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COUNTRY REPORT

CLINICAL RESEARCH LAW IN JORDAN: AN ETHICAL ANALYSIS

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ABSTRACT
An ethical analysis of Jordan's Clinical Research Law, which became effective in 2001, was performed. Accordingly, this paper discusses the major components, key strengths and weaknesses of this law. As an initial effort, the Law addresses important aspects of research ethics and, hence, should serve as an example for other Arab Countries in the Middle East. Unique aspects of the Law include the requirement that those conducting any study have insurance that can compensate for research injuries and a system of fines and punishments for noncompliance with the Law. There are, however, some key items missing in the Jordanian Law. For example, the Law does not mention the requirement of a favourable assessment of risks and benefits, the fair selection of subjects, or articles regarding the protection of the rights and welfare of children and other vulnerable subjects participating in research. The paper concludes with the suggestion that new amendments should be considered for future revisions of the Clinical Research Law in Jordan.

INTRODUCTION

In 2001, by the authority of the King of Jordan, Article 67, entitled Law of Clinical Studies (also known as the Clinical Research Law), became law.[1] This Jordanian Clinical Research Law is based on the *Declaration of Helsinki,* first issued by the World Medical Association in June 1964 and followed by several revisions, the last one being in 2000.[2] The *Declaration of Helsinki* is a statement of ethical principles providing guidance to physicians conducting medical research involving human subjects. Other

[1] Jordan Food and Drug Administration (JFDA). 2001. Clinical Research Law. Online: JFDA. Available at: http://www.jfda.jo/EN/Laws/LawInfo.aspx?id=507 [Accessed 11 Feb 2007].

[2] World Medical Association (WMA). 1964. *Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects.* Ferney-Voltaire: WMA.

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research ethics guidelines have also been developed during the past several decades.[3]

The Jordanian Food and Drug Administration (JFDA) motivated the passage of the Clinical Research Law in order to enhance the oversight of clinical studies conducted in the context of medical care, as well as to provide regulations for the increasing number of pharmaceutical companies performing clinical drug trials in Jordan. A large number of these clinical trials consist of bioequivalence studies in which generics are tested against innovator or brand-name drugs. Providing regulations for bioequivalence studies also enhances the export opportunities for the indigenous pharmaceutical industry in Jordan. Indeed, in order to export medicines to other countries, international regulations demand universal standards regarding quality standards of documentation and good clinical practice in the conduct of clinical trials. Accordingly, generics have become one of Jordan's main export commodities.

Jordan is one of the few Arab Countries in the Middle East that has national regulations governing the protection of human subjects in clinical trials.[4] As such, the Clinical Research Law should serve as an example for other countries in the Arab region regarding the importance of having national regulations that deal with drug trials. Accordingly, the aim of this paper is to analyze the *content* of the Jordanian Clinical Research Law and determine the extent to which it adheres to ethical principles in the research context: respect for persons, beneficence, nonmaleficence and justice.

ETHICAL PRINCIPLES IN THE RESEARCH CONTEXT

Ethical principals for the conduct of research were articulated in 1979 in the *Belmont Report*.[5] The *Belmont Report* describes several fundamental principles: respect for persons, beneficence and nonmaleficence, and justice. The primary sources of Sharia', the Qur'an and Sunna of Prophet Mohamed have also stressed these principles throughout Islamic history.[6]

Respect for persons

Respect for persons involves recognition of the personal dignity and autonomy of individuals; also, vulnerable persons require special protections against exploitation of their inability to provide voluntary informed consent.

Beneficence

Beneficence entails an obligation to maximize anticipated benefits for individuals involved in research and to promote research that can lead to advances in medicine that enhance the health of society. Beneficence also requires investigators and members of research ethics committees to ensure that the anticipated risks are reasonable in relation to the anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.[7] The principle of nonmaleficence requires the minimization of risks that can emanate from the conduct of research.

