Standards & Requirements for Independent Research Ethics Committee (IREC) Involved in Clinical Trials in the kingdom of Bahrain

Annex I of NHRA Clinical Trials Regulations
Version 1.0
September 2016
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Introduction

The National Health Regulatory Authority (NHRA) is empowered by law to regulate, promote, authorize and oversee the conduct of clinical trials in the Kingdom of Bahrain. NHRA’s authority to regulate clinical trials/research has been established in Law 38 in 2009, and its modifications in law 23 in 2015. Articles 3, article 4-4, article 6-2 and 6-4, and article 16-a and b of law 23 give authority to NHRA to regulate, authorize, monitor and inspect Sponsors, Investigators and Institutions conducting Clinical trials/research.

NHRA’s primary objective is to ensure that the conduct of clinical/trials research is supported by adequate ethical, scientific, regulatory and legal frameworks, and, that human subject protection is a shared responsibility within the clinical trials/research enterprise.

NHRA has established clinical trials/research regulatory requirements which define the conditions under which clinical trials/research shall be conducted in the Kingdom of Bahrain. The regulatory requirements apply to all healthcare facilities/institutions (public and/or private), and to all healthcare providers, clinicians-investigators, academic centers, sponsors and/or third parties participating in such clinical trials/research.

The regulation mandates that all research involving human beings shall be reviewed by an Institutional Independent Research Ethics Committee (IREC) to ensure that the appropriate ethical standards are being upheld. Adherence to the ethical principles of autonomy, beneficence, non-maleficence, and justice are central to proper ethical review.

The current standards and requirements for IRECs are based on international regulations and standards on Good Clinical Practice, provided by leading regulatory bodies like World Health organization (WHO), U.S Food & Drug Administration (FDA), EMA (European Medicines Agency) and International Conference of Technical Requirements For The Registration Of Pharmaceuticals For Human Use (ICH).

The purpose of this document is to support IRECs to operate in a way that is:

- robust, so that the public can be confident that clinical trials/research conducted in the Kingdom of Bahrain meets established and proven international scientific and ethical standards
- efficient, so that ethical clinical trials/research is facilitated, and so that IREC resources are used in a way that maximizes protection for research participants within the resources available
- transparent, so that applicants and IRECs can engage with each other with confidence, and so that the IREC review process can be easily understood by
- Consistent, so that applicants can expect to be treated fairly by different IRECs and at different times.
Standard 1: Responsibilities for establishing the research ethics review committee

Institutions/hospitals must ensure that the review of clinical trials/research involving human subjects is supported by an adequate ethical framework that is consistent with international standards and that institutional independent research ethics committees (IRECs) are capable of providing independent review on those researches and that a sustainable system is in place to monitor the quality and effectiveness of research ethics review.

**Article 1:** Institutions and hospitals (public/private healthcare facilities) planning to conduct clinical trials/research must establish an Institutional independent research ethics committee (IREC) that shall be responsible for the review, approval, monitoring, and reporting of the progress of clinical trials taking place at their respective Institutions. The IREC must develop written standards of operations (SOPs) that should be publically available.

**Article 2:** Clinical trials/research should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and be consistent with International Conference on Harmonization – Good Clinical Practice (ICH-GCP) and applicable NHRA regulation and requirements.

**Article 3:** Applicants/Sponsors, Institutions and hospitals (public/private healthcare facilities) planning to conduct clinical trials/research must obtain NHRA approval/no objection prior to conducting clinical trials/research.

**Article 4:** Clinical trials/research must be subject to scientific and ethical review. NHRA has developed regulatory guidelines that define the conditions under which clinical trials/research involving human subjects shall be conducted in the Kingdom of Bahrain. A favorable opinion or approval from an IREC does not imply authorization from NHRA to proceed with the research.

**Article 5:** The determination of whether a proposed clinical/research meets ethical standards must be made by IREC.

**Article 6:** IREC may solicit, at its sole discretion, the advice of scientific experts to establish the social value and scientific validity of the proposed clinical trial/research. The procedure for soliciting and obtaining an external scientific review (peer review) must be established in writing and shared with Investigators applying for IREC approval.

**Article 7:** IRECs, Investigators and study sponsors are responsible for ensuring that their clinical trials/research are compliant with NHRA clinical trials/research regulatory requirements. Where an IREC suspects that a research proposal is not compliant, it should advise the Investigator (applicant) of its concerns, and may suggest that they seek formal advice from NHRA.

