2018

The Investigator's Handbook to Human Subject Research

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List of Appendices

This manual is subject for annual review and update. The HRPP office will circulate updates via emails and ensure that the latest copies are available at KHCC's Portal. Request for updated copies shall be emailed to HRPP@khcc.jo .

Foreword

KHCC's research activities rely on sound scientific and ethical research practices. Since 2005 and over a span of ten years, different organizational components were introduced to assist, facilitate and regulate research activities within the center. The institution's primary ethical and professional obligation is to protect human subjects that volunteer themselves to research and to ensure that principles of research integrity and responsible conduct are withheld in each and every research project carried at the center.

As we anticipate more staff to initiate or be part of human research activities at the center, this handbook was designed to guide investigators and their research teams through the lifecycle of research at KHCC. It provides help on the fundamental processes that affect the work of the investigator. It will not explain every step involved in the research administration at KHCC but should provide concise information on the policies, procedures, regulations and resources specific to the conduct of human research at KHCC.

With this handbook, we aim to help you comply with the research regulations, local Laws, KHCC policies, requirements and determination of IRB, as well as, KHCC's Human Research Protection Program requirements.

What is KHCC's Human Research Protection Program?

The Human Research Protection Program (HRPP) at KHCC is a comprehensive system to protect the rights, dignity, wellbeing and privacy of human subjects in all KHCC research and assure high quality research data generated at the center.

The program recognizes the following entities as core to support the program implementation: the HRPP Steering Committee, the Institutional Review Board (IRB), the Research Council (RC), Office of Scientific Affairs and Research (OSAR), the pharmacy department's investigational drug service, investigators and the research teams.

What is Human Subject Research?

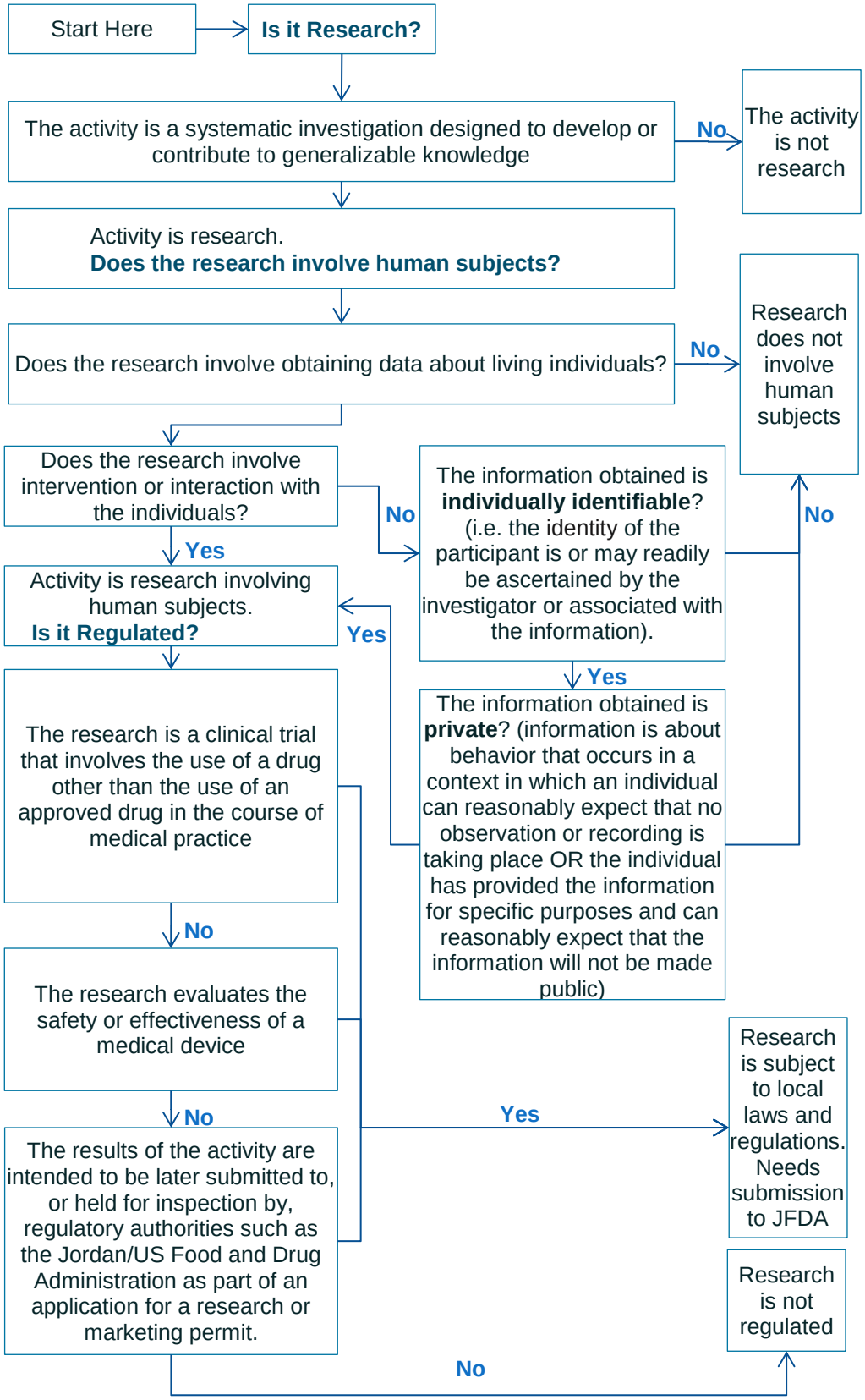
You are involved in human subject research when you

