Clinical Trial Regulations

Version 3.0 March 2021

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Contents

Preamble:

The primary purpose of clinical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

The conduct of clinical research is complex and this complexity is compounded by the need to involve a number of different individuals with a variety of expertise, all of who must perform their tasks skillfully and efficiently, and more importantly comply with laws and regulations. The primary goal is to provide public assurance that the rights and well-being of research subjects are protected and preserved, and research is conducted according to the highest ethical and scientific standards.

The National Health Regulatory Authority (NHRA) was created by law number 38 in 2009 (modified by law 23 in 2015), and has been empowered to regulate, promote, authorize and oversee the conduct of clinical trials in the Kingdom of Bahrain. In implementing its strategy and asserting its authority, NHRA has issued the following regulations governing the planning, execution and reporting of clinical trials;

- Regulatory Requirements for clinical trials in the Kingdom of Bahrain
- Requirements for Independent Research Ethics Committee (IREC) involved in Clinical Trials in the kingdom of Bahrain.

On February 11th 2016, NHRA conducted the 1st forum on clinical trials/research, and released for public comments the 1st draft of both regulations and requirements. Representatives from Research Ethics Committees, Sponsors and International experts in Ethics provided valuable comments; all of which have been compiled and some proposed changes have been integrated into the final version of these regulations.

The current regulatory requirements for clinical trials define the conditions under which clinical trials/research involving human subjects shall be conducted in the Kingdom of Bahrain. It applies 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. It also defines roles, responsibilities and obligations of each party involved in the planning, review, monitoring and oversight of clinical trials/research activities.

The current regulation is 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 requirements for IRECs and ethical review of clinical trial/research protocols are provided in a separate document. Institutions, sponsors and applicants must be aware, adhere and comply with the requirements of both regulations.

I would like to express my special appreciation and thanks to Clinical Trial Committee for helping in reviewing this document in the year 2021

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Glossary of Terms and Acronyms:

AE/SAE: Adverse Event / Serious Adverse Event

cGMP: current Good Manufacturing Practices

CRO: Contract Research Organization

CTA: Clinical Trial Authorization

EMA: European Medicines Agency

FDA: United States Food and Drug Administration

GCP: Good Clinical Practices

ICF: Informed Consent Form

ICH: International Conference on Harmonization

IP/IMP: Investigational Product/Investigational Medicinal Product

REC/IREC/IRB/: Independent Research Ethics Committee (also Research Ethics Committee) / Institutional Review Board

Definitions:

Clinical Trial: Any investigation or experiment in human subjects, either on healthy volunteers or on patients, of an investigational product (drugs, medicines, biologics, or medical devices). Clinical trials intend to discover or verify therapeutic effects, identify any adverse reactions, study absorption, distribution, metabolism, and excretion, and/or help determine the safety, effectiveness and value of medicines, devices, diagnostic products and various interventions intended for human use.

Clinical research is defined as a systematic investigation, including research development, testing, and evaluation, that is designed to develop or contribute to generalizable knowledge. It is designed to provide information about different types of outcomes and may not necessarily include an intervention.

Clinical research involves an investigator or investigators who directly observe a person or a population, and/or who collect data to answer a scientific or medical question about the safety and/or potential benefit of an intervention such as a medication, device, teaching concept, training method, or behavioral change.

Human subject (research subject) is a living individual about whom an investigator conducts research and obtains medical (clinical) data through intervention or interaction with the individual; or uses his/her Identifiable private information.

Trial (research) Subject: An individual who participates in a clinical trial, as a recipient of an investigational product(s) or a control (placebo). The trial subject can be any of the following:

i. A healthy volunteer;
ii. A patient whose disease is not related to the administration of the investigational product; or
iii. A patient whose disease is related to the use of the investigational product.

Intervention Is any treatment or investigation that impacts directly on the clinical care of the patient (study subject). This includes medicinal products, medical devices, exercise regimes, food regimes or any testing which will impact on clinical care. Testing (e.g. blood sampling, urine sampling, x-rays etc.) which is done for research purposes only and will not directly impact on the study subject's clinical care, is not considered an intervention.

