for several years now, multinational pharmaceutical companies across the globe have found Israel to be an attractive site to conduct clinical studies. Israel’s medical system, supervised by the Ministry of Health (MOH), consists of institutional and private markets. There are 29 medical institutions (10 of which are university affiliates) and approximately 20,000 physicians. The medical institution infrastructure is very modern and contains state-of-the-art equipment. Most of the medical policies in place are similar to those in the United States, where many Israeli physicians are trained via fellowship programs. Israeli physicians participate in many international activities and are thus recognized as international opinion leaders. The number of clinical studies starting in the various medical institutions throughout Israel is increasing every year. In 2004, there were 2,099 applications reviewed by the various institutional review boards (IRBs) across Israel.

Understanding the legal framework and the approval process, as well as identifying the tips and tricks to avoid the pitfalls in conducting clinical trials in Israel, are important milestones on the road to a successful start. This article reviews these milestones.

The Legal-Regulatory Framework

According to Israeli law, the legal framework is dictated first by primary legislation (laws and orders), and then by secondary legislation (rules and regulations), as well as by international declarations and rulings from the courts of law.

Israeli public health regulations on medical experiments involving human subjects were published in 1980 and incorporate the principles of the Helsinki Declaration established at the twenty-ninth world medical assembly, in Tokyo, Japan, in 1975. The 1980 public health regulations constitute the current legal framework that regulates medical experiments involving human subjects in Israel. Based on these regulations, the pharmaceutical division in the MOH occasionally publishes guidelines for the conduct of clinical studies on human subjects. These guidelines standardize the manner of submitting, approving, and supervising clinical studies on humans.

A clinical study on humans may not be carried out in Israel unless it conforms to the instructions of the public health regulations and guidelines for the conduct of clinical studies on human subjects.

The clinical study must be approved by both the medical institute’s Helsinki Committee (the Israeli name for an IRB) and by the general director of the MOH or his designee—the medical institutes’ directors to whom he has delegated his authorization, as detailed below. Only a licensed physician or licensed dentist in...
Israel (depending on the subject of the trial) can act as the principle investigator (PI) and may submit a request for clinical study approval to the Medical Institution’s Helsinki Committee.

The content of the submission documents varies in accordance with the nature of the clinical study—that is, whether it is a study on a medicinal product, a medical device study, a study with an investigational product originating from live cells and tissues, a genetic study, or a clinical study without the use of investigational product. There is a separate submission package for each category, as detailed in Table 1. The submission documents must be in Hebrew only.

In the public health regulation and its guidelines, the MOH General Manager is allowed to delegate his authorization—to give final approval for the conduct of clinical studies—to the directors of the various medical institutions. This delegation of authorization is conditional to full compliance with all the requirements detailed in the public health regulations and its guidelines; it can be easily withdrawn in the case of noncompliance.

The medical institute’s Helsinki Committee reviews the submission package (“the EC submission package”), determines whether or not to approve the study in accordance with defined criteria, and determines whether or not the clinical study falls under the definition of a “special” clinical study (see Table 2). The approval process, as detailed in Figure 1, is based on this decision.

A “special” clinical study is one whose final approval is under the authorization of the medical institution’s director. The institutional Helsinki Committee notifies the medical institution’s director of its decision regarding its approval of the request for clinical studies, and the director has the authority to approve without additional approval from the MOH. The approvals of the institutional Helsinki Committee (form #6) are forwarded to the medical institution’s director with a copy to the PI.

The director issues final approval for a clinical study to the PI, with details of the conditions and limitations (form #7), and the PI submits a copy of the approval (form #7) to the sponsor and to the medical institution’s chief pharmacist (as necessary).

A “nonspecial” clinical study requires MOH approval, following the approval of

<table>
<thead>
<tr>
<th>Table 1. EC Submission Package Required for the Approval of a Clinical Study</th>
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<tbody>
<tr>
<td><strong>Type of Study</strong></td>
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<tr>
<td>Request Form (form #1)¹</td>
</tr>
<tr>
<td>Protocol</td>
</tr>
<tr>
<td>Investigator’s brochure</td>
</tr>
<tr>
<td>Relevant literature</td>
</tr>
<tr>
<td>Informed Consent Form (form #2 or 3)²</td>
</tr>
<tr>
<td>Liability of the study sponsor (form #4)³</td>
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<tr>
<td>Sponsor declaration document identity (form #5)</td>
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<tr>
<td>Letter to the treating physician in the health fund (form #11)</td>
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<tr>
<td>Checklist (form #9)</td>
</tr>
<tr>
<td>Recruitment advertisement (form #10)³</td>
</tr>
</tbody>
</table>