Justice

There are several kinds of ethical demands regarding justice in the research context. The first one

[3] United States Department of Health and Human Services (HHS). Office for Human Research Protections. 2005. Code of Federal Regulations. Title 45. Part 46. Protection of Human Research Subjects. Washington, DC: HHS: Subpart A. Federal Policy for the Protection of Human Subject; Council for International Organizations of Medical Sciences (CIOMS). 2002. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva: CIOMS; No Named Author(s). Commission Directive 2005/28/EC of 8 April 2005 Laying Down Principles and Detailed Guidelines for Good Clinical Practice as Regards Investigational Medicinal Products for Human Use, as Well as the Requirements for Authorisation of the Manufacturing of Importation of Such Products. *Official Journal of the European Union* 2005; L91: 13–19.

[4] United States Department of Health and Human Services (HHS). Office for Human Research Protections. 2007. *International Compilation of Human Subject Research Protections*. Washington, DC: HHS. Available at: http://www.dhhs.gov/ohrp/international/ [Accessed 11 Feb 2007].

[5] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. 1979. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* Washington, DC: US Government Printing Office.

[6] G. Serour. 1994. Islam and the Four Principles. In *Principles of Health Care Ethics*, R. Gillon, ed. Hoboken, NJ: John Wiley and Sons: 75–91; S. Aksoy & A. Tenik. The 'Four Principles of Bioethics' as Found in 13th Century Muslim Scholar Mawlana's Teachings. *BMC Med Ethics* 2002; 3: 107.

[7] United States Department of Health and Human Services, *op. cit.* note 3, Article 111(a)(2).

entails the equitable distribution of the benefits and burdens of research among members of society. Hence, no one group in society should bear disproportionately the burdens of research, and no one group should obtain disproportionately the benefits of research. The second ethical demand regarding justice requires the equitable selection of subjects. Defining the appropriate group for a research project involves a variety of factors including the requirements of scientific design, the setting of the research and particular characteristics of the potential subjects, for example, susceptibility to risk, likelihood of incurring additional burdens associated with research participation, likelihood of benefit, and practicability. Fairness in subject selection also requires that one should never target vulnerable groups in research merely due to their inability to protect themselves; poverty, illness, illiteracy and institutionalization can cause prospective subjects to be vulnerable to coercion or undue influence. The inclusion of a vulnerable group in research is justifiable when a health issue disproportionately affects that group. Recently, justice in the research context has been extended to the concept of health equity.[8] Essentially, the health research agenda of the national government should take into account health disparities between the different regions of the country and, hence, not ignore the health problems of poorer communities.

These principles have been further specified in seven ethical requirements that provide a systematic and coherent framework for determining whether research is ethical.[9] These requirements include independent review of research, social value, scientific validity, fair subject selection, favorable risk-benefit assessment, informed consent, and respect for enrolled subjects.

CLINICAL RESEARCH LAW IN JORDAN

The key articles in the Jordanian Clinical Research Law will now be discussed to determine the congruency between this law and the seven ethical requirements for research.

Independent Review: The role of an independent review committee (IRC) is to ensure that research undergoes an unbiased assessment. Investigators might have competing interests when they perform clinical trials, that is, advancement of science and the protection of the welfare and rights of subjects: abuses occur when the former dominates the latter. Accordingly, the review of research must be free from political, personal, religious and financial influences. An independent committee comprised of competent individuals, with broad representation of the institution and community, ensures that the welfare and rights of subjects are not overridden by other interests.

The Jordanian Clinical Drug Law requires the formation of an IRC. Specifically, Article 7 states:

> A committee shall be formed within any of the entities stated in Article (4) of this law and be called The Institutional Review Committee, consisting of at least five members from both sexes with enough experience and comprised of medical specialists (e.g. physicians, pharmacists, nurses), a lawyer, and representatives of the local community.

Entities that can conduct clinical trials and, hence, are required to form IRCs include public and private hospitals, universities, academic institutions, research institutions and pharmaceutical manufacturing companies.