Clinical Trial Protocol: A document that states the background, rationale, and objectives of a clinical trial and describes in detail the design, methodology, and organization of a trial as well as the statistical methods and the situations likely encountered during the trial and their possible remedies. The term protocol refers to the protocol, successive versions of the protocol and protocol amendments;

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol.

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

Clinical Trial Agreement (CTA): A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract or form part of a contract (e.g. as an appendix to the CTA).

Investigator: A person who is responsible for the execution and conduct of the clinical trial and also responsible for the rights, health, and well-being of the human subjects involved in the trial.

Principal Investigator: The Investigator responsible for coordination of all activities, among different centers of a multi-center clinical trial. For a regulated clinical trial, the Investigator must be suitably qualified and have sufficient experience.

Clinical trials Sponsor: A sponsor can be a pharmaceutical and/or a CRO, a biotechnology, medical device or healthcare industry company, a medical center, an academic institution, an investigator, and/or a health related organization (for example a medical society or association, or a patient association). A Sponsor takes responsibility for the planning, initiation, management and/or financing of a clinical trial; An Investigator is considered as a sponsor if he or she independently plans, conducts and is totally responsible for a clinical trial.

Contract Research Organization: A person, company or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

Applicant: An individual, company, institution, or organization which takes responsibility for submitting a clinical trial authorization on behalf of a Sponsor, and act as an agent/legal representative of a Sponsor, even if the Sponsor elects to use a CRO as a study monitor.

A Sponsor submitting a clinical trial authorization directly is considered a sponsor-applicant.

An Investigator is considered as a sponsor-applicant if he or she independently plans, conducts and is totally responsible for the clinical trial (including the financing of the clinical trial/research). Investigator must submit a no-objection letter from the head of the institution/healthcare facility to conduct a clinical research/trial on their premises/facilities.

Pharmaceutical and/or biotechnology clinical trials include all phases of drug development phase I to III and may include comparative trials. An observational study, in which the sponsor is a member of the healthcare industry, and in which private data are collected is considered a clinical trial and is subject to the current regulation.

A **multi-center** clinical trial is a clinical trial conducted according to a single protocol but at more than one site, and therefore by more than one investigator, in which the trial sites may be located in a single country, or in a number of countries,

A non-interventional trial is a study where an investigational product(s) is (are) (medicines, biologics, or medical devices) prescribed in the usual manner in accordance with the terms of the marketing authorization and approved indication(s). The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods are used for the analysis of collected data. Whether such a trial should have a full application to the CT committee will be determined by the CT algorithm (Appendix 1)

An investigational product is a pharmaceutical or biotech form of an active substance, a medical device, biologics, or therapy or placebo being tested or used as a reference in a clinical trial, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or when used for unapproved indications, or when used to gain further information about the approved form.

Investigational Medicinal Products A specific type or subtype of medicinal product that includes but not limited to: Chemical entities; biotechnology products; cell or gene therapy products; plasma derived products; other extractive products; immunological medicinal products (such as: vaccines, allergens, immune sera); herbal medicinal products; radiopharmaceutical products; and homeopathic products.

Comparator (Product): An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

Investigator's brochure: a compilation of the clinical and non-clinical data on the investigational medicinal product or medical device products which are relevant to the study of the product or products in human subjects; A document prepared for Investigators about any relevant available information regarding investigational product(s) prior to the conduct of the clinical trial which includes physical, chemical, and pharmaceutical properties; experience regarding toxicity, safety, pharmacokinetics and pharmacodynamics obtained from animals and human subjects; and results of previous clinical trials or experience. For marketed products, the Summary of Medicinal Product Characteristics (in the EU) or Prescriber Information (in the USA) may take the place of the Investigator's Brochure.

Trial Monitor: A qualified individual who is assigned by and also directly reports to the sponsor, CRO, or research institution. The Monitor's responsibilities are to oversee the progress of a clinical trial and validate the authenticity and integrity of all its source documents and data and to ensure that the clinical trial is conducted, recorded, and reported according to the protocol and Good Clinical Practices.

Trial Monitoring: The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, Standard Operating Procedures (SOPs), ICH-GCP, and the applicable regulatory requirement(s).

