CLINICAL TRIALS IN JORDAN:

Current Status and Improvement Opportunities

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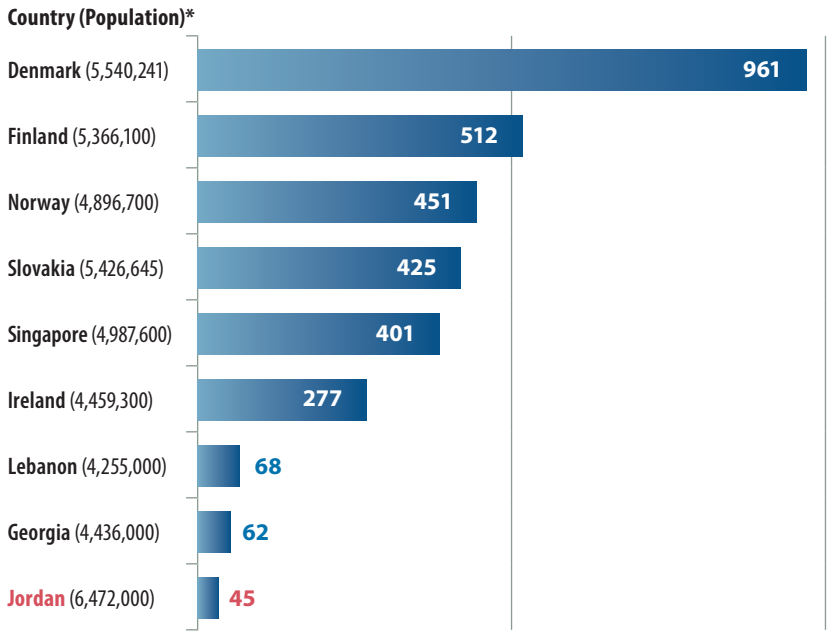
Performing research under conditions of robust methodology is key for the development of new drugs and medical devices. However, the conduct of clinical trials within countries in the Middle East and North Africa (MENA) is not yet optimal. Even though MENA populations represent 9% of the world population,[1] in 2012, MENA countries, excluding Israel, hosted only approximately 0.4% of global clinical trial sites and patients.[1]

In the mid-1990s, clinical trials started to gain recognition in Jordan, one of the MENA countries, with a very limited number and types of trials. A decade later, Jordan was recognized as one of the important research sites in the MENA area. Several contract research organizations (CROs) were established there in the early 2000s, focusing solely on bioequivalence and bioavailability studies.[2]

There are several reasons for the recognition Jordan has earned, including its highly qualified healthcare professionals and well-established and accredited healthcare organizations. It is a referral country, with regional healthcare centers receiving patients from all surrounding countries in the region as they seek advanced medical treatment. Further, the country features high bioethical standards, resources availability, and a supportive regulatory body. This environment fosters a heterogeneous patient population with various ethnic and cultural origins, which is ideal for clinical trials.

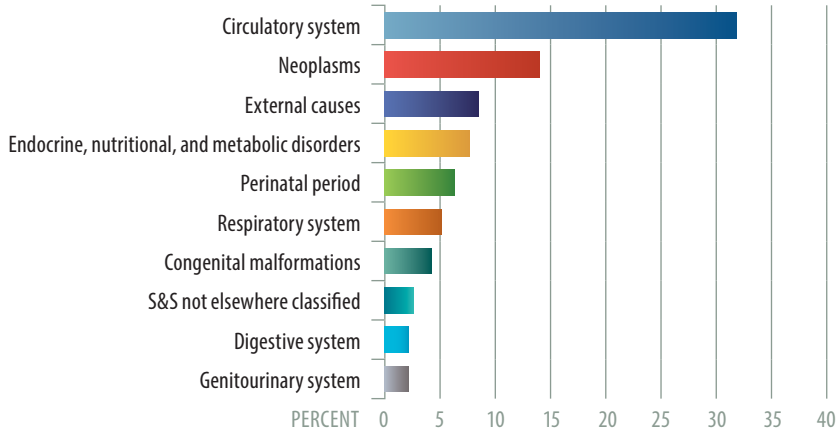
Concerning clinical trials, Jordanian law does not distinguish between the different kinds of pharmaceutical studies, even though there are clear definitions for therapeutic vs. nontherapeutic trials. This article reviews mainly Phase I to Phase IV clinical trials.

