. This provision for supplying the drug even after the end of the trial is unique to the State of Israel.

After approval by the Helsinki Committee of the institution, the proposal for research undergoes additional discussion and approval by the Ministry of Health, except in the case of a "special" trial (within the meaning of the fourth supplement of the public health regulations). Finally, the director of the hospital in which the trial is conducted approves the research.

Section 15 of the procedure for medical trials obligates the head researcher to report within 48 hours to the chairman of the institutional Helsinki Committee and to the director of the institution regarding any case of death or a serious adverse event. An adverse event refers to an unexpected incident, in which one cannot exclude a connection between it and the use of the research product. The head researcher must also report within 48 hours to the chairman of the institution Helsinki committee only, regarding a malfunction to a medical accessory/ instrument of the trial that has ramifications regarding the safety of use and effectiveness of the equipment.

In the event of death, the chairman of the institution Helsinki Committee examines the notice immediately. If he reaches the conclusion that there is no connection between the event and use of the research product and/or the patient's participation in the trial, he must report the event and this conclusion to the Helsinki committee and to the Ministry of Health within 30 days. In contrast, if the chairman of the institution Helsinki committee cannot rule out a connection with use of the product or participation in the trial, he must

notify the director of the institution immediately.
In such a case, the director of the institution must appoint an examination team to discuss the matter within 14 days. Depending on the conclusions of the examination team, he may order the continuation of the trial or, alternatively, recommend to the Helsinki committee to halt the trial. The Helsinki Committee shall notify the director of the institution and the Ministry of Health of the conclusions of the discussion of the examination team and of its own decisions.
In adverse safety events that do not involve death, the researcher is obligated, pursuant to section 15.1.2.2 of the procedure for medical trials, to update the Helsinki Committee regarding continuation of treatment of a patient following an incident, and the Helsinki Committee shall discuss the reports and their ramifications on the participants in the trial and indicate this in the protocol of their meeting. The Helsinki committee is obligated to send to the Ministry of Health their reports and conclusions, including the possible connection between the event and the person's part in the trial, within 30 days, or upon sending the protocol of the next meeting.
In contrast, in the case of reports received by the Helsinki Committee from the initiator of the trial, the Helsinki Committee is exempt from sending them to the Ministry of Health, since the obligation of reporting lies with the initiator.
In order to improve the system for supervision and control of the conduct of the medical trials on humans in the State of Israel, the Ministry of Health, in the Director-General circular issued dated 6.3.2005, ordered the setting up of a monitoring system. In accordance with this circular, a body must be set up in every institution whose function is to monitor the execution of medical research and to verify that the research is conducted in accordance with the customary strict criteria.
The function of this monitoring system is to verify that patients who participate in a trial have received an adequate explanation of the trial and have duly signed the informed consent forms, that the trial was conducted in accordance with all the rules of good medical practice, and that every side effect was reported in a timely fashion to the Helsinki committee. The Director-General circular is in its infancy, and consequently the time has not yet come to evaluate to what extent it has actually been implemented.
As a result of the ongoing improvement in the conduct of clinical trials in Israel, including the setting up of permanent monitoring entities, professional training of the researchers and raising the standard of functioning of the Helsinki committees, the system of medical trials on humans in Israel now complies with the strictest international criteria, recognized by the FDA.
Together with the trend for constant improvement, and although most clinical trials comply with the existing rules, there is still room for improvement. For example, most medical trials in Israel are "multi-center international research". Such a trial is conducted in several hospitals at the same time in Israel. In such circumstances, duplication and

complications are liable to result, since each medical center is required to approve the same research, by means of its own Helsinki Committee, separately and in parallel to the other centers. This is so even after the research has undergone all the relevant stages of approval and even after it has been approved as a multi-center trial by the Ministry of Health. This results in unnecessary work that takes up valuable and protracted time for approval of the trial.

The position of the Israeli Medical Association is that the investment of considerable time for the approval of clinical trials is not necessarily a guarantee for the quality of the approval process and is even liable to be harmful. Particularly with multi-center research, the process for receipt of the approvals must be made more efficient and the time required for conducting the trial must be reduced, and steps taken to simplify the process.