Standard 2: Composition of IREC

An Institution’s IREC is an independent body constituted of medical, scientific, non-scientific and non-affiliated members whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial. Such IRECs are mandated by these standards to the reviewing, approving, monitoring and reporting of trial protocols and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
Article 8: An Institutional IREC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed clinical trial/research.

It is required that the IREC shall include no less than five (5) members, including:
   a) At least two persons with experience and expertise in the design and conduct of intervention studies
   b) At least one member whose primary area of interest is in a nonscientific area
   c) At least one member who is independent (non-affiliated) of the institution/trial site.

All members should have experience, or receive proper training in reviewing the ethical aspects of clinical trials/research. IREC should establish its own requirements for how members achieve such experience and should document when members have obtained such body of knowledge.

Article 9: Members that are independent of the Institution/trial site should have the following attributes:
   - They are not registered health professionals, and have not been registered health professionals at any time during the five years preceding the date of their appointment,
   - They may not otherwise be construed by virtue of employment, profession, relationship or otherwise to have a potential conflict or bias,

Standard 3: Conflict of Interest

There should be assurances regarding the independence of the IREC operations, in order to protect the decision making from influence by individuals or entities that sponsor, conduct, or host the research it reviews.

Article 10: IREC members must be mindful to avoid situations that might compromise their impartiality and/or the integrity of the EC review process. In particular, members should declare any conflict of interests they may have in relation to any item of business of IREC.

Article 11: Members who are also investigators on studies submitted for IREC review should declare their conflicts of interest. Where a member of an IREC is also an investigator on a study, IREC should usually require the member to leave the meeting room and take no part in the discussion or decision, especially when another investigator is available to attend the meeting to speak to the application.

Members with conflicts of interest should not participate in the voting process of the research protocol

Article 12: It is a mandatory requirement for IREC Chair to remind all members present at all meetings to declare potential conflicts of interest prior to the discussion of each item of business.

Article 12-1: Members shall declare to the Committee any interests they may have in relation to an application for ethical review or any other matter for consideration at that meeting. Such a declaration may be made orally at the meeting, prior to the matter being considered or in writing to the Chair prior to the meeting.

Article 12-2: Examples of conflict of interests include being a member (or having a family member) of the research team of the protocol under IREC review, having any type of financial relationship with the sponsor (e.g., consultant or speaking fees), or having investments with the sponsor.
Article 13: Where an IREC member declares a potential conflict of interest, the IREC must clearly record the declaration and its decision on how it was managed in the IREC meeting minutes.

Article 14: The terms and conditions of appointment for Institutional Research Ethics Committee members include requirements to declare conflict of interest and to keep confidential the business of IREC.

Standard 4: Operations – Procedures
IRECs shall have the authority to review and to approve, require modifications in (to secure approval), defer, or disapprove all research activities covered by these regulations. Their decision-making is impartial and transparent, following the processes defined by these requirements and procedures and to give applicants fair opportunity to be heard and to hear the deliberations of IREC.

Required policies
Article 15: IREC must establish and follow written procedures for:
   a) conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution;
   b) determining which projects require continuing review more often than annually
   c) determining which projects need verification from sources other than the investigator;
   d) establishing a list of categories of research that may be reviewed by IREC through an expedited review procedure;
   e) requiring investigators to promptly report to IREC of any substantial and non-substantial changes (amendments) in the research activity since the previous IREC review;
   f) ensuring that changes in approved research, during the period for which IREC approval has already been given, may not be initiated without IREC review and approval except where necessary to eliminate apparent immediate hazards to the human subjects.
   g) Requiring investigators to promptly report to IREC:
      i. any unanticipated problems involving risks or might serve as a potential risk to human subjects;
      ii. any instance of serious or continuing noncompliance with these regulations or the requirements or determinations of IREC; and
      iii. serious adverse events.
   h) IREC shall report to NHRA any suspension or termination of IREC approval.

Article 16: Institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IREC, or similar arrangements aimed at avoidance of duplication of effort, provided that the IREC is located in the Kingdom of Bahrain.

Article 17: Investigators must submit a complete application to IREC along with the letter of authorization from NHRA for review and approval prior to commencing research activities (Phase II-III).