¹ For each type of study there is different request form as noted above.
² According to the guidelines, only the MOH format can be submitted. This is either form #2 for studies in which the subject is capable to sign, or form #3 for studies in which a legal representative signs on behalf of the subject.
³ This form is submitted if needed.
⁴ There is extended information, and more forms need to be submitted, for genetic studies (details can be found in the relevant guideline, as published in the MOH website).
the institutional Helsinki Committee. If the committee determines that a clinical study is “nonspecial,” the relevant documents are submitted to the MOH, which evaluates the submission and decides on the manner of handling in accordance with one of three possibilities:

- **Clinical study approval is given:** The MOH forwards its approval (form #8) to the Helsinki Committee chairperson, with a copy to the medical institution’s director. The director issues final approval for a clinical study to the PI, with details of the conditions and limitations (form #7). The PI submits a copy of the approval (form #7) to the sponsor and to the medical institution’s chief pharmacist (as necessary).
- **The request is transferred for recommendation from a group of experts:** A notification is sent to the Helsinki Committee chairperson, and then to the PI, specifying what documents or data are required in order to continue handling the request. If the experts approve the submission, the MOH will forward its approval on form #8. If there is no recommendation to approve the clinical study, the request is transferred for a discussion in the clinical studies’ central committee.
- **The request is transferred for a discussion in the clinical studies’ central committee or in the supreme Helsinki Committee:** A notification is sent to the Helsinki Committee chairperson, and then to the PI, specifying what documents or data are required in order to continue handling the request. Following a discussion at the central or supreme committee, the MOH will notify the Helsinki Committee chairperson of the committee’s decision and thence to the PI. The decision could be an approval (form #8), nonapproval, or requirement for further information and/or documentation.

In both special and nonspecial clinical studies, the PI may start the clinical study only after receipt of the medical institution director’s final approval (form #7). An approval from the institutional Helsinki Committee (form #6) is not an authorization to start the clinical study.

There are no declared timelines for approval in the 2006 guidelines. Based on experience, the average timelines for clinical study startup are as follows, provided that the submission package is complete and on time (see Figure 2):

### Table 2. Criteria for “Special” Clinical Study

<table>
<thead>
<tr>
<th>Categories</th>
<th>Definition/Types</th>
<th>Conditions</th>
</tr>
</thead>
</table>
| Approved registered medicinal products (MPs) and medicinal devices (MDs) | 1. Registered MP in Israel and/or MP with marketing approval in the recognized countries 1  
2. Registered MD in Israel and/or:  
   - CE mark and marketed in Europe  
   - FDA approval and marketed in USA | 1. Usage for an approved indication and within the registered restriction  
2. Treatment and followup of patients as in standard clinical practice and at accepted dosage |
| Efficacy testing of MP or MD                     | Prior clinical studies for safety have been successfully carried out in a recognized country 1, and the results have been reported | 1. Efficacy testing relates to indication, dosage form, and mode of administration used in previous clinical studies  
2. Efficacy testing is not planned to be conducted on special population 2 |
| Nonspecial multicenter study  
(i.e., also needs MOH approval) | All centers use same protocol and same informed consent form | MOH approved the study for at least one such center |
| Bioequivalence study                             | Comparison between oral formulations of MP | Generic MP vs. registered MP in Israel or with marketing approval in recognized country 1 |
| Clinical study without MP or MD                  | 1. Clinical study with non-MPs, such as cosmetics, herbal medicines, food additives, and homeopathic products  
2. Collection of data from adults (i.e., by blood or body fluids sampling, via questionnaires, etc.)  
3. Voice recording as accepted in speaking-difficulties studies  
4. Moderate physical exercise conducted with healthy volunteers | 1. The MP or MD is registered  
2. In MD study, the device is not invasive  
3. In MD study, the participant is not exposed to ionic radiation  
4. Body fluid sampling is not intended for genetic research |

1 Recognized countries are the United States, European Union member nations, Switzerland, Norway, Iceland, Australia, New Zealand, and Japan.

2 Special populations are pregnant women, minors, patients whose physical or psychological state adversely affects their judgment, and incarcerated individuals.
For special clinical studies, the institutional Helsinki Committee’s approval takes approximately two to three weeks and the medical institution director’s final approval takes another two weeks.

For nonspecial clinical studies, the institutional Helsinki Committee’s approval takes approximately two to three weeks; the MOH approval takes another four to 12 weeks; and the medical institution director’s final approval takes another two weeks.