The Law states the following obligations of the IRC:

(1) Assure the authenticity of scientific justifications for conducting the study;
(2) Review and approve the entire study protocol;
(3) Assure the expertise of the research team, their ability to conduct the study, and their commitment to adhere to good clinical practices for conducting the drug study;
(4) Assure the voluntary and informed consent of the human subjects;
(5) Report to the Clinical Studies Committee of the Jordanian Food and Drug Administration (JFDA) of any adverse events involving the drug that appear during or after the study.

[8] P. Braveman & S. Gruskin. Defining Equity in Health. *J Epidemiol Community Health* 2003; 57: 254–258.
[9] E.J. Emanuel, D. Wendler & C. Grady. What Makes Clinical Research Ethical? *JAMA* 2003; 283: 2701–2711; H.J. Silverman & F. Lemaire. Ethics and Research in Critical Care. *Intensive Care Med* 2006; 32: 1697–1705.

These roles are instrumental in enhancing the rights and welfare of human subjects.

Social Value: Clinical research must be valuable to society. That is, the research should investigate or test a hypothesis that will advance the health of society by generating new knowledge concerning the functionality of the human system. Without social value, the risks to which research subjects are exposed cannot be justified, thus making such research unethical. The Jordanian Clinical Research Law requires individuals requesting to perform a clinical trial to prepare a protocol that 'must include the scientific justifications for conducting the study'.[10] Also, the Law requires that IRCs must 'assure the authenticity of scientific justifications for conducting the clinical study'.[11] These stipulations ensure that the results of the planned research will hold value for the community. The Clinical Research Law does not address the requirement of social value when international research is performed. International research ethics guidelines require that when investigators and sponsors from the developed world perform research in developing countries, the research must be responsive to the health needs of the country in which the research it is to be carried out.[12]

Scientific Validity: Research must be conducted in a scientifically rigorous methodological manner to ensure that the study will be able to answer the hypothesis of the study. If the study cannot produce interpretable results or valid data, then one cannot justify exposing subjects to the potential risks of the study.

Although the presence of scientific validity is not mentioned specifically in the Clinical Research Law, it does requires the IRC to approve the study protocol (Article 8) and permits the Clinical Studies Committee of the JFDA to form technical subcommittees to help in carrying out its responsibilities (Article 14). The oversight provided by these two committees ensures that the study will have the appropriate methodology to realize the stated research objectives.

Fair Subject Selection: Fairness in subject selection typically concerns the equitable distribution of the benefits and burdens of research, the equitable selection of subjects, and ensuring that vulnerable subjects are not targeted for research participation unless their participation is necessary for the conduct of the research. Essentially, scientific considerations, the setting of the research and particular characteristics of the potential subjects should determine which individuals are to be approached for participation in the study. The Jordanian Clinical Drug Law is silent on the issue of fair subject selection.

Favorable Assessment of Risks and Benefits: Ethical research requires that the risks are reasonable in relation to the benefits anticipated from the research, if any, to the subjects, and to the importance of the knowledge that may reasonably be expected to result from the study. Reaching such an assessment requires that all risks are identified, that all risks are minimized to the extent possible using sound research design, and that risks are reasonable in relation to the potential benefits.

There are several places in the Jordanian Clinical Research Law that address the issue of risk minimization. For example, Article 5 states that clinical studies 'shall not be performed on human beings unless . . . [they have undergone] the medical tests necessary for his/her safety'.[13] The performance of such tests would serve to minimize potential risks for human subjects.

In Article 4, the Law requires that the research team and institutions performing the research have the necessary technical clinical capabilities. Specifically, the article states:

The drug study will be conducted in any of the following institutions by the research team:

(1) Public and private hospitals that have the technical capabilities to provide emergency and intensive care as well as any necessary clinical laboratory and diagnostic tests.
(2) Universities, academic institutions, specialized scientific research institutions, and pharmaceutical companies provided that they have the

[10] Jordan Food and Drug Administration, *op. cit.* note 1, Article 5.
[11] Ibid: Article 8.
[12] Council for International Organizations of Medical Sciences, *op. cit.* note 3, p. 51; National Bioethics Advisory Commission (NBAC). 2001. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries.* 2 Vols. Rockville, MD. NBAC.
[13] Jordan Food and Drug Administration, *op. cit.* note 1, Article 5.