FIGURE 1: Number of Trials in Selected Countries



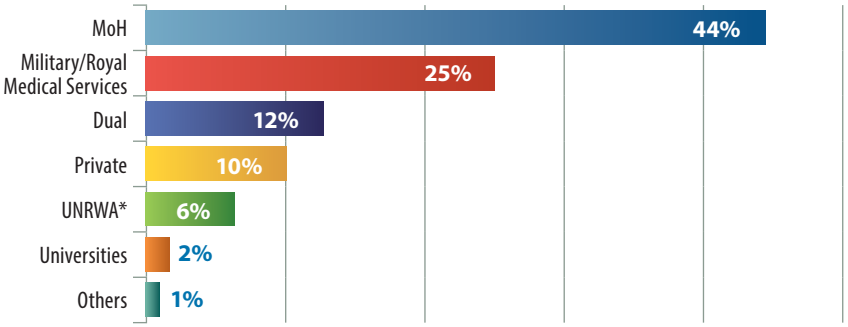
**World Atlas.com*

FIGURE 2: Top Ten Causes of Death for 2010 According to ICD-10



Source: MoH, Directorate of Information and Research, Mortality Data, Issue Dated May 1, 2011

FIGURE 3: Insurance Distribution 2010



**United Nations Relief and Works Agency for Palestine Refugees in the Near East.*
Source: High Health Council and Directorate of General Statistics, Medical Insurance and Payment, Issue Dated September 2011

FIGURE 4: Health Research Priorities 2009-2012

1	**Noncommunicable Diseases:** cardiovascular, cancers, injuries, endocrine, obesity, osteoporosis, and neuropsychiatric
2	**Maternal and Child Health:** prenatal and nutritional deficiencies
3	**Reproductive Health**
4	**Health Behavior:** smoking, dietary habits, drug abuse, etc.
5	**Health System and Health Policy**
6	**Environmental Health**
7	**Communicable Diseases:** hepatitis B and C, respiratory infections, diarrheal diseases, etc.
8	**Demographic Transitions**
9	**Oral Health**

DEMOGRAPHICS

The estimated population of Jordan at the end of 2012 was 6,388,000, with an annual growth rate of 2.2%. Approximately 60% of the Jordanian population are between 15 and 64 years old, and the life expectancy of the country's citizens is 73 years.[3]

Despite the fact that the Jordanian population is small, sponsors and clinical trial stakeholders recognize the research potential of Jordan. Figure 1 presents details on clinical trial activity and population in a selection of countries with a similar or smaller population than that of Jordan.

The most common cause of death in Jordan is circulatory disease, such as ischemic heart disease, cerebrovascular disease, hypertension, and heart failure. The top 10 causes of death in the country, according to the International Classification of Diseases (ICD-10) in 2010, are shown in Figure 2.[4]

The Jordanian health system is highly acclaimed, including primary and advanced healthcare services. Further, approximately 70% of the Jordanian population has healthcare insurance (Figure 3 demonstrates the distribution of insurance for the Jordan population).[3]

Circumstances related to the causes of death, management of the healthcare system, and availability of insurance in Jordan have had an impact in identifying research priorities. The Ministry of Health/Directorate of Information and Research has identified the "National Health Research Priorities 2009–2012," which has shown that noncommunicable diseases have the highest priority, while oral health has the lowest (see Figure 4).[4]

Although Arabic is Jordan's official language, all source documents are in English, including medical notes, progress notes, laboratory results, radiology reports, and medication prescriptions. English is the primary language of education for all healthcare professions, including medicine, dentistry, nursing, pharmacy and pharmacology, and rehabilitation sciences. However, patient materials such as questionnaires and consent forms should be in Arabic.