1) Intervene or interact with living persons for research purposes, or

2) Obtain individually identifiable private information about a person for research purposes.

You, as an investigator, may not decide whether an activity is human subject research. You will need to complete the "Human Subject Determination" form and submit it to the HRPP office to obtain their ruling of whether or not your research is human subject research.

The following chart is provided as a guidance to help you understand how the HRPP office makes the determination.


Start Here
Is it Research?
The activity is a systematic investigation designed to develop or contribute to generalizable knowledge
No
The activity is not research
Activity is research.
Does the research involve human subjects?
Does the research involve obtaining data about living individuals?
No
Research does not involve human subjects
Does the research involve intervention or interaction with the individuals?
No
The information obtained is individually identifiable? (i.e. the identity of the participant is or may readily be ascertained by the investigator or associated with the information).
No
Yes
Activity is research involving human subjects.
Is it Regulated?
Yes
Yes
The information obtained is private? (information is about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place OR the individual has provided the information for specific purposes and can reasonably expect that the information will not be made public)
The research is a clinical trial that involves the use of a drug other than the use of an approved drug in the course of medical practice
No
The research evaluates the safety or effectiveness of a medical device
No
Yes
Research is subject to local laws and regulations. Needs submission to JFDA
The results of the activity are intended to be later submitted to, or held for inspection by, regulatory authorities such as the Jordan/US Food and Drug Administration as part of an application for a research or marketing permit.
Research is not regulated
No

What is an IRB?

The Institutional Review Board (IRB) at King Hussein Cancer Center (KHCC) is a standing independent committee charged with the responsibility to protect the rights, safety, and well-being of human subjects participating in research. It is constituted of medical, scientific, and nonscientific members.

The KHCC's IRB will review all human subject research at KHCC and are authorized to approve, disapprove, suspend or terminate the approval of human subject research.

Depending on the risk involved and the categorization of your research, the IRB Chair may exempt your research from IRB review, expedite the review or require it to be discussed at a convened meeting (Full-Board Review). Additional information on the IRB review process can be found in the HRPP manual.

The IRB will require that your provide updates on your research for continuing review, annually or more frequently.

No individual or entity at any level can approve research that has not been reviewed and approved by the IRB.

What Requirements Apply to Clinical Research?

When you work on human subject research at KHCC you will need to abide to the ethical principles described in the Declaration of Helsinki (1964) and its amendments.

Furthermore, you will need to understand and abide to the requirements of the human subject protection program described in its manual.

What Regulations Apply to Clinical Trials?

If you are working on a clinical trial involving investigationa products (biologics, drugs or devices) at KHCC you will need to comply with:

1. Jordan's law on clinical trials: law 2 for year 2011 and applicable directives.
2. International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use: Guidance on Good Clinical Practice (ICH E6).

Can I be a Principal Investigator?

If you are a KHCC's employee, with a full time or part time appointment, having appropriate scientific, experiential and technical training in the area of research, then you qualify to act as a Principal Investigator (PI) with the following considerations:

1. If you are a resident you will be limited to do research that is deemed to be no more than minimal risk and under supervision
2. If the research is a clinical trial involving the use of investigational medicinal products, only full-time consultants or staff holding a PHD in pharmacy can serve as PI (JFDA mandate).

The IRB will approve exceptions on a case-by-case basis and the PI designation will be limited to the proposed research under consideration.

If you are a non-KHCC researcher or a postgraduate student (MSc/PHD), you must work under the auspices of a KHCC's Site Principal Investigator. The site PI is a member of KHCC staff required to review and approve supervising the research. The

site PI is responsible for the ethical performance of the research at KHCC, helping to ensure that the research procedures are complying with the policies and procedures for the protection of human subjects at KHCC. The site PI is expected to monitor the progress of the research, assist in resolving problems, assure prompt reporting of unanticipated problems, and available to the IRB should questions or issues develop. Seek assistance in matching you to KHCC site PI from the HRPP office.