Monitoring Report: A written report from the monitor to the sponsor after each visit to the investigational site (institution) and/or other trial-related communication according to the sponsor's SOPs.

Compliance is the adherence to all the clinical research/trial-related requirements, ICH-GCP guidelines, and applicable regulatory requirements.

Informed Consent is a decision, which must be obtained in writing from the research subject or legal representatives (in case of a minor), to take part in a clinical trial, taken freely after being duly informed.

The Informed Consent Form: is a document in which a trial subject voluntarily confirms his or her willingness to participate in a clinical trial. It is signed and dated by the trial subjects or their legal representatives only after they have been informed by the Investigator, prior to initiation of the trial, of all aspects of the trial, including experimental setting, trial objectives, possible benefits, side effects and dangers of participation in the trial, currently available alternative procedures or treatment regimens, the rights and responsibilities of the trial subject, and other information that is relevant to the subject's decision to participate.

Ethics committee (Institution's independent ethics committee 'IREC') is an independent body consisting of healthcare (medical/scientific) professionals and non-medical/non-scientific members, whose responsibility it is to protect the rights, safety and wellbeing of human subjects involved in clinical research/trials and to provide public assurance of that protection, by, among other things, reviewing and approving the clinical research/trial protocol, the suitability of the investigator(s) and the adequacy of facilities, and the methods, documents and material to be used to inform human subjects and obtain their informed consent.

Ethics Committee Approval (or favorable opinion) is the affirmative decision of IREC that the clinical research/trial protocol has been reviewed and may be conducted at the institution/investigational site within the constraints set forth by the IREC, the institution, ICH-GCP, and the regulatory requirements established by the National Health Regulatory Authority (NHRA). No CT study application can be made to NHRA without a prior favorable opinion from an NHRA/IREC ethics committee

Inspection is the act by NHRA, or an independent third party contracted by the NHRA, or foreign regulatory authority inspectors of conducting an official review of documents, facilities, records, quality assurance arrangements, and any other resources that are deemed by Inspectors to be related to clinical research and that may be located at the site of the investigator, at the sponsor's and/or contract research organization's facilities, at the office of the Independent Research Ethic Committee, or at other establishments which NHRA or Inspectors sees appropriate to inspect; in order to ensure compliance of the current regulation and/or ICH GCP.

Audit: A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), ICH-GCP, and applicable regulatory requirements.

Clinical Trial/Study Report: A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses of findings and results are fully integrated into a single report.

Adverse Event is any untoward medical occurrence in a patient or clinical trial subject administered with an investigational product and which does not necessarily have a causal relationship with this treatment (see also Serious Adverse Event|).

Adverse Reaction is all untoward and unintended responses to an investigational product related to any dose administered.

Serious Adverse Event or serious adverse reaction is any untoward medical occurrence or effect that at any dose/rate, specified and unspecified mean of use, results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect;

Unexpected Adverse Reaction': an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics for an approved product).

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, chromatograms and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

Source Data: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

Good Clinical Practice (ICH-GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.
The ICH GCP E6 Guideline (ICH-GCP), first published in 1996, is a process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects.

Compliance with ICH-GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines and ensures the integrity of clinical research data.

The responsibility for ICH-GCP is shared by all of the parties involved, including sponsors, investigators and site research staff, contract research organizations (CROs), independent research ethics committees or, regulatory authorities and research subjects.

It is a requirement that the clinical staff and coordinators directly involved with the conduct of the clinical trial (and specified in the delegation log) would have underwent a GCP course within a 2-year period with re-training in GCP every 2 years. Eligibility to participate in the conduct of the clinical trial can be revoked if the GCP certification is expired.

Legally Acceptable Representative: An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

Institution (medical) / Investigational Institution/" Trial Site": Any public or private entity or agency or medical facility where clinical trials are conducted. An expression meaning "the investigator and/or institution, where required by NHRA. "The locations where clinical trial-related activities are actually conducted".

Investigational Product Brochure: A compilation of the clinical and nonclinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

Clinical Trial Phases: There are four categories of clinical trials, which may be described as follows:

- **Phase I:** Initial trials carried out to determine the metabolism and pharmacological actions of medicinal products in humans, the most commonly occurring adverse reactions associated with increasing doses, and to gain early evidence of effectiveness. These studies may include healthy participants and/or patients.