TYPE AND STATUS OF STUDIES

The number of clinical trials in the MENA region remains very low compared to the United States, Canada, Europe, and most of the Asian countries. However, Jordan is a leading country in the region in this field, especially in bioequivalence and bioavailability studies.[5] The approximate number of these studies submitted between 2005 and 2013 was 1,470 studies (for registered and unregistered products). Of these and the 135 Phase I–IV studies conducted between 2005 and 2013, only six were rejected, while the rest were approved or received at least conditional approval.[2]

The first registered clinical trial under the Jordan Food and Drug Administration (JFDA) was initiated in 2001. In 2010, there were 34 clinical trials: 19 Phase I and the rest Phase II to IV. In 2014, up to early October, there were 26 clinical trials submitted (four Phase IV and 22 Phase I to III).[2]

The main sources of clinical trials coming to Jordan are global pharmaceutical companies from Europe and the U.S., in addition to a few studies from U.S. biotechnology companies. Most of these studies were conducted in collaboration with regional or global CROs.[2]

To date, the most common phase of clinical studies conducted in Jordan is Phase III, followed by Phase IV. Although pediatric and medical device studies are permitted, there is no significant increase to the total from the number of studies conducted in these areas.[2] Figure 5 shows the number and type of submitted studies per year from 2005 to 2013, as well as the approved number of studies vs. rejected or conditionally approved studies. Figure 5 also shows the distribution of clinical trials according to therapeutic areas.[2]

REGULATORY

The highest governing body of all types of clinical trials in Jordan is the Ministry of Health (MoH)/ JFDA, which was established in 2003. By late 2004, the clinical studies division was initiated.

JFDA plays a very important role in the protection of the rights and safety of participants and in maintaining a high level of ethical standards through continuous visits, inspections, and monitoring of clinical sites and institutional review boards (IRBs). In addition, JFDA is responsible for training and maintaining an increased awareness of research among healthcare professionals and the public through educational meetings and conferences.

FIGURE 5A: Approved vs. Rejected Studies 2005-2013

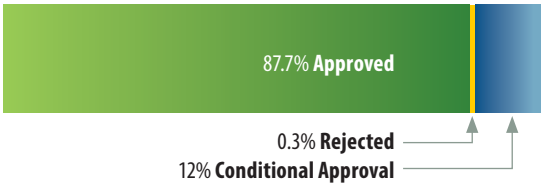


FIGURE 5B: Total Number of Studies from 2005 to September 2014

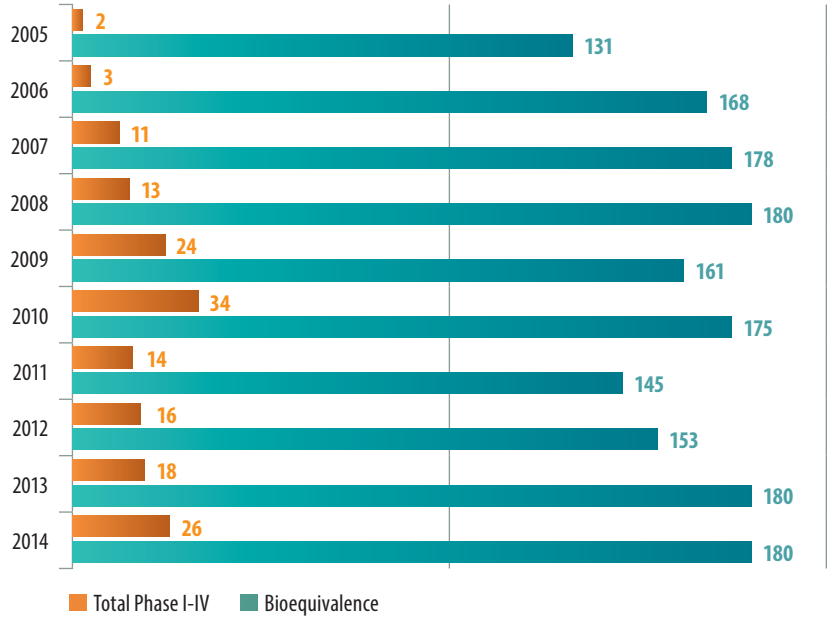
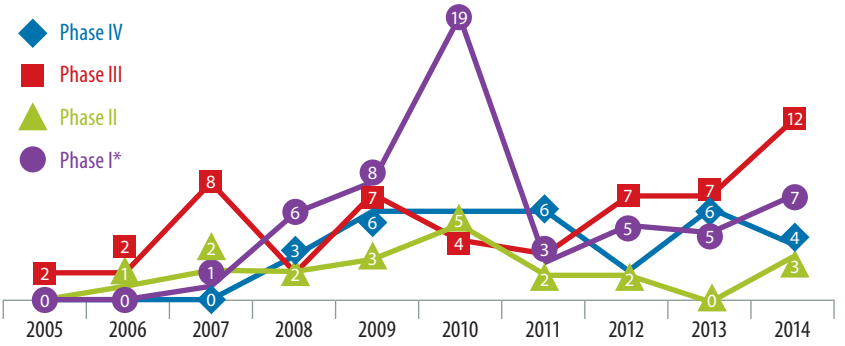


