Addendum: Saudi Arabia Law

Governing Research Involving Human Participants

General Comments

Standards and Elements listed below address areas where policies and procedures must address specific requirements in:

- Implementing Regulations of the Law of Ethics of Research on Living Creatures, Royal Decree No. M/59, Dated 14/9/1431H – 24/8/2010
- Informed Consent Requirements, National Commission of Bioethics (NCBE)
- Local Committee of Research Ethics Requirements, National Commission of Bioethics (NCBE)
- Guidelines for Investigational New Drugs, Version 1.1, Saudi Food and Drug Authority
- Medical Device Interim Regulations, Decree number 1-8-1429, Saudi Food and Drug Authority

Domain I: Organization

Standard I-7: The Organization has and follows written policies and procedures to ensure that the use of any investigational or unlicensed test article complies with all applicable legal and regulatory requirements.

Element I.7.A. When research involves investigational or unlicensed test articles, the Organization confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.	The Local Committee of Research Ethics ("Local Committee") determines that requirements for investigational use of drugs and devices meet SFDA regulatory requirements.
	
	When research involves the use of a drug other than the use of a marketed drug in the course of medical practice, prior authorization is required from the Saudi Food and Drug Authority (SFDA):
	
	• The SFDA has approved an Investigation New Drug application; or
	• The protocol meets one of the SFDA exemptions from the requirement to have an IND.
	  ○ Exemption 1
	  ▪ The study is not intended to support an approval of a new indication or a significant change in the product labeling.
	  ▪ The study is not intended to support a significant change in the advertising for the product.
	  ▪ The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product
	  ▪ The study is conducted in compliance with Local Committee and informed consent regulations
	  ▪ The study is conducted in compliance with promotion and charging for investigational drugs regulations
	  ○ Exemption 2
	  ▪ A clinical investigation is solely for an *in vitro* diagnostic biological product.
	  ○ Exemption 3
	  ▪ A clinical investigation involving use of a placebo is exempt from the requirements of this part if the investigation does not otherwise require submission of an IND.
	
	Policies and procedures describe the process to ensure that research involving medical devices shall comply with the relevant regulatory requirements applicable in one or more of the jurisdictions of Australia,

	Canada, Japan, the USA and the EU/EFTA, and additionally with provisions specific to the SFDA concerning labelling and conditions of supply or use. Policies and procedures specify which regulations the Organization is following for research involving investigational devices. If the Organization meets the SFDA requirements by following US FDA regulations for research to determine the safety or effectiveness of a device, policies specify: • The device has authorization to conduct research issued by the SFDA, or • The device fulfills the requirements for an abbreviated IDE. o The device is not a banned device. o The sponsor labels the device in accordance with SFDA requirements. o The sponsor obtains Local Committee approval of the investigation after presenting the reviewing Local Committee with a brief explanation of why the device is not a significant risk device, and maintains such approval. o The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care. o The sponsor complies with the SFDA requirements for monitoring investigations; o The sponsor maintains the records and makes reports required by the SFDA; o The sponsor ensures that participating investigators maintain the records required by the SFDA and reports to the sponsor and SFDA; and o The sponsor does not advertise or sell investigational devices prior to approval from the SFDA. • The device fulfills one of the IDE exemption categories: o A diagnostic device, if the testing: ▪ Is noninvasive. ▪ Does not require an invasive sampling procedure that presents significant risk. ▪ Does not by design or intention introduce energy into a participant. ▪ Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. o A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put participants at risk. o A custom device, such as a prosthetic leg, unless the device is being used to determine safety or effectiveness for commercial distribution. • The Local Committee determines whether or not the device is a