If any of the following apply to you, you will not be allowed to assume the role of PI for human subject research:

1. Undergraduate students
2. Volunteers
3. Anyone deemed insufficiently qualified by the IRB or KHCC
4. Anyone restricted from serving as PI by KHCC or the IRB
5. Anyone banned or prohibited from serving as PI by KHCC, the IRB or regulatory.

What are my Responsibilities as a Principal Investigator?

As a PI you are responsible to:

1. Provide scientific and technical leadership and administrative management of research.
2. Follow the HRPP policies and procedures to protect the rights, safety and welfare of study participants.
3. Adhere to the protocol, policies and procedures of research at KHCC and regulatory requirements.
4. Obtain the appropriate approvals on the research from the RC, the IRB and regulatory.
5. Supervise the conduct of research.
6. Assure the compliance of your research team to the policies and procedures of research at KHCC.

7. Report on the progress of the research to the appropriate bodies at KHCC.

You are also responsible to ensure that you have adequate resources to carry out the research safely. This includes but is not limited to, sufficient investigator time, having appropriately qualified research team members, equipment and space.

You are responsible to ensure that your research team is qualified to perform the procedures assigned to them during the study. That your team has taken the required training for the study.

When conducting a clinical trial, as a PI you will adhere to the requirements of the ICH E6, "Guideline on Good Clinical Practice". You should understand the responsibilities described in GCP E6. The guidance can be found on the portal.

Who can be a co-investigator?

A co-investigator is a designated member of the research team that can perform critical tasks in the study and can make critical decision in the study under the PI's supervision. The co-investigator can make decisions on behalf of the PI during his or her absence.

Can I Delegate my Responsibilities?

As the PI, you need to maintain oversight over your research study and research staff and trainees. When delegating responsibilities you need to match tasks and functions to the appropriate research staff based on their relevant qualifications.

In clinical trials, you should maintain a list of the appropriately qualified persons ("delegation list") to whom you have delegated significant clinical trial-related duties indicating roles and the duties assigned before the initiation of the trial. The delegation

list must be updated with the changes in the research team and/or the respective assignments as they become available.

The following should be delegated to a qualified physician:

1. Medical decisions related to the subject's overall treatment for his or her disease.

2. Determining of causality between an adverse event and a protocol therapy or intervention.

The overall responsibility and accountability for the trial cannot be delegated.

What Training is required to Conduct Human Subject Research?

As principal investigator, you are responsible to ensure that all individuals involved in the research are properly oriented and educated with respect to regulatory requirements for human subject protection, the study protocol, as well as, policies and procedures related to research activities.

The IRB require that you, the PI, and your research team members, who are involved in the design, conduct, and reporting of human subject research, complete "Protecting Human Research Participants", an online Course provided by the National Institute of Health (NIH). This course is accessible at https://phrp.nihtraining.com/users/login.php. The Certificate is considered to be valid for a period of three-years. You will need to redo the training once that period elapses.

Other training sources covering human subject protection are accepted.

When to take a course in Good Clinical Practice?

If the research project is a clinical trial involving the investigation of drugs or devices, the IRB will require that you and your research team complete a course in Good Clinical Practice (GCP). The course is provided online by the National Institute of Health (NIH) at https://gcp.nihtraining.com/. Other training sources are accepted. The GCP certificate is considered to be valid for a period of three-years. So, if the trial is still ongoing by the time your training expires, you will need to redo the GCP training.

What Do I Need To Write a Research Protocol?

A protocol guides the execution of the study and helps streamline the activities of the study team to achieve the desired outcome. As a PI you should establish and coordinate the protocol development team. The team should be selected to provide technical and scientific input for the study design and procedures. Ideally, the team should include a biostatistician and a data manager.

A research study can be described using the following main sections:

- Introduction and background
- Aim and objectives
- Rationale
- Risk and benefit assessments
- Materials and Method
- Subject Selection and Recruitment
- Data Management
- Statistical Analysis

For clinical trials a more comprehensive protocol will be required. Templates are available to help you develop you research study protocol. They are available at the KHCC portal at Portal Link. The protocol document should be version controlled.

How Do I Create a Consent Document?

Individuals invited to participate in research need to be properly informed and their consent to participation obtained. The standard method to present the research and obtain participant consent is by preparing an "Informed Consent" document. You are encouraged to use the templates for consent documents available at Portal Link. Make sure you satisfy **the elements for informed consent** described in the HRPP manual.