FIGURE 5C: Number of Phase I-IV Studies per Therapeutic Area 2005-2013



*Only one study in 2014 was first-in-humans; the rest were drug-drug interaction and pharmacokinetics.

FIGURE 5D: Number of Phase I-IV Studies per Therapeutic Area 2005-2013

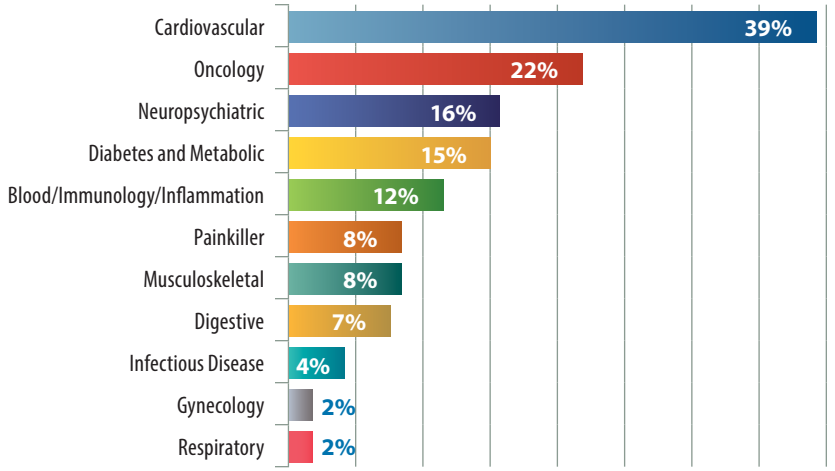
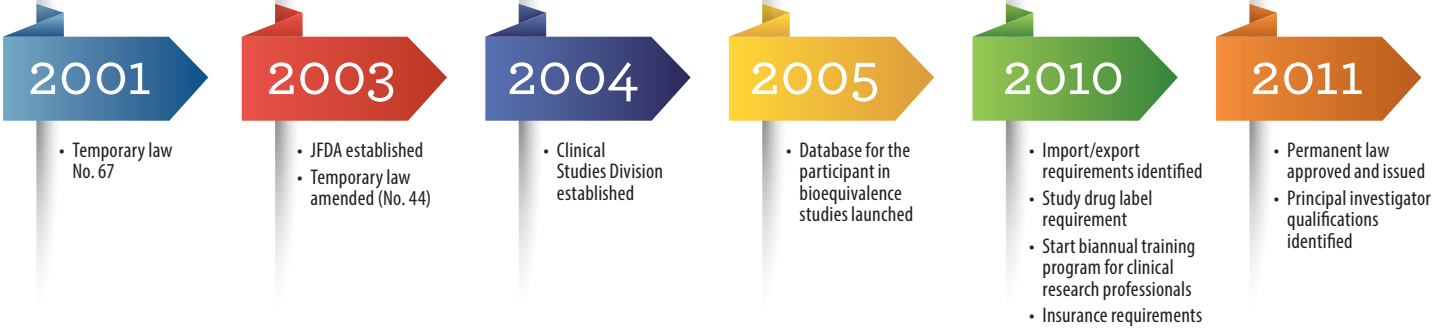


FIGURE 6: Significant Milestones in Clinical Trial Regulations in Jordan



The CSC has all the required powers to carry out its mission, especially since it was formed according to Jordanian law.