Consequently, when a trial has been approved in a specific institution in all its stages, and approved by the Ministry of Health as a multi-center trial, the institution Helsinki Committees of the additional institutions in which the multi-center trial is requested should avoid discussing all the ethical aspects of the trial that have already been addressed by the first institution, and should instead make use of the recommendations and conclusions of the Helsinki Committee that discussed the trial and approved it in the first institution. This will not only shorten the time of the processes for approval of the trial, but will also contribute to the creation of uniform rules regarding the execution of the same trial in the various institutions.

In addition to the institution Helsinki Committees, there is an independent, Supreme Helsinki Committee, whose composition, legal quorum, and ways of appointment are specified in the public health regulations. This committee's function is to provide an opinion regarding trials related to the human genetics, artificial fertilization of a woman, and other subjects the Director-General of the Ministry of Health raises, including trials regulated by the Genetic Information Law.

The medical trials procedure also establishes a central committee for medical trials on humans, appointed by the Director-General of the Ministry of Health, which advises on medical preparations, medical devices and instrumentation/medical equipment, products containing living cells and tissues from a human source and xenotransplantation, or any other subject to be decided upon in the future.

The Israeli Medical Association calls for the formation of a Supreme Helsinki Committee to serve as a multi-disciplinary steering committee for the discussion of any ethical, medical, legal, philosophical, social, or other question that may arise from time to time during the approval and execution of any kind of clinical trial. This committee should comprise representatives from various disciplines who are specialists in a variety of fields and possess suitable qualifications to provide an answer to the questions and issues that may arise. This will serve to formulate uniform, final, and binding rules for the execution of every clinical trial, in any institution whatsoever, to be consistently updated in accordance

with the needs and questions that arise.
The position of the Israeli Medical Association is that its representatives should be included in this supreme steering committee. In the light of the active participation of the Israeli Medical Association in the revision of the Helsinki Declaration in recent years, its representatives will be able to reflect for the members of this committee the international situation related to clinical trials and the changes taking place from time to time in the international documents related to clinical trials.
In addition, the Israeli Medical Association will, by means of its professional associations, be able to place senior physicians in every field of medicine at the disposal of this committee. By means of its Scientific Council, the Israeli Medical Association will be able to increase the training of physicians in the professional knowledge required for execution of clinical trials, and by means of the Ethics Board, the Israeli Medical Association will also be able to assimilate the ethical code required in these trials.
The Israeli Medical Association holds that the work of the members of the various Helsinki Committees should be regarded as an integral part of their routine work. This recognition will permit members of the committee to devote the time required to study the requests before them and to judge them in accordance with the scientific background material. This recognition will indicate the considerable importance that the public in Israel attaches to the work of the committee, and its vital role, as well as the expectation that members of the committee will carry out their jobs in the most professional manner possible.

Physician training

The Israeli Medical Association attaches great importance to activities in the field of medical education, qualification of specialists and research grants in order to train physicians to conduct clinical trials. Consequently, the Israeli Medical Association has begun acting in the following three fields:
The Israeli Medical Association, by means of its Scientific Council, has initiated joint activities with the Association of Deans of Medical Schools, with the aim of including the relevant subject matter for conducting medical research on humans in the study programs of the four medical schools in Israel. The aim is to have the mandatory curricula in all the medical schools include courses in ethics, management of medical research, and the study of good clinical practice (GCP) in medical research.
The Israeli Medical Association, by means of its Scientific Council, has initiated the preparation of a course in the ethics of medical trials and the methodology of clinical research, including familiarity with the regulatory frameworks of the research and with GCP. The Israeli Medical Association will take steps to make these studies mandatory so that every resident in the State of Israel will be obligated to undertake these studies and pass exams in them during his specialization.
The Israeli Medical Association has initiated a change, according to which starting from

a specific date in the future, only a physician who has undergone recognized additional studies in GCP and has received a certificate from an internationally recognized body may become a head researcher in a trial. Furthermore, the Israeli Medical Association is taking steps to ensure that on a later future date, every researcher (and not only the head researcher) who participates in a clinical trial will have received such training.
The aim of this training program, including its various stages, is to obligate physicians to assimilate throughout their professional career, beginning at the outset, (whether during their academic years, their practical work, or when conducting a medical trial) the rules to be observed when involved in a medical trial on humans. Apart from these steps, the Israeli Medical Association shall specify a transition period in order to permit all the physicians to become familiar with these new rules of qualification.