- **Phase II:** Controlled clinical trials conducted to evaluate the effectiveness of the medicinal product for a particular indication in patients with the disease or condition under study and to further determine the common adverse reactions and risks associated with the product.

- **Phase III:** Expanded controlled and uncontrolled clinical trials after preliminary evidence suggesting effectiveness of the medicinal product has been obtained. These studies are intended to gather additional information to evaluate the overall benefit-risk profile of the medicinal product and provide a basis for the product information.

- **Phase IV:** Clinical trials carried out following authorisation and designed to detect less commonly occurring or longer-term adverse reactions in larger patient populations and over longer periods of time than is possible during initial clinical trials. 'Noninterventional' Phase IV studies, i.e. those where the medicinal product is prescribed in accordance with the terms of the marketing authorisation and assignment of patients to treatment is not decided in advance by a clinical trial protocol, do not require authorisation under the above-mentioned clinical trials regulations.

- **NHRA defines CT phases as follows:**

  Phase I-III: **Experimental clinical trials on:**
  - (i) unapproved products regulated by NHRA, or
  - (ii) products that are legally marketed in the Kingdom of Bahrain but used outside the conditions of approval (off label, new indication, changes to the approved dose regimen, method of administration, changes in formulation, etc.)

  Phase IV: **Any study or trials involving**:
  - (i) an NHRA registered product, or
  - (ii) involving a commercial Sponsor including 'observational studies' whether interventional or not, or
  - (iii) Studies initiated by investigators-institutions using approved and registered products which are regulated by NHRA.

Protocol Violation: Any departure from the approved protocol, associated trial documents or any other information relating to the conduct of the study. All violations should be recorded, risk assessed and corrective actions instituted. Protocol violations where the safety of subjects or the validity of study data is significantly impacted should be reported to the NHRA and IREC.

Non-compliance: Failure to comply with the protocol, NHRA regulations, IREC or Institutional policies and SOPs, GCP and/or other applicable regulatory requirements:

I. **Minor non-compliance:** Non-compliance involving isolated incidents, minor or technical violations which result from unintentional mistake, an oversight or a misunderstanding, or failure to follow operational procedures, protocol, GCP which do not pose risk to subjects and/or violate subject's rights and welfare and do not impact on the validity of study data.

II. **Serious Non-compliance**: Non-compliance involving one or more of the following: (1) bringing harm to research participants; (2) exposing research participants to a significant risk of substantive harm; (3) compromising the privacy and confidentiality of research participants; (4) causing damage to scientific integrity of the research data that has been collected; (5) engaging in willful or knowing noncompliance; (6) impacting ethical principles adversely; (7) fraud. All non-compliances should be recorded, risk assessed and corrective actions instituted. Serious non-compliances should be reported to the NHRA and IREC.

Examples of serious non-compliance include:

1. conducting human participant research without NHRA and IREC approval (e.g., before approval; in the absence of a continuation application submitted to the IREC; during a suspension of IREC approval; after termination of IREC approval);
2. disregarding or otherwise violating IREC approved informed consent procedures (e.g., failing to obtain consent, using unapproved consent, missing signatures, failing to document consent process);
3. deviating from the protocol approved by NHRA and IREC;
4. modifying an approved protocol or exceeding the number of approved research subjects without IREC approval;
5. use of investigational products outside the clinical trial;
6. failing to report Serious Adverse Events (SAEs) in a timely manner;
7. failing to maintain adequate records;
8. failing to train research team members in the proper procedures; and
9. failing to follow recommendations of IREC to ensure the safety of research participants.

Continuing noncompliance: Is a persistent failure to adhere to the GCP, laws, regulations, or policies governing human research.

Examples of types of continuing non-compliance include:

1. missing data such as persistent missing key data in the Case Report Forms (CRFs);
2. inadequate source documents, such as persistent errors recording study information in the source documents or errors of documentation of the informed consent process;
3. protocol non-compliance such as persistent failure to perform procedures specified in the protocol, including inclusion of study participants who do not meet eligibility criteria;
4. GCP non-compliance includes: persistent late reporting of serious adverse events; medical decisions being made by non-medical staff (e.g. ECG interpretation, dosing changes).