In 2004, the JFDA created the Clinical Studies Committee (CSC) to be responsible for reviewing and issuing approval or rejection for submitted studies. This committee is the highest authority for the initial decision on any new or ongoing study in human subjects.

The CSC has all the required powers to carry out its mission, especially since it was formed according to Jordanian law. Headed by the JFDA General Director, the committee includes the JFDA Director of Drug Directorate, the JFDA Head of the Clinical Studies Division, a pharmacist from the Drug Directorate, a clinician from the MoH, a clinician from the Physicians Labor Board, a member from the Royal Medical Services (military), and five representatives from academic and private institutions. The committee also has the right to consult external specialists as needed.

Healthcare research is now recognized and supported by governmental and private agencies, and Jordan is a leading country in clinical trials legislation in the Arab world. A temporary law issued in 2001 became permanent in early 2011; that law states that all clinical trials in Jordan should adhere to the Declaration of Helsinki as confirmed in Article 11. The law also specifies that one of the main duties for all local ethics committees is to ensure that the research team is able to conduct the study according to, and in adherence to, good clinical practice (GCP) guidelines (Article 8-a-2). Per Article 13-d, one of the main responsibilities of the CSC is to ensure that all licensed facilities for clinical trials adhere to GCP and good laboratory practice guidelines.[6]

However, the Jordanian law is currently written using wide and vague statements that are open to individual interpretations. Clearly written specific detailed guidelines or requirements would be of great benefit to all stakeholders. Since 2001, JFDA has issued more than 55 supportive memos, guidelines, and requirements to organize and improve the submission process, monitoring, and reporting. The most important examples of such memos and guidelines concern investigational drug labeling requirements and investigators' qualifications.

Figure 6 illustrates some important steps in clinical trials regulation. All these additions are made available in separate documents, but it is highly recommended that the documents be merged (including all clarifications), so that sponsors can consider all of the requirements together, rather than reviewing each individual memo from over the years.

SUBMISSION AND REVIEW

The expected time from full protocol package submission to final approval for conduct of a trial as estimated by JFDA is four to six weeks for Phase I–III studies, if there are no comments or additional requirements requested.[7] Otherwise, the approval time will vary based on the nature of the comments or requirements as well as on the sponsor's feedback. Next, the sponsor seeks approval from an IRB/ethics committee, based on any new requirements and with a commitment of adherence to them by the principal investigator and the sponsor. However, if the sponsor does not reply to the board's/committee's feedback regarding further changes that may be requested within six months, the application will be considered withdrawn.

One of the main issues for clinical studies in Jordan is the time the studies take to get approved; this has a negative impact on patient recruitment and study progress, and means that any eventual approval of a new drug or device is delayed. Therefore, the current submission procedures should be reviewed and more time-efficient strategies developed.

One issue of timeliness is that, currently, JFDA uses the sequential submission system as described where and does not accept parallel submission at the same time as IRB/ethics committee submission. Electronic submission is definitely a good approach for improving the submission process, yet all submissions must be delivered by hand to the JFDA at this time. The use of electronic submissions will save up to two to three weeks, with study documents reaching CSC members directly and with external reviewers facing no need to wait for the next meeting to receive materials for consideration.

JFDA plays a very important role in the protection of the rights and safety of participants and in maintaining a high level of ethical standards through continuous visits, inspections, and monitoring of clinical sites and institutional review boards.

The sponsor can submit all documents in English, except those for the patient (informed consent form, information sheet, patient's cards, questionnaires, diary cards, etc.), which should be in Arabic.