technical capabilities according to clause (1) of this paragraph, and where such technical capabilities are lacking, any of the parties can contract to perform the clinical part of the study in any licensed hospital.[14]

Similarly, Article 9 states that:

The party conducting the drug study is obligated to: assemble a research team from scientifically qualified members who have the scientific experience to conduct the study according to the study's requirements.[15]

Essentially, the Jordanian Law ensures proper protection of human research subjects by mandating those conducting the study to have the necessary expertise. As such, these measures serve to minimize risks that might occur from the procedures in the research.

In addition, other sections of the Law outline the following obligations of those engaged in human subject research:

(1) The principal investigator (PI) is the responsible party for the appropriate conduct of the study.
(2) Assure the presence of a *physician* to supervise the clinical trial and be responsible for the medical care of the participants during the trial.
(3) The party conducting the trial (sponsor) is legally responsible for any injuries that might occur to the human subjects.[16]

In Article 11, the Jordanian Law also states the following general obligations of the parties involved in the conduct of the drug studies:

(1) Adhere to the study protocol as approved by the Clinical Study Committee
(2) Adhere to the Articles in the Helsinki Declaration regarding the conducting of drug studies involving human subjects.[17]

The Clinical Research Law does not contain any statement regarding making an assessment of the proper balance between risks and potential benefits (to research subjects or to the community), which is an important criteria for the approvability of any research study.

Informed Consent: The obtainment of informed consent ensures that research participation reflects the free choice and self-determination of individuals who enrol in research. Article 5 of the Jordanian Clinical Research Law states that 'Clinical studies shall not be performed on human beings unless by his written approval (signed consent form). . . .'[18] Furthermore, as mentioned above, an IRC must assure that such consent is voluntary (Article 8). The Clinical Research Law does not mention important aspects of informed consent. These include the presence of the basic elements of informed consent required for adequate disclosure, assurance of subjects' understanding of information, and acceptable consent procedures that are acceptable within local communities.[19]

Respect For Enrolled Subjects: After informed consent is obtained, researchers must continue to treat subjects with respect and, hence, they have ongoing obligations to research subjects. Examples of activities that respect enrolled subjects include implementation of procedures to maintain the confidentiality of the collected information, permitting subjects the right to withdraw, providing subjects with new information about the study (e.g. newly discovered risks) and monitoring the welfare of the subjects throughout their research participation.[20] For these activities, the Jordanian Law states the requirement of monitoring activities. Specifically, it requires the IRC to coordinate with the Clinical Studies Committee of the JFDA on the monitoring of adverse events related to the study drug. Furthermore, the Clinical Studies Committee is also charged with the responsibility to assure that the parties authorized to conduct clinical studies are complying with the principles of good clinical practice and good laboratory practice.

The Jordanian Law also requires respect for enrolled subjects when it states in Article 5.2 that the party conducting the study is obligated to 'Establish

[14] Jordan Food and Drug Administration, *op. cit.* note 1, Article 4.
[15] Ibid: Article 9.
[16] Ibid: Article 9.
[17] Ibid: Article 11.
[18] Ibid: Article 5.
[19] A. Z. Bhutta. Beyond Informed Consent. *Bull World Health Organ* 2004; 82: 771–777.
[20] Emanuel et al., *op. cit.* note 9, p. 2707.

an insurance agreement with an established insurance company in the Kingdom to cover any damages that might result from the trial, especially injuries to human subjects.'[21] Finally, the Jordanian Law incorporates a sense of retributive justice (a legitimate moral response to a crime is proportionate punishment) by having a section devoted to 'Fines and Punishments' in Article 17. For example, in section (a), it states the following:

> Any person who conducts clinical studies, supervises or performs the same without observing the terms and requirements specified by the law shall be punished either by one to three years of imprisonment or by payment of a fine not less than five thousand Jordanian Dinars and not more than twenty thousand Dinars, or by both penalties.[22]

Slightly lower fines and terms of imprisonment are specified for others involved in such a research study.