The written informed consent to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB's approval in advance of use.

How Do I Prepare Material to Assist in Recruiting Participants?

The following information should assist you in preparing appropriate material to assist in recruiting subjects you're your research.

Recruitment material must include:

1. The name and address of the principal investigator.
2. Statement that the project is research and a description of its purpose or the condition under study. If it is a clinical trial it should include the use of an investigational drug or device.

3. In summary form, the criteria that will be used to determine eligibility for the study. Make it simple.
4. A straightforward unexaggerated description of potential benefits to study participation, if any.
5. A brief list of procedures involved.
6. The time or other commitment required of the participants (number of visits, duration of study, etc.).
7. Any compensation or reimbursement without emphasis.
8. It may state that subjects will be paid but should not use bold or enlarged print or other means to emphasize payment or the amount to be paid (No reference to payment should be made in the header of the material).
9. The location where the research will be conducted and the contact (name and phone/address) for further information.

In preparing the material, you must not:

1. State or imply a certainty of favorable outcome or other benefits (e.g. Claims of safety, effectiveness, equivalence or superiority in reference to the drug, device or procedure under investigation) beyond what is outlined in the consent document and the protocol.
2. Use terms, such as "new treatment," "new medication," or "new drug," without explaining that the test article is investigational.
3. Make claims, either explicitly or implicitly, about the drug, biologic, or device under investigation that are inconsistent with the regulatory approved product labeling.
4. Use of the term "free" in reference to treatment or procedures when the intent is only to say participants will not be charged for taking part in the investigation.
5. Use of bold or enlarged print or other means to emphasize payment or the amount to be paid.

6. Use of exculpatory language.
7. Use a statement or an implication of IRB or other institutional endorsement of the study.
8. Use any inappropriate pictures or images that would be inconsistent with IRB policies on equitable subject recruitment.
9. Allow compensation for participation in a trial offered by a sponsor to include a coupon good for a discount on the purchase price of the product once it has been approved for marketing.

You may not use the recruitment material without it being first reviewed and approved by the IRB.

Where Can I Get Funds for my Research?

Financial support for your research project may be obtained internally at KHCC and externally from funding agencies. The KHCC's Intramural Grants Program is available in two cycles, spring and fall. Rolling grants are run through-out the year. For assistance contact the Center for Grants and Contracts, Office of Scientific Affairs and Research.

How Do I Prepare the Research Budget?

For every research project you need to determine the underlying costs and how you plan to cover such costs (e.g. grant, sponsorships). Costs are analyzed under the headings direct and indirect costs:

- Direct Costs are those costs that are absolutely necessary, or directly involved, in the conduct of the research e.g. costs for procedures and tests.

- Indirect Costs are the costs of supporting the research and are often associated with administrative processes.

Review the protocol and identify all study related processes and procedures. It is important that all procedures are properly selected to avoid the need for corrections later. List each process and procedure and describe its related cost. List any administrative processes and their costs. Compute the total budget by summing the direct and indirect costs.

Contact the finance for an up-to-date price list for hospital procedures included in the protocol. Contact the Grants and Contracts to get help in budgeting. The Clinical Trials Unit can help with budgeting clinical trials.

How Do I Submit My Research for approval?

Complete the research application form. You will find it available at KHCC portal or request a copy form the HRPP office.

Make sure that you have listed all your research team members and specify their roles. Include the following with your application:

- Research financial disclosure form completed by everyone on the research team
- Resume for each person listed in the application
- Proof of completing Protecting Human Research Participants training and GCP training when applicable.
- Up-to-date version of the study protocol
- Up-to-date version of informed consent and assent document(s) in Arabic/English, as appropriate.
- Up-to-date version of subject recruitment materials (e.g., advertisements), when applicable.
- Proposed participant instructions and any other written information to be provided to study participants.

- Other ethics committees' submissions made with related decisions, as appropriate.
- Data collection instruments (including all surveys and questionnaires), when applicable.
- Current copy of the investigator's brochure or device specifications (or product information sheet), when applicable.
- Data safety monitoring plan, as appropriate.
- Other information requested to support the application

Non-KHCC researchers are required to provide a letter of support from their respective organization.

You, the Principal Investigator, should sign the application and obtain the approval from your department's Chair on the application. The signature will mean that: all departmental requirements are met and that the investigator has adequate resources to conduct the Research in terms of time, facilities, staff, access to a subject population, and resources for care that subjects may need. If you are the Head of your department, obtain the signature from the person to whom you report.

Contact the Research Administrator for assistance if you are submitting for the first time.