Article 18: IREC must develop the application content requirements for clinical trials/research; however, NHRA recommends that the application contains the following:
   a) Study Protocol with version number and date, and Clinical Trial Registration Number
   b) Investigator’s Brochure
C) Sample Informed Consent Form(s)\(^1\) and Case Report Forms (data collection instruments)
D) Copy of the Clinical Trial Insurance
E) Information about the terms of payment or compensation to subjects who participate in clinical trial
F) CV’s of Investigators and Sponsor’s study monitor(s)
G) Financial Disclosure and conflict of interests statements of Investigators
H) Copy of the Clinical Trial Agreement (or a draft sample)

The decision-making process

Article 19: IRECs should determine their requirements for a quorum for voting. For all voting on decisions, there should be at least one clinician and one independent member who have participated in the discussions and participate in the voting.

IRECs decisions shall be made decisions through:
   a) Full review process
   b) Expedite review process

Article 20: Chairs are responsible for ensuring that IRECs make one of the following decisions on all new applications and substantial amendments through the full and expedited review pathways:
   a) approve
   b) provisional approval
   c) defer
   d) disapprove

Conditions of IREC approval

Article 21: All IREC approvals are subject to the following NHRA regulatory conditions:
   a) Applicants must obtain all necessary approvals and regulatory authorizations before the study commences in the Kingdom of Bahrain and at the Institution
   b) If the study is an intervention study, it must be registered in a clinical trials registry approved by the World Health Organization before it commences.
   c) A duly executed and legally enforceable clinical trial agreement must be signed by the Sponsor, Investigator and Head of the Institution.

Article 21-1: NHRA shall authorize Phase II-III clinical trials prior to IREC review and approval
Article 21-2: NHRA shall issue a no objection for Phase IV clinical trials after IREC has issued an approval to conduct the research at their institution.

Article 22: In order to approve a clinical trial/research covered by these regulations the IREC shall determine that all of the following requirements are satisfied:
   a) Risks to subjects are minimized:
      (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and
      (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.
   b) Risks to subjects are reasonable in relation to anticipated benefits, if any, and the importance of the scientific knowledge that may be expected to result. In evaluating risks and benefits, IREC should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research).

\(^1\) Both English and Arabic versions of the ICF
IREC should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

c) Subjects’ selection is equitable. In making this assessment IREC should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons.

d) Informed consent will be sought from each prospective subject or the subject’s legally authorized representative, in accordance with and to the extent required by ICH-GCP.

e) Informed consent will be appropriately documented, in accordance with and to the extent required by ICH-GCP.

i. Where appropriate: the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

f) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

g) When some or all of the subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, or economically or educationally disadvantaged persons, are likely to be vulnerable to coercion or undue influence, additional safeguards have been included in the study to protect the rights and welfare of these subjects.

Article 23: The full review pathway is required for any intervention or observational study that is within the scope of IREC review and that involves one or more of the following:

a) a new medicine (drug or biologics) being used for the first time in the desired indication, or

b) an approved medicine (or biologics) being used for a new indication or through a new mode of administration, or

c) a medical device that is not defined as a low-risk medical device (class II and III devices), or

d) a new surgical intervention, or

e) one or more participants who will not have given informed consent to participate, or

f) one or more participants who are vulnerable (that is, who have restricted capability to make independent decisions about their participation in the study), or

g) standard treatment being withheld from one or more participants.

Article 24: Full review is also required for substantial amendments to previously approved studies that were themselves reviewed by this pathway (full review).

Article 25: IREC shall develop a list of types of research that could be reviewed through the Expedite Review Process. It is recommended to use this review process for:

a) all new applications for which full review is not required (including studies of low risk medical devices ‘class I’ where none of the other features making full review appropriate are present)

b) substantial amendments to approved studies that were INITIALLY reviewed through the expedited review pathway or were determined to be low risk studies.

c) annual progress reports of studies that were initially reviewed through the expedited review pathway or those studies that were determined to be of low risk;

d) final reports

e) protocol deviations or violations

f) notifications of the conclusion or early termination of a study.
Letter of Rejection

Article 26: Letters declining an application must clearly state (1) the ethical standard(s) that the EC believes the study would not meet its requirements, (2) the reasons for disapproval, and (3) options open to the applicant in the event that their application is declined.

Article 27: An applicant may make a second application in respect of a study that an EC has declined at any time. In such cases, the second application is considered to be a new application, and assigned a new reference number.

Article 27-1: In case of a second application, IREC shall require from Investigator-applicant a new letter of authorization from NHRA.