DISCUSSION

The conduct of clinical drug trials is important in advancing the health of society. However, such trials must involve human beings, and therefore there needs to be in place a coordinated and comprehensive human subject protection program to protect the rights and welfare of human subjects.

To help ensure the existence of a human subject protection program, the presence of national regulations is necessary, although not sufficient. The Jordanian Clinical Research Law of 2001 incorporates many of the seven ethical requirements for the conduct of research, resulting in a contemporary and coherent law.[23] Important aspects of this Law include the requirement of an IRC in each institution. Several such committees exist in Jordan; these include those in the Ministry of Health, King Hussein Cancer Center, Jordan University, the Royal Medical Services, and the Jordan University of Science and Technology. All of these review committees are working under the supervision of the JFDA Clinical Studies Committee. The formation of these IRCs is timely, as Jordan has witnessed an increase in the numbers of clinical trials. For example, international research-based companies have carried out clinical trials in partnership with the King Hussein Medical Center and hospitals in Amman. In 2004, multinational companies conducted 17 clinical trials, hastening Jordanian access to cutting-edge therapies for such conditions as cancer, diabetes and schizophrenia.[24] Recently, accreditation standards for hospitals were issued mandating the review of research by ethics committees.[25]

The Jordanian Clinical Research Law of 2001 also stipulates the requirement of informed consent from each research subject. There are also several sections in the Law that address the requirement to minimize risks, including the performance of medical tests to ensure subject safety and the requirement that members of the research team have the technical expertise to perform the research and to provide required emergency and intensive care to the human subjects.

Unique aspects of the Clinical Research Law include the requirement that parties conducting any study should have insurance to cover any damages that might result, especially injuries to the human subjects. This is a form of civil or compensatory justice that is stipulated in recent research ethics guidelines.[26] For example, the Council for International Organizations of Medical Sciences (CIOMS) guidelines state that human subjects are entitled to compensation for research injury and that they should be told which organizations will be responsible for providing compensation.[27]

The Jordanian Clinical Research Law also mentions fines and punishments concerning certain violations that might occur during the conduct of drug

[21] Jordan Food and Drug Administration, *op. cit.* note 1, Article 5.2.
[22] Ibid: Article 17(a).
[23] Emanuel et al., *op. cit.* note 9, pp. 2701–2711.
[24] M.P. Ryan & J. Shanebrook. 2004. *Establishing Globally Competitive Pharmaceutical and Bio-Medical Technology Industries in Jordan: Assessment of Business Strategies and the Enabling Environment.* Online: International Intellectual Property Institute. Available at: http://www.iipi.org/reports/Jordan_Report.pdf [Accessed 11 August 2007].
[25] Guidelines for Hospitals to Prepare to Meet Hospital Accreditation Standards. Unpublished. 2006. Jordan.
[26] Commission Directive 2005/28/EC of 8 April 2005, *op. cit.* note 3, p. 13–19; Council for International Organizations of Medical Sciences, *op. cit.* note 3, p. 79.
[27] Ibid: 79.

studies. The establishment of fines and punishments is one way to ensure compliance to a clinical research law, because depending on the ethics of those involved in research might not be sufficient. Imposition of fines and punishments are notably lacking in other major research ethics regulations.

Despite these virtues of the Jordanian Clinical Research Law, several important issues are not addressed. For example, the Law does not mention specifically that a criterion for the conduct of research is the presence of a reasonable balance between the risks and potential benefits. While there are several aforementioned sections of the Law dealing with risk minimization, the principle of beneficence requires that investigators and members of research ethics committees carry out an analysis of the risks and benefits, to ensure that anticipated risks are reasonable in relation to the potential direct benefits to the subjects, if any, and the potential benefits to society.