	significant risk device.
Domain II: Institutional Review Board or Ethics Committee	
Standard II-1: The structure and composition of the IRB or EC are appropriate to the amount and nature of the research reviewed and in accordance with requirements of applicable laws, regulations, codes, and guidance.	
Element II.1.A. The IRB or EC membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB or EC roster. The IRB or EC has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB or EC regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants.	Policies and procedures describe the composition of the Local Committee. Policies and procedures specify that: • Each Local Committee has at least five members with varying backgrounds to promote complete and adequate review of research commonly conducted by the organization. • No Local Committee has members who are all males or all females. • No Local Committee has members who represent a single profession. • Each Local Committee has at least one member whose primary concerns are in scientific areas. • Each Local Committee has at least one member whose primary concerns are in nonscientific areas. • Each Local Committee has at least one member who is not otherwise affiliated with the organization and who is not part of the immediate family of a person who is affiliated with the organization. • Each Local Committee has at least one member who represents the perspective of research participants. • Each Local Committee has at least one member with expertise in biomedical ethics. • Each Local Committee has at least one member with expertise in research design and statistical analysis. • Each Local Committee has at least one member who is adequately familiar with the customs, values, and traditions of Saudi Society. • When the Local Committee reviews research involving children or adults unable to consent, the Local Committee must have at least two members with expertise in the nature of psychological and systemic diseases which lead to incapacitation. Policies and procedures specify that the Chair or deputy shall be of Saudi nationality with experience in the fields of biological research and biomedical ethics.
Standard II-2: The IRB or EC systematically evaluates each research protocol or plan to ensure the protection of participants.	
Element II.2.C: The IRB or EC has and follows written policies and procedures for conducting meetings by the convened IRB or EC.	Policies and procedures indicate that at Local Committee meetings: • At least two-thirds of the members have to be present. • At least one member whose primary concerns are in non-scientific areas has to be present. • For research to be approved it has to receive the approval of a majority of members present at the meeting. • When the Local Committee reviews research involving children, pregnant women, or prisoners, at least two members with expertise in these populations are present.
Element II.2.D. The IRB or EC has and follows written policies and procedures to	Policies and procedures specify that: • Continuing review of research is required every three months for

conduct reviews by the convened IRB or EC.
1. Element II.2.D.1. – Initial review
2. Element II.2.D.2. – Continuing review
3. Element II.2.D.3. – Review of proposed modifications to previously approved research
	clinical research, and six months for non-clinical research.
	• Continuing review of research is not required if the Local Committee has determined and documented that:
	  ○ The study does not pose more than minimal risk
	  ○ There are no other risks from the research
	• Continuing review of research is not required if:
	  ○ The study is open only for long-term follow-up of participants, and no other risks have been identified
	  ○ The study is open and the remaining activities are limited to data analysis

Element II.2.E. The IRB or EC has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used. **Element II.2.E.1. – Initial review** **Element II.2.E.2. – Continuing review** **Element II.2.E.3. – Review of proposed modifications to previously approved research**	Policies and procedures specify that: Continuing review of research is not required if the convened Local Committee has determined and documented that: • The study does not pose more than minimal risk. • There are no other risks from the research. Continuing review of research is not required if: • The study is open only for long-term follow-up of participants, and no other risks have been identified. • The study is open and the remaining activities are limited to data analysis. The chair of the Local Committee or other member of the IRB is authorized to approve modifications to research, except the following: • Addition of new medication. • Addition of new equipment. • Addition of invasive of interventional procedure. • Increase or decrease of medication dose which may lead to increased risks. • Addition of volunteers as a demographic study. • Extending time period for participating subjects for other purpose than observation. • Changes to the inclusion or exclusion criteria which may involve an increase in risk. • If new potential hazards are identified • Collection of additional blood specimens exceeding 10ml, provided that weight of adult or non-pregnant woman is not less than 50kg. • Changes to research involving children. The reviewer is provided and reviews the investigator's current curriculum vitae or other documentation evidencing qualifications.
Element II.2.F. The IRB or EC has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate.	Policies and procedures have reportable events communicated to the Local Committee verbally or by phone within 48 hours from the time the incident occurred, and a written report submitted within five days from the time the incident occurred.
Standard II-3: The IRB or EC approves each research protocol or plan according to	