Tips and Tricks to Avoid the Pitfalls

As in every country, there are some tips that are not written in the regulations and guidelines. These tips are important for expediting the commencement of the study. The following is a list of some of the important tips:

EC submission package

- One should have the exact information from each medical institute regarding the dates for the EC submission package, the recommended format for the submission, the number of required copies of each document in the package, etc. Most of the medical institutions publish their standard operating procedures with this information on their website.
- Although the EC submission package is the PI’s responsibility, in order to meet the timeline of the institutional Helsinki Committees, one should prepare the EC submission package on behalf of the PI, ask for his review and signature, and then submit all required copies to the institutional Helsinki Committee. Most institutional Helsinki Committees meet every four to six weeks, and the EC submission package needs to be at the Helsinki Committee office at least two weeks before the meeting.
- For a nonspecial clinical study, one should have the dates of the various MOH committees in order to verify that the submission of required documents following the institutional Helsinki Committee will get to the MOH committee on time. The central and supreme committees meet every six to eight weeks, and the relevant submission documents need to be received at least two to three weeks before the meeting.

Service Fees

Each medical institution may charge a service fee to handle the request for approval, so one should collect this information in advance. Not all medical institutes charge the same fee, if any. For a nonspecial clinical study, the 2006 guidelines set the service fee maximum at $1,000, to be divided between the medical institute and the MOH.

Informed Consent Form (ICF)

The ICF must be written in Hebrew in accordance with the MOH format, as instructed in the 2006 guidelines. The Hebrew-ICF template is then translated to the various spoken languages in Israel, i.e., Arabic, Russian, Amharic, and English, as needed.

The Medical Institution Pharmacy

Storage and issue of the Investigational Product (IP) to the clinical study participants are under the responsibility of the PI/medical institute. If the IP is a medicinal product, then the supply, storage, and issue to the clinical study participants will be done in conjunction with the medical institution’s pharmacy, unless the institutional Helsinki Committee had decided otherwise.
Clinical Trials Agreement (CTA)

- Each CTA between a sponsor and a PI conducting the clinical study must be ratified by the commercial committee and the director of the medical institute in which the study is to take place, or by an individual authorized by the director to give that approval, such as the research fund manager for that institute.
- Each medical institute has its own CTA format. One should obtain the institution’s CTA and negotiate around this format, rather than sending the sponsor’s CTA to the institute for discussion. With the various CTAs across Israeli medical institutes, all the parties who sign on the CTA are the sponsor on one hand and the medical institute or its research fund on the other hand. The PI is not a party to the signature of the contract. The PI signs only a declaration statement, which is part of the CTA, declaring his commitment to perform the clinical study in accordance with the ICH-GCP (and/or ISO 14155 in medical devices) and in accordance with the MOH guidelines.
- Final approval to start the clinical study, given by the medical institute’s director (form #7), is pending not only on the ethical approval but also on the approval of the CTA. Thus, in order to avoid delays, one must start the process of CTA negotiation towards approval in conjunction with the EC submission.

IP Importation

To import the IP into Israel, one must submit a proforma invoice together with the final approval of the medical institute’s director (form #7) from one of the centers conducting the study, to a specific division at the MOH. Consequently, the IP can be imported to Israel only following the first form #7 receipt.

Clinical Studies in Israel: Uniqueness and Advantages

As mentioned at the beginning of this article, Israel serves as an attractive site to conduct clinical studies for many reasons. Israel’s population originates from many countries and ethnicities. This diversity serves as an important advantage when conducting clinical studies.

Since 1995 the Israeli population is insured through national health insurance, which allows each individual the choice of being insured by one of four health insurance funds. The medical system in each health fund is computerized in a way that allows one to follow the medical history of its insured members, and easily locate and track each individual over time. Such a system has important value when conducting clinical studies, since subjects can be monitored from beginning to end, and count them as “evaluable” subjects.

As the number of clinical studies conducted in Israel increases from year to year, the stakeholders see the need for formalized Good Clinical Practice (GCP) training. It is well acknowledged nowadays by the MOH, Israeli Medical Association (IMA), and medical institution managements that a high level of GCP training is crucial for the conduct of clinical studies. Thus, in the last few months many Israeli medical institutions have demanded a certificate of attendance at a GCP course from their investigators as a requirement for performing clinical studies.

Finally, during September 2006, the IMA published its viewpoint regarding proper and advanced conduct of clinical studies. In this viewpoint the IMA makes recommendations on education and adoption of the GCP medical culture as well as the relevant ethical norms. The recommendations encompass educational programs at the various medical schools, medical traineeship programs, and the requirement that the investigator attend a GCP training program given by an international recognized body.

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