Enforcement

As set forth above, the issue of medical trials on humans has still not been addressed by primary legislation, with the existing legal basis for regulation of the issue found in the public health regulations, enacted by virtue of the Public Health Order. The Order includes a provision for punishment according to which a person infringing one of its provisions is liable to six months' imprisonment or a fine.
The private bill for Medical Trials on Humans, 5765-2005 specifies punishments for conducting trials contrary to the law. Among other things, the bill states that a person who initiates, conducts, or permits conducting a medical trial on humans in contravention of the law shall be liable to one year's imprisonment or the payment of a significant fine (and in the case of a corporate initiator – a double fine). In the case of a high-risk trial, the penalty shall be increased to three years' imprisonment. It is also proposed that infringement of the law will also constitute an infringement of the Physicians Order and the Psychologists' Law, and punishment shall be determined accordingly.
The position of the Israeli Medical Association is compatible with the trend to increase the penalties imposed on those infringing provisions related to medical trials on humans. The Israeli Medical Association is convinced that the full strictness of the law should be implemented against physicians who infringe the law or the public health regulations and the existing provisions regarding clinical trials. Such infringement harms the public's trust in physicians and medicine.
Consequently, when it has been duly established that a physician has infringed these rules, he shall not receive the protection of the Israeli Medical Association. The Israeli Medical Association is convinced that it is important to have criminal sanctions whenever there is infringement of the relevant rules, and that it is necessary to grade the gravity of the various offences, to evaluate every infringement on its own merits, and to determine the appropriate punishment in accordance with the gravity of the offence. Furthermore, when speaking of the gravest offences, even heavier punishments than those proposed in

the private bill should be imposed.
The Israeli Medical Association believes that it is necessary to strengthen the mechanisms for the supervision and monitoring of research, starting from the proper allocation of resources and positions, through the determination of clear, specific rules to define the types of trials requiring more frequent supervision and monitoring and, finally, providing effective enforcement mechanisms. In addition, the obligation for reporting as set forth in the law, described above, should be strictly observed and the committee should be empowered to impose sanctions on a head researcher who does not report in a timely fashion, even during the interim period until the legislation of suitable regulations in the subject.
The Israeli Medical Association regards the participation of patient representatives and representatives of the Association for Civil Rights as vital for the various processes taking place in connection with the issue of medical trials on humans in general, and in all matters related to supervision and monitoring, in particular.

Summary and recommendations

The continuation of clinical trials in Israel is an interest shared by patients, physicians, and the medical establishment in Israel.
Clinical trials benefit the patients participating in them and allow them the most advanced means of treatment and therapy in the world, years before these means are included in the national drugs basket, all this under skilled and close medical monitoring and without any cost on their part.
The physicians also benefit from clinical trials: They are exposed to a unique medical field in which they significantly increase their knowledge and acquire valuable clinical skills. The execution of trials obligates the existence of a strict and inflexible system of regular transfer of information to the patients, medical documentation and monitoring, while maintaining very strict international standards.
The exposure of researchers in Israel to additional researchers from other countries opens a window for them onto the most advanced international medicine, while creating professional and social connections with the international medical leadership.
The State and the medical organizations also benefit from the execution of clinical trials. The trials also permit the peripheral hospitals and community physicians to participate, and thus benefit from a high academic standard. The State and the health care organizations benefit from medical manpower possessing improved clinical capabilities, who acquire better insight and diagnostic and treatment capability for the patients. The professional knowledge acquired during treatment of the patients who participate in clinical trials is used, in the final analysis, for better medical treatment of the entire population.
Let us not forget the important economic value of the clinical trials conducted in Israel. Based on accepted estimates, the pharmaceutical industry invests about $300 million a