criteria based on applicable laws, regulations, codes, and guidance.	
Element II.3.F. The IRB or EC has and follows written policies and procedures to evaluate the consent process and to require that the researcher appropriately document the consent process.	When research involves tissue samples previously extracted for another research purpose or a purely medical purpose: • If it is possible to link the samples to the person, consent of the person from whom the samples have been collected is required prior to conducting research. • If the samples do not contain identifiers and it is not possible to identify the person from whom the samples have been collected, then permission of the Local Committee is sufficient.
Element II.3.G. The IRB or EC has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation.	Requirements to obtain consent may be waived under the following: • The research involves no more than minimal risk to the participants. • The waiver or alteration will not adversely affect the rights and welfare of the participants. • The research cannot practicably be carried out without the waiver or alteration. • When appropriate, the participants will be provided with additional pertinent information after participation.
Standard II-4: The IRB or EC provides additional protections for individuals who are vulnerable to coercion or undue influence and participate in research.	

Element II.4.A. The IRB or EC has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance.	**Pregnant Women or Fetuses**
	In order to approve research involving pregnant women, the Local Committee must determine and document:
	• Where scientifically appropriate, studies, including studies on pregnant animals, and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses, provided the results of such research are published in internationally recognized scientific journals in accordance with provisions of law and regulations.
	• The risk to the pregnant women and fetus are not great greater than minimal
	  ○ Research that poses risks to the pregnant woman or fetus that are greater than minimal may not be approved
	• No inducements, monetary or otherwise, will be offered to terminate a pregnancy.
	• Individuals engaged in the research have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy.
	• Individuals engaged in the research have no part in determining the viability of a neonate.
	• Permission of both parents is required
	In order to approve research involving fetuses, the Local Committee must determine and document:
	• Research involving fetuses may occur only when there is a direct benefit and the risk to the fetus is not greater than minimal.
	• Research is limited to studies designed to:
	  ○ Find a treatment for reproductive problems, in which case the research shall be conducted in an institution approved for treatment of such problems.

- Conduct a new experiment expected to benefit human fetuses;
- Acquire new knowledge about the condition of fetuses if it is not expected to achieve a direct benefit.

- The research shall not harm the life of the fetus.
- The research project shall aim to provide health requirements for the fetus and to acquire information that cannot otherwise be obtained;
- No research may be conducted on a living fetus unless it is nearly certain that its life is threatened or that the level of risk the fetus may face in case it remains in the uterus could be lessened, provided there is no safer means to achieve the same.
- Permission of both parents is required

Additional Protections for Prisoners

The Local Committee determines whether the criteria for approval of research are met when research involves prisoners. The Local Committee determines and documents that:

- The research represents one of the following categories:
  - Study of the possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
  - Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects.
  - Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is much more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults).
  - Research on practices, both innovative and accepted that has the intent and reasonable probability of improving the health or well-being of the subject.

Policies and procedures should describe equivalent protections for research involving prisoners, which might include having the Local Committee review research to determine:

- Any possible advantages accruing to the prisoner through his or her participation in the research, when compared to the general living conditions, medical care, quality of food, amenities and opportunity for earnings in the prison, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages in the limited choice environment of the prison is impaired.
- The risks involved in the research are commensurate with risks that would be accepted by non-prisoner volunteers.
- Procedures for the selection of participants within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners.

- Unless the principal investigator provides justification in writing for following some other procedures, control participants are selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project.
- Adequate assurance exists that parole boards will not take into account a prisoner's participation in the research in making decisions regarding parole.
- When there is a need for follow-up examination or care of participants after the end of their participation, adequate provisions are made for such examination or care, taking into account the varying lengths of individual prisoners' sentences, and for informing participants of this fact.

Additional Protections for Children, Incompetent, and Mentally Disabled Persons

In order to approve research involving children, incompetent, or mentally disabled persons the Local Committee must determine and document:

- It is not possible to conduct the research on a competent person.
- Participating in the research is in the best interest of the child, incompetent, or mentally disabled person, provided risk is not greater than minimal.
- The research protocol includes clear and appropriate measures to minimize potential risk as much as possible.
- Evaluation of potential risk and expected benefit from the research shall indicate type, nature, degree and possibility of risk as well as the direct benefit for the child, incompetent or mentally disabled person subject of the research and for similar persons.
- The research shall be conducted in a school, camp, hospital, or institution where the majority of occupants are incompetent or disabled, provided the research subject belongs to this category.