Contact the Head of the Clinical Trials Unit if you are approached for industry sponsored clinical trials/registry studies or when you intend to do a clinical trial of your own (Investigator Initiated Trial).

Submit the application and supporting materials as hardcopy to the Research Administrator. Email your complete application to hrpp@khcc.jo.

What Approvals are Required for my Research Application?

Before you can start your research at KHCC:

1) The Scientific Review Committee should review your research to verify its scientific merit. You may request exemption from the scientific review if your research was subject to a formal peer review process. Scientific review is not required for Non-KHCC sponsored projects e.g. industry sponsored trials.

2) If you are applying for an intramural grant, the Research Council should approve funding your research.

3) The Institutional Review Board (IRB) should approve your research.

4) If you are carrying out a clinical trial involving drugs or devices, your research should be approved by the Jordan Food and Drug Administration (JFDA).

5) Depending on your research, you may be required to sign a research agreement.

What Timelines Should I Expect for My Research Application?

You will receive an email message within 2 days from submitting your application to confirm that the submission was accepted. The review will follow the timelines below:

Scientific Review		Up to 21 days
Research Council funding decision		Up to 60 days
IRB Decision	*Exempt*	Up to 14 days
	Expedited	Up to 30 days
	Full-Board	Up to 90 days

Additional time may be required depending on your response to feedback and comments. You will be given 30 days to respond.

If you fail to respond within 30 days, your application will be cancelled.

When required approvals for your research are obtained, the research administrator will inform you that you can start your research.

Can I Waive Informed Consent Requirements or Documentation of Informed Consent?

Under specific circumstances, you may request to leave out or alter one or more of the consent elements or waive the consent requirement altogether if your research fulfills the following criteria:

1) the research involves no more than minimal risk to participants

2) The waiver does not adversely impact the potential participants' rights and welfare

3) The research cannot be carried out without the waiver or alteration

When appropriate, the IRB may require that you provide the study participants with pertinent information about the research after participation.

You may apply to waive the documentation of informed consent for any particular reason for some or all participants if your research meets the following criteria:

1) Only record linking the participant and the research would be the consent document and the principle risk would be potential harm resulting from a breach of confidentiality, and the research is not governed by regulatory bodies such as clinical trials,

2) The research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context.

You will find a specific section in the research application that you can complete in order to request the waiver.

Contact the HRPP office if you have additional questions regarding waiving consent requirements or documentation.

What Should I Do If I Want to Make Changes to the Study?

You are not allowed to implement any changes of, or deviations from, the protocol until you receive IRB written approval or exemption for an appropriate amendment. The only exception is when the change is necessary to eliminate immediate hazards to the study participants.

Complete and submit "Amendment of Research application" form. Modified documents should be supplied with the proposed changes underlined or "tracked for changes" and should be issued with a new version number and effective date. Make sure that specify what documents have changed on the application.

What Financial Interests Are Required to Be Disclosed?

You and your research team should identify and disclose any financial interests related to the research according to requirements of KHCC's policy on Conflict of Interest.

The "Research Financial Disclosure" Form is available as part of the research application.

What Needs to Be Reported During the Course of the Study?

You need to report the following to the IRB:

1. Events that indicate that there is a breach of the research participant's confidentiality.
2. Deviations from the study protocol that may significantly affect the safety of the participants or the conduct of the study
3. Deviations that were implemented to eliminate an immediate hazard to participants.
4. Incarceration of a research participant.
5. Complaints of participants that indicate unexpected risks or which the research team was unable to resolve.
6. Undue influence to investigators and research staff
7. Adverse Events (AE) including suspected unexpected serious adverse reactions (SUSARS) both internal and external.
8. New information that indicates a change to the risks or potential benefits of the Research. For example: (a) An interim analysis or safety monitoring report indicates that frequency or magnitude of harms or benefits may be different than what was initially presented to the IRB (b) A new publication shows that the risks or potential benefits of the research may be different than what was initially presented to the IRB. (c) Change in product labeling or withdrawal of drug, device, or biologic used in a research protocol from the market.
9. Noncompliance to human research protection program policies, IRB determinations or regulations..
10. Suspensions or terminations of research whether imposed by the sponsor, regulatory or the investigator

11. Any other event that could affect the safety or well-being of participants.

Follow the timeframes and requirements in appendix I

How Do I Submit a Continuing Review?

During continuing review the IRB must determine if the criteria for approval continues to be met. The IRB office will send you an expiration notice 30 days before the expiration of the IRB Approval. You must complete and submit Continuing Review form at least 14 days ahead of the expiration date.