The Law also fails to mention important aspects of the process of informed consent. Indeed, informed consent in the developing world context requires special considerations due to the extent of the poverty, chronic illnesses and illiteracy that exists in these countries. Furthermore, Western bioethics notions of informed consent might not be transferable to the different cultural contexts existing in many developing countries.[28] Interestingly, the Jordanian Law requires signed informed consent, whereas appropriate alternative procedures for documenting informed consent might be more culturally sensitive in local communities.[29] Other than the monitoring of adverse events, the Jordanian Law is silent on other activities that aim to treat enrolled subjects with respect. Emanuel and colleagues cite the following such activities:

(1) assurance of the confidentiality of the information obtained from the subjects;
(2) permitting subjects to withdraw at anytime during the study; and
(3) provision of any information to subjects that that might affect their decision to continue in the study.[30]

Although the Clinical Research Law includes a sense of compensatory and retributive justice, it fails to mention the issue of distributive justice in regards to the ethical requirement of fair subject selection. Additionally, the Law does not mention children as a separate vulnerable subgroup. Studies involving children require careful attention due to children's status as a vulnerable population, based on their incapability to provide voluntary informed consent. Other research ethics regulations require that parental permission coupled with child assent (when applicable) must be obtained in order for children to be enrolled in research.

Children have been categorized into subgroups according to their age. It has been widely agreed that children under the age of seven are most likely not competent in understanding aspects of a research study and therefore are unable to provide assent or consent. Children between the ages of 7 and 14 can have awareness of the consequences of their decisions and therefore their assent should be required. Assent represents the affirmative agreement to participate in an activity. However, since children of this age do not fully understand all aspects of the research study, written consent from their legal guardian is still required. Children above the age of 14 should be considered able to understand the important aspects of a research study and therefore be considered capable of providing assent and consent, although parental permission should also be required.

A final ethical requirement not mentioned in the Clinical Research Law, as well as other research ethics guidelines, is that of professional integrity. Even with the prospect of fines and punishments, regulatory mechanisms to ensure the ethical conduct of clinical research will be limited.[31] Accordingly, professional integrity should be viewed as a necessary requirement for ethical research. If researchers conducting the study have integrity and honesty, then one can trust them to involve human

[28] P.A. Marshall. Informed Consent in International Health Research. *J Empir Res Hum Res Ethics* 2006; 1: 25–42.

[29] E. Emanuel et al. What Makes Clinical Research in Developing Countries Ethical? The Benchmarks of Ethical Research. *Am J Infect Dis* 2004; 189: 930–937.

[30] Emanuel et al., *op. cit.* note 9, pp. 2701–2711.

[31] F.G. Miller, D.L. Rosenstein & E.G. DeRenzo. Professional Integrity in Clinical Research. *JAMA* 1998; 280: 1449–1454.

subjects and subject them to the potential risks of a research study. Those who lack such professional values tend to violate all humanitarian values and thus should not be trusted within the domains of advancement, cure and science.

CONCLUSION

Conducting clinical trials involving human subjects is an activity that, on one hand, advances the well-being of society, but, on the other, might jeopardize the rights and welfare of subjects. It is this potential conflict that forms the basis of the need to establish mandates that govern the ethical conduct of research.

This paper has discussed important aspects in the Jordanian Clinical Research Law and has uncovered some deficiencies that prevent the Law from being complete. The Clinical Research Law does not focus on important aspects of the balancing of risks and benefits, confidentiality protections, permission to withdraw from the research, and issues involving distributive justice, including fairness in the selection of research subjects. It also fails to consider children as a separate vulnerable subgroup on their own. Finally, the Law does not refer to professional integrity as a key aspect to be considered in the ethical conduct of clinical trials on human subjects. We therefore suggest that there be amendments to the Law, or the formulation of guidelines to address these omissions. Finally, anecdotal reports reveal that general knowledge of the Law is lacking in Jordan and, therefore, a national awareness campaign is needed to ensure that investigators and potential research participants are aware of the Law, and that individuals know their rights as research participants. Correcting these deficiencies will further enhance the protection of the rights and welfare of those who volunteer in research studies in the Kingdom of Jordan.