Fraud and Misconduct: Is the fabrication, falsification, plagiarism or deception in proposing, carrying out or reporting results of research or deliberate, dangerous or negligent deviations from accepted practices in carrying out research. It includes failure to follow established protocols if this failure results in unreasonable risk or harm to humans and facilitating of misconduct in research by collusion in, or concealment of, such actions by others. It also includes intentional, unauthorized use, disclosure or removal of, or damage to, research-related property of another, including apparatus, materials, writings or devices used in or produced by the conduct of research. It does not include honest error or honest differences in the design, execution, interpretation or judgment in evaluating research methods or results or misconduct unrelated to the research process. Examples of types of fraud and misconduct includes: (1) filling in the CRF or Diary Card with fictitious information; producing reports when no tests were performed; photocopying data related to one subject to use for another; and

creating fictitious subjects; (2) changing clinical data in the CRF or Diary to make a patient eligible for inclusion into the study; or changing or intentionally misinterpreting data to provide illegitimate results; (3) removing subjects from the study for illegitimate reasons; and not reporting or disguising adverse events or other clinical data. All fraud should be treated as serious non-compliance and reported to the NHRA and IREC.

General Considerations:

Article 1: The National Health Regulatory Authority (NHRA) is responsible for regulating, reviewing, authorizing and monitoring all clinical trials or human subject research (other industry sponsored clinical research, and sponsored observational studies) undertaken in the Kingdom of Bahrain and which require authorization or a letter of no objection as defined in Article 2-1 below.

NHRA's authority to regulate clinical trials/research has been established in Law 38 in 2009, and its modifications in law 32 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 and to protect Personal Information Data according to Law #30 issue by his Majesty King of Kingdom of Bahrain. (Annex I)

Article 2: Clinical trials shall not take place in the Kingdom of Bahrain until they fulfill and meet specific requirements and a letter of authorization/no objection is issued by NHRA along within paying processing fees. What is considered to be a clinical trial to be submitted to NHRA is shown in the Clinical Trials algorithm in Appendix 1

Article 2-1: The NHRA authorization process is as follow:

a. Phase I: Currently NHRA does not allow the conduct of Phase I trials in the Kingdom of Bahrain; however, these will be considered by the CT committee on a case by case basis as per criteria in Appendix 2.
b. Phase II-III: Sponsors-applicants must obtain National Health Regulatory Authority Independent Research Ethics Committees (NHRA-IREC) review prior to submission to the CT committee.
c. Phase IV: Sponsors-applicants must await a no objection letter from NHRA after obtaining an approval from IREC before commencing subject recruitment (NHRA-IREC first).

NHRA authorization process flow charts are available in Annex IV.

Article 3: Applicants, Sponsors, Healthcare Institutions and Investigators must comply with regulations established by NHRA, the highest ethical standards of ethics and the ICH-GCP, which may all be revised and/or amended from time to time.

Article 4: A clinical trial must be subject to scientific and ethical review, authorized and conducted in accordance with this Regulation and ICH-GCP.

Article 5: Institutions and hospitals planning to conduct clinical trials must appoint an 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.

a) Specific requirements for Institution's IREC reviewing and approving clinical trials are set in Annex II (document title: Requirements for Independent Research Ethics Committee (IREC) involved in Clinical Trials in the kingdom of Bahrain).

b) Institutions having and IREC that do not meet NHRA minimum requirements, and/or do not comply with ICH-GCP will not be allowed to conduct clinical trials, until they meet such requirements and become compliant.

Article 6: Pharmaceutical, biotechnology, medical device or healthcare industry companies or their legal representatives operating lawfully in the Kingdom of Bahrain, and having a qualified trial monitor, can initiate and conduct clinical trials as study Sponsors-Applicants.

Article 7: Contract Research Organizations (CRO) operating in the Kingdom of Bahrain must be registered and properly licensed by NHRA in order to undertake clinical research activities on behalf of a Sponsor. Licensed CROs can submit application for a clinical trial authorization as an Applicant on behalf of a Sponsor.

Conditions and requirements for registration and licensing of CROs are established by NHRA.