year in medical research in Israel. This is a very small share, not exceeding 0.3% of the entire international investment in medical research, which totals $100 billion every year.
We need to utilize the advantages existing in the medical system in Israel and international recognition of its quality, in order to turn Israel into a preferred destination for international pharmaceutical companies. This is an attainable goal.
The contribution of patients who participate in trials to the advancement of medicine and science is endless and is worthy of appreciation and esteem on the part of each one of us. In return, we must guarantee that the clinical trials are conducted in strict observance of all the applicable laws, regulations and ethical rules in Israel.
We must also guarantee to the patients that the trials will be conducted with full academic freedom, without any influence by the pharmaceutical companies, with full transparency, and while preserving the freedom to publish all the results of the research, even if they do not meet the expectations of those who initiated or financed it. In this way, we shall act in accordance with the mandatory directions published and recently updated by the International Association of Editors of Bio-medical Journals (ICMJE).
In order to advance the execution of clinical trials in Israel, the Israeli Medical Association proposes the following steps:

1. Education and assimilation of the medical culture of GCP and the relevant ethical rules:
   a) The Israeli Medical Association, by means of its Scientific Council and in cooperation with the association of deans in Israel, shall take steps to include the subject of clinical trials, including the principles of GCP and the relevant ethical rules, in the mandatory study program of the medical schools in Israel
   b) The Israeli Medical Association, by means of its Scientific Council and its scientific associations, shall take steps to establish a national central course to teach the principles of GCP and the relevant ethical rules. Every resident during his period of specialization shall be required to participate in this course and pass a final examination.
2. Obligatory further studies for researchers:
   a) The Israeli Medical Association, in cooperation with the Ministry of Health, shall take steps so that starting from an agreed date in the future, every head researcher in a clinical trial shall be obligated to undergo a GCP course and possess a GCP certificate awarded by an internationally body recognized and qualified for granting such a certificate.
   b) The Israeli Medical Association, in cooperation with the Ministry of Health, shall take steps so that starting from an agreed date in the future, every researcher in a clinical trial (not only the head researcher) shall be obligated to undergo a GCP course and possess a GCP certificate awarded by an internationally body recognized and qualified for granting such a certificate.

3. Change of the structure and functioning of the Helsinki committees:
   a) Steps shall be taken to improve the efficiency of the various Helsinki committees, especially in cases of multi-center research, and to reduce the period of time required for approvals of clinical trials in general and of multi-center clinical trials in particular.
   b) The work of the Helsinki Committee members shall be regarded as an integral part of their routine work.
   c) Steps shall be taken to set up a Supreme Helsinki Committee that shall serve as a multi-disciplinary steering committee for the purpose of discussion of and response to any ethical, medical, legal, philosophical, social, or other question that may arise during approval and execution of a clinical trial, and that shall comprise representatives of the various disciplines.
4. Enforcement
   a) The Israeli Medical Association shall cooperate with the Ministry of Health in order to enforce the laws, instructions, and ethical directions during execution of clinical trials in Israel.
   b) A physician who has been duly proven to have infringed the rules of this system shall not enjoy protection from the Israeli Medical Association.
   c) The gravity of the infringements shall be graded and sanctions to be employed against a physician who infringes the relevant rules shall be specified in accordance with this grading.
   d) A physician who has been found guilty by a court of such an infringement shall be brought before a clarification committee of the Ethics Board.
5. Primary legislation
   a) The Israeli Medical Association calls for addressing the subject of clinical trials in primary legislation as soon as possible.
   b) The Israeli Medical Association calls to adopt in primary legislation the principles embodied in the Helsinki Declaration, as updated from time to time, since this is the most advanced document in the field of clinical trials that obligates physicians throughout the world.