Letter of Approval

Article 28: Approval letters must confirm that IREC operates in accordance with NHRA regulations the principles set forth in the Declaration of Helsinki, and ICH-GCP.

Article 29: The approval letter must state the approved documents; study protocol, informed consent(s), patient information document(s), investigator brochure (if required), any advertisement material, and other information to be shared or given to subjects (if any).

Article 30: IRECs may impose minor conditions on approval. By way of example, such conditions might include a request to appoint an independent safety monitoring committee, or minor corrections or changes to study documentation.

Article 30-1: Where the required changes may necessitate further ethical consideration (for example, significant or unspecified revision of study documentation), the IREC could provisionally approve the study and formally review these revisions before giving final approval.

Article 30-2: If the changes resulting from IREC provisional approval are substantial, IREC may proceed with the review and approval, However, the study may not commence unless NHRA re-authorize the study.

Article 30-3: Where NHRA agrees to a conditional approval subject to minor changes, it may decide to delegate authority to IREC to review and give final approval once the required revisions are made.

Article 32: It is the responsibility of the Principal Investigator and study sponsor to ensure that applicants meet all standard and minor conditions of IREC approval before the study commences at a given institution.

The letter of approval must state the responsibilities of the principal investigator, which shall include the following:

1. Conduct of the research according to accepted ethical and legal standards.
2. Report to IREC any changes in the research protocol, the research team, or any changes to the informed consent form.
3. Report to IREC any serious adverse event within 48 hours or two (02) working days.
4. Report any protocol violations or protocol deviations.
Letter of Provisional Approval

Article 33: IREC may provisionally approve a new application or substantial amendment pending receipt of further information or satisfaction of non-minor conditions. This decision may only be made once in respect of any new application or substantial amendment.

Article 34: Provisional approval letters must clearly state:
   a) the established ethical standard(s) that the IREC is not satisfied the study would meet on the basis of the information in the original application
   b) the further information (or non-minor conditions) that the IREC requires (or imposes) in order to make a final decision
   c) the date by which the IREC must receive a response from the applicant.
   d) A complete response must be received within 30 calendar days of the date of the provisional approval letter. IREC Coordinator should send a reminder of this request after 15 calendar days.
   e) Where IREC does not receive a complete response after 30 calendar days, the application or substantial amendment will be considered to have been withdrawn. IREC Coordinator must confirm this in writing to the applicant. No further deliberation or action is required from IREC.

IREC Records

Article 35: An institution, or IREC, shall prepare and maintain adequate documentation of IREC activities, including the following:
   a) Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.
   b) Minutes of IREC meetings which shall be in sufficient detail to show attendance at the meetings; actions taken by the IREC; the vote on these actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution.
   c) Records of continuing review activities.
   d) Copies of all correspondence between IREC and the investigators.
   e) A list of IREC members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each member's primary anticipated contributions to IREC deliberations; and any employment or other relationship between each member and the institution; for example: full-time employee, part-time employee, a member of governing panel or board, paid or unpaid consultant.
   f) IREC written procedures
   g) Statements of significant new findings provided to subjects.

Article 36: Records required by this regulation shall be retained for at least five (05) years after completion of the research, and the records shall be accessible for inspection and copying by authorized representatives of NHRA at reasonable times and in a reasonable manner.

Article 37: NHRA may refuse to consider a clinical investigation conducted in the Kingdom of Bahrain in support of an application for a research or marketing permit if the institution or IREC that reviewed the clinical trial refuses to allow an inspection under this section.
Standard 5: Reports

Investigators Reports

Article 38: As part of the continuing review of approved research, Investigators must submit and IREC must review:
   a) Progress Reports (annual or as determined by IREC)
   b) Individual Reports of Serious Adverse Events
   c) Periodic Safety Updates
   d) Protocol Deviations and Violations
   e) Any new safety findings or decisions issued by Independent Safety Review Boards
   f) Final Reports

IREC Reports to NHRA

Article 39: IREC must submit an annual activity report to NHRA. The reports must include the following:
   a) Membership, including names, titles and functions of IREC members.
   b) Number of meetings conducted during the year and attendance.
   c) Number and status of ongoing clinical trials/research studies at their respective institutions.
   d) Studies/amendments reviewed/approved via ‘Expedite Review’ process.
   e) Monitoring activities of clinical trials/Investigators and corrective actions taken by IRECs.
   f) Number and management of deviations and violations by investigators.
   g) Number of complaints filed by patients against Investigators or research team.
   h) Any planned changes to IRECs membership or functioning.
   i) Statement of compliance with NHRA regulatory requirements and ICH-GCP.
   j) Any other activity such as trainings or quality improvement initiatives undertaken by institution/IREC to strengthen and build capacity in clinical research.