CLINICAL SITES AND IRBS

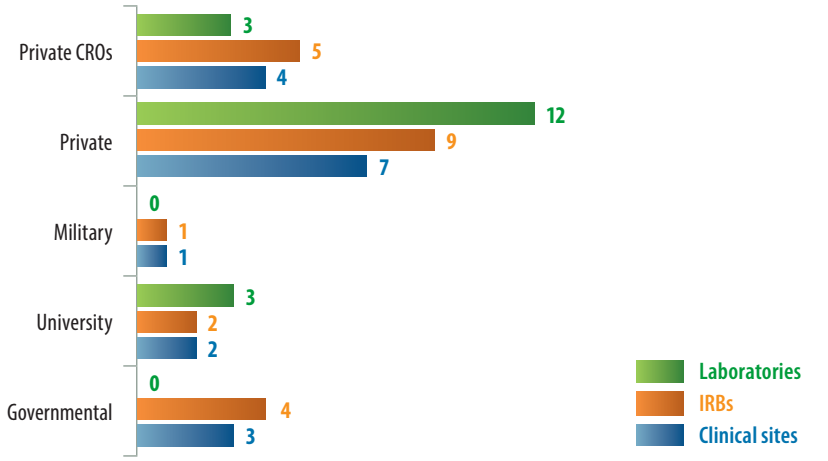
According to Jordanian law, clinical trials can be conducted only at licensed sites; the same process applies to all other involved facilities, including IRBs/ethics committees, safety labs, and analytical labs.

As of 2012, Jordan had 106 hospitals with a total capacity 12,106 beds.[3] These hospitals can be divided into four main categories: MoH hospitals, university hospitals, military hospitals (Royal Medical Services), and private hospitals. Most of the private, military, and university hospitals are accredited by one or more of the local or international accreditation bodies; they also have the most recent diagnostic and treatment equipment, use the Internet, and have no difficulties using electronic case report forms. In addition, these hospitals have local laboratories and/or research units to facilitate lab samples processing as well as shipping to central labs if needed. However, less than 20% of Jordanian hospitals are licensed as clinical trials sites (see Figure 7).[8]

Governmental and private hospitals need to make greater efforts to become involved in clinical studies. Currently, only three of 31 MoH hospitals are licensed for clinical trials; their physicians are interested in being involved in trials, but many issues—such as site facilities, medical documentation, and lack of experience and encouragement by top management—need to be resolved in collaboration with the MoH, sponsors, and regulators.

The military hospitals are well established and have an advanced documentation system for use in clinical trials. However, the number of clinical trials conducted in these hospitals is very low, due to the long time required to get IRB/ethics committee approval and contract negotiation. The top management in such settings needs to encourage greater interest and to establish research activity benchmarks against similar institutions.

FIGURE 7: Number of Licensed Facilities as of August 2014



For private sites as well, sponsors and investigators should clarify to patients the benefits of clinical trials, regardless of where they are treated, and healthcare workers should get more training and experience in clinical trials. Of the 18 licensed hospitals, only four have dedicated research units managing trials and providing the required logistic support to investigators.

Jordan does not use a central ethics committee; only IRBs/ethics committees based within individual institutions are used. Each licensed clinical site must have such a body, which should be approved by the JFDA. According to Jordanian law, the board/committee should consist of at least five members from both sexes with sufficient experience and competency.

An IRB/ethics committee is required to include at least one legal advisor in addition to a representative from the local community.[6] Board/committee membership is valid only for two renewable years.[6] Figure 7 shows the number of approved IRBs/ethics committees in Jordan.

CONCLUSION

Clinical trials are growing in the MENA region, and Jordan is a leading country in this area. Conducting a clinical trial in Jordan is protected by the government via the Clinical Studies Law and monitored by IRBs/ethics committees. The healthcare systems of the country are ready to be more involved in clinical trials.

All stakeholders must be willing to participate in clinical research, to provide more training and educational programs, and to develop more creative solutions for facilitating and expediting protocol submission, review, and monitoring, such as electronic submission, detailed guidelines for all trial steps, and benchmarking. Also, governmental hospitals require greater research awareness, training sessions, and improved support in terms of facilities, systems, and guidance.

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