You may be required to submit:

1. Status report on the progress of the research, it should include:
    a. The number of participants accrued.
    b. A summary since the last IRB review
    c. Adverse events and adverse outcomes experienced by participants.
    d. Study events that involve risks to participants or others.
    e. Participant withdrawals and the reasons for withdrawal.
    f. Complaints about the research
    g. Any interim findings
2. Amendments or modifications including any newly proposed consent documents, recruitment material and study instruments (surveys, questionnaires..etc)
3. Any relevant recent literature especially information about risks associated with the research
4. Any relevant multi-center trial reports.
5. Current risk-potential benefit assessment based on study results.
6. Data and safety monitoring reports (if applicable)

You must submit an end of study report if the research is complete. For additional questions, please contact the HRPP office.

What If My Study Expires?

There is no grace period extending the conduct of the research beyond the expiration date of IRB approval. If you fail to provide continuing review information to the IRB, or the IRB has not reviewed and approved a protocol by the expiration date:

- You will be restricted from submitting new research applications; and,
- You must stop all research activities, including recruitment, enrollment, interventions, interactions, and collection of research data.

You should contact the IRB Chair if you believe that stopping the research will place the currently enrolled participants at unnecessary risk and potential harm. Provide a list of participants for whom suspension of the research would cause harm.

Continuing human research procedures without IRB approval is a violation of Jordan Food and Drug Administration regulations.

Can I Provide Compensation to research participants?

Compensation can be offered to healthy participants or patients to acknowledge their contribution in the research process or to reimburse expenses resulting from participation. The IRB must approve all compensations planned for participants. Compensation can be in the form of payments, gift cards, gift items, or reimbursement for travel or other expenses. All forms of compensation must be specifically mentioned in the protocol

and consent document. Compensation should be justified and not contingent upon the participant completing the entire study.

Payment in exchange for referrals of prospective participants from others, finder's fees, are not permitted.

What If a Participant Withdraws?

Although a participant is not obliged to give his or her reasons for withdrawing prematurely from a research study, you should reasonably ascertain the reason, while fully respecting the participant's rights. Keep a log of participants and the reasons for withdrawing.

How Do I Close-Out a Study?

Complete and submit "End of Study" Application when one of the following occurs:

- All study participants have completed the study and all data have been analyzed.
- The investigator, sponsor, IRB or the JFDA decides to terminate or suspend the study.

If the study is prematurely terminated or suspended for any reason, you should stop recruitment activities and contact active participants to provide them with the necessary follow-up (as per protocol). You should inform the sponsor, IRB or JFDA, as appropriate. Provide a written explanation of the termination or suspension.

What Should I Do with the Study Records after the Study Ends?

Submit your study documents to the data management unit, OSAR, for retention. Study records, including signed and dated consent documents will be retained for five years from

completing the research. The clinical research agreement will specify the retention period for sponsored research.

What If I Want to Leave KHCC?

If you are planning to move to another location and leave KHCC, you must inform the HRPP Office and OSAR. You can either have another KHCC investigator assume the Principal Investigator responsibilities, or you can close your research studies.

If you choose to close your research studies, you may not dispose of the data, documents or records but should hand them over to the Data Management Unit. Research study data, documents and records are the property of KHCC and must remain at KHCC.

Where Can I Find Additional Information?

Reference policies and manuals that include reading material are as follows:

1. HRPP Plan; provides information about KHCC HRPP organization, scope, authority and responsibilities.

2. Research Council Policies and Procedures; It includes KHCC's governing research policies: responsible conduct of research, authorship, research data governance, intellectual property and research agreements.

3. HRPP Manual; Provides all the requirements of the human subject protection program.

4. KHCC's policy on conflict of interest.

How to Request Research Support Services?

The Office of Scientific Affairs and Research (OSAR) provides different research support services for investigators. To request research support services from the office, contact the director of the office or the respective units of interest:

Questions about research, research application and review process

Dr. Amal Al-Omari, PhD
OSAR Director
Extension: 1550
Email: asomari@khcc.jo

Razan Gharaibeh
Administrative Assistant
Extension: 1403
Email: rgharaibeh@KHCC.JO

Help with Survey Research

Khawla Ammar
Head Survey Unit
Extension: 1409
Email: KA.11148@KHCC.JO

Help with data Management including creation of data collections tools or databases

Hadeel Abdel Khaleq
Data Manager
Extension: 1407
Email: habdelkhaleq@KHCC.JO

Help with estimation of sample size, data analysis and biostatistics

Dalia Al-Rimawi,
Senior Statistical Programmer
Extension: 1558
Email: drimawi@KHCC.JO

Ayat Taqash,
Statistical Programmer
Extension: 1062
Email: ataqash@KHCC.JO

Help with Clinical Trials whether sponsored or investigator initiated

Farah Zahran,
Head, Clinical Trials Unit
Extension: 1342
Email: FZahran@KHCC.JO

Help with Grants and budgets

Raed Marashdeh
Senior Grants Specialist
Extension: 1045
Email: RMarashdeh@KHCC.JO

Access to cancer registry data

Khaled Jamal,
Supervisor, Cancer Registry
Extension: 1229

Email: kjamal@KHCC.JO

Who to Contact for Additional Support?