Standard 6: Continuing Review and Monitoring:

Continuing Review & Monitoring of Ongoing Trials

Article 40: IREC shall keep under review the favorable ethical opinions or approvals given to any research study in the light of regular progress reports and significant developments during the conduct of the research.

Article 41: Where IREC decides that it no longer has a favorable opinion/approval of a trial, the Chair should write to NHRA. IREC may recommend that consideration should be given to suspending or terminating the trial authorization by NHRA. Any such recommendation should relate to serious concern about one or more of the following:
   a) the scientific validity of the trial
   b) the health or safety of participants
   c) the competence or conduct of the investigator(s)
   d) a delay of at least 1 year in the commencement of the trial leading to doubts about the continuing validity of the ethical opinion given on the original application
   e) changes in the adequacy of the site or facilities.

Article 42: If a clinical trial is terminated prematurely or suspended by the sponsor, the sponsor shall promptly inform the investigators/institutions, NHRA and IREC of the termination or suspension and the reason(s) for the termination or suspension.
**Article 43:** If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, inform IREC and NHRA of the research subjects management plans.

**Sponsored Research**

**Article 44:** Other than by means of the reports that the sponsor and investigators are required to submit; IREC has no obligation for proactive monitoring of research studies. The accountability for this lies with the sponsor and the employing organization.

**Article 45:** The sponsor must ensure that the trials are adequately monitored. The purposes of trial monitoring are to verify that the:
   a) rights and well-being of human subjects are protected.
   b) reported trial data are accurate, complete, and verifiable from source documents.
   c) conduct of the trial is in compliance with the currently approved protocol/amendment(s), with ICH-GCP, and with applicable regulatory requirement(s).

**Article 46:** IREC shall be promptly notified of any serious breach of the conditions or principles of ICH-GCP or of the protocol. A breach should be regarded as serious if it is likely to affect to a significant degree the safety or physical or mental integrity of the subjects of the trial, or the scientific value of the trial. The sponsor should notify IREC and NHRA in writing within 7 days of the matter coming to their attention.

**Article 47:** Approval conditions are binding and they set out important guidance which Principal Investigators and sponsors are expected to follow. Failure to comply with the conditions may lead to a change of IREC opinion and a recommendation to NHRA that the authorization should be suspended or terminated.

**Investigator/Institution Initiated Clinical Trials:**

**Article 48:** Where clinical trials/research is sponsored by Investigators or Institution, IRECs must ensure that research conducted at their institutions is properly monitored. Such monitoring activities should be performed by a qualified and trained monitor.

**Article 48-1:** The extent to which IREC mandates active monitoring of clinical trials/research could be determined by the risk level of the study. Hence, low risk studies do not require active monitoring, and IREC may make determination during the review of regular progress reports.

**Article 48-2:** Active monitoring may not be performed by a simple review of progress reports or a discussion with Investigator. Monitoring reports should be developed at the conclusion of each monitoring visit, describing the documents reviewed and monitored, as well as any deviations, actions recommended by the monitor.

**Clinical Research/Trial Application Content**

**Article 49:** An application for ethical review of a clinical trial/research proposal shall be made by the Principal Investigator for that study to their Institutional IREC. Applications shall be submitted to the IREC-Coordinator using IREC application form.

**Article 50:** Study sponsors are prohibited from making direct submissions to IRECs, however, they can assist the Principal Investigator with the preparation of the application content and submission package, and ensure that language requirements are met.
Article 51: All documents should carry the trial identification (Clinical Trial Registration number, sponsor’s protocol code number, date and/or version).

Article 52: An application is considered to be valid if all required documents are complete. If that is the case, the applicant will be informed and the review period starts. If an application is not valid IREC will inform the applicant of the deficiencies.

Every valid application shall receive a unique IREC reference number.

Content of the Initial Submission

Article 53: The Principal Investigator/applicant should submit and sign a cover letter along with the application.