If the Local Committee determines the research is greater than minimal risk but holds out the prospect of direct benefit for the child, incompetent or mentally disabled person but that its risk, it may grant its approval provided it determines and documents that:

- The potential risk shall be within acceptable levels in accordance with medical standards, if compared with expected benefits.
- The relationship between the anticipated benefit shall exceed that of other methods available outside the scope of the research.
- The research shall lead to a better understanding of an important problem that affects the minor, incompetent or mentally disabled person or his interest, help reduce such problem, or prevent some of its negative effects.
- Permission must be obtained from either parent or from the legal guardian.

If the Local Ethics Committee determines the research is not greater than minimal risk, but holds out the prospect of direct benefits, it may grant its approval provided it determines and documents:

	• If precautionary measures taken for his protection are adequate and acceptable. • If there are sufficient reasons that make it possible to obtain significant • information through the research for understanding the case under study • If the prospective participant had given consent prior to the disability, or a parent or legally authorized representative has granted permission. Whenever research involves children, incompetent, or mentally disabled persons, the Local Ethics may require the appointment of an attorney with appropriate qualifications and experience to act in, and agrees to act in, the best interests of the child, incompetent, or mentally disabled person for the duration of the child's participation in the research. • The advocate is not associated in any way (except in the role as advocate or member of the Local Committee) with the research, the investigators, or the guardian. **Additional Protections when the Research involves Genetic Information or Genetic Treatment** Policies and procedures describe additional protections when research involves genetic information and genetic treatment, including the requirement to obtain permission from the National Committee, in addition to the Local Committee, prior to commencing research.
Domain III: Researcher and Research Staff	
Standard III-1: In addition to following applicable laws and regulations, Researchers and Research Staff adhere to ethical principles and standards appropriate for their discipline. In designing and conducting research studies, Researchers and Research Staff have the protection of the rights and welfare of research participants as a primary concern.	
Element III.1.C. Researchers employ sound study design in accordance with the standards of their discipline. Researchers design studies in a manner that minimizes risks to participants.	Policies describe the following researcher responsibilities: • During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial. • The researcher follows the clinical trial's randomization procedures, if any, and ensures that the code is broken only in accordance with the protocol. If the clinical trial is blinded, the researcher promptly documents and explains to the Sponsor any premature unblinding. • A qualified physician (or dentist, when appropriate), who is a researcher or a co- researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions. • Researchers inform participants when medical care is needed for other illnesses of which the researchers become aware.
Standard III-2: Researchers and Research Staff meet requirements for conducting research with participants and comply with all applicable laws, regulations, codes, and guidance; the organization's policies and procedures for protecting research participants; and the IRB's or EC's determinations.	
Element III.2.A. Researchers and Research Staff are	Policies and procedures describe the qualifications and experience of the

qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the organization's policies and procedures regarding the protection of research participants.	researcher: • Policies and procedures have researchers register with the National Committee of Biological and Medical Ethics by completing the medical ethics test available at: http://www.kacst.edu.sa/bioethics/ • The researcher provides evidence of his or her qualifications through up-to-date curriculum vitae or other relevant documentation requested by the sponsor, the IRB, or the regulatory authority. • The researcher is familiar with the appropriate use of the investigational product, as described in the protocol, in the current investigator brochure, in the product information, and in other information sources provided by the sponsor. • A qualified physician (or dentist, when appropriate), who is a researcher or a co-researcher for the clinical trial, is responsible for all clinical trial-related medical (or dental) decisions. • During and following a participant's participation in a clinical trial, the researcher ensures that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the clinical trial. • The researcher ensures the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor. • The researcher permits monitoring and auditing by the sponsor and inspection by the appropriate regulatory authority. • The researcher maintains the clinical trial documents as specified in Essential Documents for the Conduct of a Clinical Trial and as required by the applicable regulatory requirements. • Essential documents are retained until at least two years after the last approval of a marketing application ion and until there are no pending or contemplated marketing applications or at least two years have elapsed since the formal discontinuation of clinical development of the investigational product.