Questions/Concerns for the Research Council

Dr. Abdulghani Tbakhi, M.D.
Chair, Research Council
Extension:
Email: atbakhi@KHCC.JO

Dr. Amal Al-Omari, PhD
OSAR Director
Co-Chair, Research Council
Extension: 1550
Email: asomari@khcc.jo

Concerns or suggestions regarding KHCC's HRPP or concerns about the ethics review process

Dr. Maysa Al-Husseini, M.D. FRCPath
Chair, Institutional Review Board
Acting Manager, HRPP Office
Extension: 1308
Email: mhussaini@khcc.jo

Linda Al-Kateb,
Coordinator, Institutional Review Board
Extension: 1669
Email: irb@khcc.jo

Amal Tabaa,
Coordinator, HRPP
Extension: 1669
Email: AA.11661@KHCC.JO

We Value your Feedback

The investigator handbook was developed with your benefit in mind. No work is, however, whole or complete.

We conduct surveys every now and then to evaluate and enhance our practices, your participation in the surveys is essential, so keep it in mind.

We are interested in hearing from you. Your feedback will surely help us improve. If you have suggestions that you would like to share or ideas on how to improve this handbook, do not hesitate to send them to hrpp@khcc.jo.

Appendix 1 Timeframes for reporting study events

Event	Definition	Timeframe for Reporting	Reported to	Forms and Format required
Suspected Unexpected Serious Adverse Reactions (SUSARS) that are experienced by participants at KHCC	Serious adverse reactions that results in: • Death • Life threatening (subject at immediate risk of death) • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in congenital anomaly/birth defect • Results in persistent or significant disability or incapacity	Death/immediate life threatening events Within 24 hours of becoming aware of the event followed by a full written report no later than 7 calendar days All other SUSARs: As soon as possible, but no later than 7 calendar days of becoming aware of the event followed by complete report within 8 additional calendar days	Sponsor IRB	Event Report Form and CIOMS I or Sponsor SUSAR form
External SUSARS (experienced by participants at other sites)	Serious adverse reactions that results in: • Death • Life threatening (subject at immediate risk of death) • Requires inpatient hospitalization or prolongation of existing hospitalization • Results in congenital anomaly/birth defect • Results in persistent or significant disability or incapacity	At least every 6 months	IRB	Line listing accompanied by a brief report by the sponsor highlighting the main points of concern. Those periodic reports should only include SUSARs reported within the period covered by the report to avoid duplication of reporting In blinded trials the line listing should present data on all SUSARs, regardless of the medication administered (e.g. active/placebo)
All other AE	---	Annually	IRB	Annual safety report

Event	Definition	Timeframe for Reporting	Reported to	Forms and Format required
Protocol Deviations	Departure from the IRB approved protocol that may involve risks to participants or others or that may significantly impact the conduct of the study.	No later than 7 calendar days from when the situation occurred or the investigator or study team becoming aware of the deviation	Sponsor IRB	Event Report Form
Other Protocol Deviations	Departure from the IRB approved protocol that does not meet the above definition	Within 14 calendar days	Sponsor IRB	Event Report Form
Incidents of noncompliance, **Suspension or termination of research** **and other events required to be reported**	---	No later than 7 calendar days from when the situation occurred or the investigator or study team becoming aware of the suspension or termination	Sponsor IRB	Event Report Form

Appendix 2 Guidelines to Protect Confidential Information

The following guidelines should assist you in assuring that data and information related to the study subject or to a sponsor of a study are protected:

1. Limit discussions concerning research subjects to areas directly related to the conduct of research and necessary to complete the activity at hand. Do not discuss personal information in public areas, such as elevators, waiting rooms, cafeterias, and hallways.
2. Carry out study visits in a private treatment room or office.
3. Share confidential information about a subject only with other staff members who have a need to see such information as part of their duties and limit the amount shared to the minimum necessary.
4. Limit access to confidential information to staff members who require access to perform their jobs.
5. Written information should not be held in public areas, not taken off premises and not handled in a manner that allows unauthorized access.
6. Essential study documents and records should be kept in a secure area that is locked.
7. Counters, desks and shelves should be clear when not in use and all source documents filed out of sight.
8. Transmittal of Written information or documents should be done by authorized staff using secure methods
9. Print or fax documents should not be left in the printer or fax tray and should be collected promptly

Appendix 3 Obtaining Informed Consent or Assent from Potential Participants

The informed consent is a continuous process and involves three key features: (1) disclosing to potential research subjects information needed to make an informed decision; (2) facilitating the understanding of what has been disclosed; and (3) promoting the voluntariness of the decision about whether or not to participate in the research.