Article 54: The letter’s heading should contain the Clinical Trial Registration Number and the sponsor protocol number with a title of the clinical trial. The text should:

a) draw attention to any special issues related to the application such as special trial populations, first administration of a new active substance to humans, unusual investigational products, unusual trial designs, sub-studies etc. and indicate where the relevant information is in the application.

b) specify, for each Investigational Product, the reference document(s) chosen by the sponsor to identify the unexpectedness of a serious adverse reaction in accordance with the appropriate detailed guidance.

c) In addition, it should draw attention to any scientific advice or opinion, regulatory approval(s) in other regions/countries related to the clinical trial or other Ethics Committee of any other country and indicate where in the application IREC can find a copy of the advice.

Article 55: A duly completed IREC application form should be dated and signed by the sponsor or the sponsor’s legal representative and/or by the principal investigator responsible for the conduct of the trial at the Institution. Curriculum Vita of all Investigators involved at the institution must be attached to the application form.

Article 56: The Principal Investigator must submit a clinical trial/research protocol. The content and format of protocol should comply with the ICH-GCP guidance.

Article 57: The clinical trial/research protocol must be identified by the title, a sponsor’s protocol code number specific for all versions of it, a number and date of version that will be updated when it is amended, and by any short title or name assigned to it should be signed by the sponsor and principal investigator (or coordinating investigator for multicenter trials of the sponsor).

The version submitted should include all currently authorized amendments and a definition of the end of the trial.

Article 58: The protocol must be dated and signed by the Principal Investigator, the Sponsor or the Sponsor’s legal representative, and the study monitor. In case of an International multicenter trial, the international coordinating Investigator must also date and sign the protocol.

Article 59: The application must contain information regarding the investigational product. The clinical trial application form contains some information to identify the investigational product(s),
the form(s) and strength(s), dose(s) route(s) of administration and treatment period(s). However, the bulk of the information is contained in the Investigator’s brochure.

**Article 60:** The Investigator’s Brochure should reflect all the clinical and non-clinical data on the investigational medicinal product(s) which is relevant for the trial and provide evidence that supports the rationale for the proposed clinical trial and the safe use of the product(s) in the trial.

**Article 61:** Study sponsors must ensure that sufficient safety and efficacy data are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied. The content and format of the investigator’s brochure should comply with the ICH-GCP guidance.

**Article 62:** Study sponsors should update the Investigator’s Brochure as significant new information becomes available. Updates of Investigator’s brochure may result in the submission of an amendment of the protocol, informed consent and study protocol.

**Article 63:** If the investigational product has marketing authorization in the Kingdom of Bahrain, and the Investigational product is to be used as authorized, the Investigator’s Brochure could be substituted by the authorized Summary of Products Characteristics (SmPC).

**Article 64:** Principal Investigator/applicant must submit for review and approval all information to be provided to the subjects (and/or, where appropriate, the parent(s)/legal representative) before their decision to participate or abstain from participation together with the form for written informed consent.

Minimum requirements for the content of the informed consent form are set in the ICH-GCP E6.

**Article 65:** Principal investigator/applicant may use information sheets to be given to the subject and/or the parent(s)/legal representative, or utilize advertisement material to enhance subject recruitment. Such subject information should be kept short, clear, relevant, and understandable to a lay person.

**Article 66:** Informed consent forms, and patient information sheets must be submitted in both English and Arabic languages.

**Article 67:** IREC must ensure that there is sufficient provision for indemnity or compensation in the event of injury or death attributable to an investigational product and/or protocol required procedures (clinical trial insurance), and insurance or indemnity to cover the liability of the sponsor(s). When an institution or investigator is the sponsor, they must contract both clinical trial insurance and medical malpractice insurance.

**Article 68:** Applicants must show that:
   a) financial arrangements, including insurance or indemnity, cover the research study concerned
   b) sponsor, protocol authors, investigators/collaborators and, where applicable, Site Management Organizations, Contract Research Organizations will all be protected by insurance or indemnity arrangements
   c) the arrangements will provide adequate cover to meet the potential liability assessed by the sponsor
**Article 69:** IRECs are not expected to undertake detailed expert scrutiny of insurance policies. The responsibility for ensuring that cover is adequate lies with the Institution’s management, investigators and sponsors themselves.

**Article 70:** Phase IV or post approval studies are exempt from the product or trial insurance requirements.

**Submission of Amendments:**

**Article 71:** A substantial amendment to an approved and authorized clinical trial/research study requires IREC approval prior to seeking NHRA authorization.