Participant's consent should be obtained before the initiation of a study procedure, test or treatment.

Meeting the trial subject for consent will be done face-to-face in a closed office space. The environment and circumstances should minimize the possibility of coercion or undue influence and allow a voluntary decision to be taken.

Apart from monitors, auditors, legally authorized representatives or witnesses, no one should be allowed to attend the participant's consent.

Verify that you have the most recent version of the IRB approved informed consent document and any related subject information documents.

Before starting the discussion, verify literacy of the potential participant (or legally authorized representative (LAR)). If the potential participant (or LAR) is unable to read, bring in an impartial witness to attend the whole consent discussion or postpone the consent until an appropriate impartial witness is available.

Introduce yourself and give a copy of the IRB approved consent document and any written information about the study to the potential participant (or LAR) to read through during the consent. Avoid using technical language or terms that will not be understood by the potential participant.

Brief the participant on the study and its purpose. Allow the participant to read the consent document while you explain its content. Allow time to verify that the subject understands or if the subject would like to ask questions.

Assess the initial reaction by asking the potential participant (or legally authorized representative) to give the first impression of what he has just been told:

- A definite No. Thank the potential participant for the time to listen and leave.

- Unsure. Ask the potential participant to go over the consent document and any subject information sheet. Ask him/her to go home and think about it. Provide contact information (name and telephone numbers) for any questions. Let the potential participant (or LAR) know when you will contact him/her again. Assure the voluntariness of participating and that nothing will affect future care. Encourage the potential participant (or LAR) to seek another opinion if he or she wishes to do so.

- Yes. Give the potential participant (or LAR) the opportunity to go over and read the consent document and any subject written information. You may propose to schedule another appointment so that the potential participant (or LAR) takes the documents home and consider the study. Encourage questions and seeking another opinion regarding study participation. Reaffirm the subject decision "yes" before proceeding any further.

If you are obtaining a child's assent, verify the child has the ability to give assent (age, experience, maturity, condition, emotion, talkativeness and willingness to ask). Talk to the child in the presence of his legal guardian. Read and discuss the IRB approved assent document in simple understandable language. Ask the child if he or she wants to be in the study. The child's

failure to object or absence of affirmative agreement should not be mistaken as assent. If the child objects, respect his or her wishes.

Appendix 4 Adverse Events Management

AEs can be identified through the voluntary reporting of the participant, while examining the participant, through observations by clinical research staff, reports by family or medical care providers or when reviewing the participant test results and medical records.

The investigator should evaluate all adverse events for seriousness, causality and expectedness. The investigator should consider the requirements of the study protocol when evaluating adverse events.

An AE is serious if it meets one of the following

- results in death
- life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- Based upon appropriate medical judgment, it may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed.

The AE has a causal relationship with the research if it cannot be satisfactorily attributed to the underlying disease condition or any other cause other than the research procedures or the use of the investigational product. The causality assessment given by the investigator should not be downgraded by the sponsor.

The AE is expected if it is consistent with the information provided in the protocol, the investigator brochure, summary of product characteristics or other relevant sources of information.

AEs and/or laboratory abnormalities identified in the protocol as critical to safety evaluations shall be managed and reported

according to the requirements of the study protocol and followed up until stabilized or resolved. The investigator should determine if an AE requires changes in the protocol or consent or whether other actions are needed to protect the safety, welfare or rights of the research participants or others

When a trial is blinded, removing the blind from investigational products should only be performed if relevant for the safety of the trial participant. The code should generally only be broken in the case of SUSAR where it is necessary for the Investigator to know which treatment the patient is receiving before the condition can be treated. The blind should be broken only for that specific patient.

The codes may be contained in individual envelopes stored at the study site to be opened by the Investigator or the investigational drug pharmacist, or the code may only be available via the sponsor. Research staff must know where any code envelopes are stored.

When the code is broken for an individual patient, this must be documented on the case report form (data collection form) with the reasons for breaking the code. The code envelope that was opened should also be annotated with the reason.

The investigator will still report the event according to the reporting requirements even when the product in question is a placebo. The Sponsor must be notified of the code beak.