**Article 72:** Principal investigator/applicant shall not implement substantial amendments prior to obtaining IREC approval and NHRA re-authorization. However, Applicants-sponsor may continue the clinical trial/research based on the ongoing approved clinical trial protocol and associated documents.

**Article 73:** Applicants may make non-substantial (‘minor’) amendments to any approved study at any time without seeking NHRA authorization.

**Article 74:** Submission to IREC of non-substantial (minor) amendments requires confirmation by IREC (preferably by the IREC Chair only, or through the expedite review process) that the proposed changes proposed in the amendment are non-substantial. IREC shall notify the applicant in writing within 05 working days of the confirmation.

**Article 75:** Principal Investigator/applicant must submit for review and approval all amended documents along with the new version and date of the amended documents.

**IREC Management of Amendments**

**Substantial Amendment:**

**Article 76:** A substantial amendment is an amendment that is likely to affect to a significant degree any of the following:
   a) the safety or physical or mental integrity of participants
   b) the scientific value of the study
   c) the conduct or management of the study
   d) the quality or safety of any medicine or item used in the study
   e) key documents submitted with the applications to NHRA or the IREC

**Article 77:** The following should normally be regarded as substantial amendments:
   a) significant changes to the design/methodology of the study
   b) significant changes to the type or number of procedures participants will undertake in the study
   c) changes relating to the safety of the physical or mental integrity of participants, or to the risk/benefit assessment for the study
   d) significant changes to the study’s documentation (such as participant information sheets, informed consent or advertisement material)
   e) the appointment of a new Principal Investigator for the study
   f) any other significant change to the study protocol or the information provided in the application for approval.
Article 78: The following should usually be regarded as minor amendments:
   a) minor or administrative changes to study documentation
   b) updated versions of the investigator’s brochure (where the study involves a new medicine)
   c) changes to the research team other than the appointment of a new Principal Investigator
   d) changes in funding arrangements, except where these may alter the ability of participants to access publicly funded compensation in the event of injury
   e) changes in arrangements for recording or analyzing study data, or for storing or transporting samples
   f) extension of the study beyond the expected end date given in the application form, except where this is related to other changes that are substantial.

Deciding whether an amendment is substantial
Article 79: In the first instance, it is the responsibility of the study team to decide whether or not a given amendment to a study is substantial. In making this decision, applicants should consider whether the amendment will change the study to a ‘significant degree’. Applicants should take particular account of any implications for the safety or welfare of participants, and of any information that participants might require to give informed consent to continue to participate in the amended research.

Article 80: Where there is doubt as to whether an amendment is substantial, applicants may submit it for review. Where an amendment submitted for review is not validated as non-substantial, the IREC Coordinator must communicate this decision to the Principal Investigator within five (05) working days.

This confirmation must contain details of all documents submitted with the amendment.

Review pathways for substantial amendments
Article 81: Substantial amendments to studies reviewed through the expedited review pathway must themselves be reviewed through this pathway. Substantial amendments to studies reviewed through the full review pathway may also be reviewed through expedited review, at the discretion of IREC Chair.

Article 82: Where IREC rejection is given, the sponsor or Principal Investigator may modify the amendment.

Article 83: IREC must render its decision for substantial amendments within 30 days of receiving the proposed amendments.

Article 84: Amendments involving the submission of a separate protocol shall always require the submission of a new application.

Amendments requiring a new Application
Article 85: Where a proposed amendment would fundamentally alter the nature of the research and the extent of the involvement of, or risk to, existing and/or potential participants, the REC may request submission of a new application for full ethical review instead of rejecting the amended protocol along with the proposed changes.

Changes in Principal Investigator
Article 86: The appointment of a new Principal Investigator for a study is considered as a substantial amendment.
**Article 87:** Where the Principal Investigator for a study is to be absent for any reason for a period of less than 90 calendar days, any other qualified investigator (that was submitted as part of the initial application as an Investigator or Co-investigator) on the study may act in his/her place during this period. Such interim arrangements are not substantial amendments and do not require NHRA approval and re-authorization.

**Article 13:** The named ‘Interim’ Principal Investigator remains responsible for the conduct of the study while such interim arrangements are in place.

**Article 14:** The addition of investigators is not a substantial amendment. This is because the Principal Investigator himself or herself is responsible to IREC and NHRA for the ethical and responsible conduct of the entire research team at all localities.