Article 8: Pharmaceutical, biotechnology, medical device or healthcare industry companies, and CROs not registered in the Kingdom of Bahrain, must have an authorized Agent or Legal representative. Such Agent will act in a capacity of a study sponsor and submit an application for a clinical trial authorization as an Applicant. Sponsor's Agent or Legal Representative will bear all legal liabilities on behalf of the study Sponsor.

Clinical Trial Application Process:

Article 9: Sponsors-Applicants must submit to NHRA a valid request for authorization/no objection to conduct a clinical trial or a clinical research study; (i) A Request for Authorization to conduct Phase II-III clinical trial, or (ii) a Request for a No Objection to conduct a Phase IV clinical trial/research.

a) 'Valid request' means that the application must contain all the documents and supporting information required for review.
b) Sponsors-Applicants are responsible for ensuring that all requested supporting documents are submitted to NHRA.

Article 9-1: Applications must be submitted electronically via e-mail: ct@nhra.bh along with all required documents stipulated by the application checklist available on www.nhra.bh

Article 10: Within one month of receiving the application for a clinical trial authorization, NHRA will either; (a) accept the filing of a complete and valid application and initiate the review, (b) issue a letter of deficiency and put the application on-hold, or, (c) refuse the filing in case of an incomplete application, unqualified Applicant or invalid documents. In certain cases of urgency, an expedited review may be granted on a case by case basis.

NHRA encourages sponsors-applicants to contact and interact with NHRA prior to the submission to further clarify NHRA's regulatory requirements regarding specific investigational products or Sponsors-Applicants not registered in the Kingdom of Bahrain.

Article 11: Following acceptance for review of an application, NHRA will render a decision **within 3 months for:**

- International Phase III studies (which involve US FDA (under an approved IND) and/or EMA (under an approved European CTA),
- (i) Phase II International Clinical Trials,
- (ii) Phase III International trials conducted in geographic areas other than USA or EU,
- Phase IV studies

- Studies conducted only in the Kingdom of Bahrain.
- Re-authorization following substantial amendments of approved clinical trials[1]**.**

NHRA will render its decisions based on recommendations of NHRA's Clinical Trial Committee.

Article 12: Sponsors-Applicants must obtain an IREC approval/favorable opinion from each institution in which they plan on conducting the clinical trial/research.

> **Article 12-1:** Sponsors-Applicants planning to conduct a Phase II, III or IV clinical studies and trials with healthcare professionals working in private practice must ensure that all participating investigators have obtained approvals from NHRA-IREC located in the Kingdom of Bahrain. In multi-center trials (nationally/internationally), an IREC review done by the principle hospital which is then agreed upon by other participating institutions may be considered and accepted by NHRA-CTC after NHRA-IREC review and approval.

Article 12-2: Applications and minimum submission requirements to the NHRA-IREC under the current regulation are found in Annex II (document title: **Requirements for (NHRA-IREC involved in Clinical Trials in the Kingdom of Bahrain).**

Article 13: Sponsors-Applicants applying for an authorization to conduct a Phase III clinical trial must submit a letter of approval of at least one of the NHRA-approved independent ethics committee prior to requesting an import license for the investigational products and commencing clinical trial activities.

Application and requirements for obtaining an import license for Investigational Products and Supplies are detailed in article 48.

Article 14: Sponsors planning to conduct a Phase IV study/trial must submit an abbreviated application along with a letter of approval/favorable opinion of at least one Independent Research Ethics Committee & NHRA-IREC. NHRA shall issue a No Objection within 3 months (waiting period) from the date of submission prior to commencing the study.

Should NHRA issue an objection to the conduct of the research within the 3-month waiting period, Sponsors-applicants must notify all /NHRA-IRECs and Investigators of such objection.

Article 15: NHRA will withdraw or suspend a clinical trial authorization, as a whole or in part, if the Sponsor and/or the Applicant fail to comply with any NHRA relevant regulatory requirement.

[1] IRECs must approve substantial Amendments prior to NHRA re-authorization.

Clinical Trial Application Content:

Article 16: Sponsors-Applicants must submit one (01) hard copy (binder) and one (01) copy in an electronic format (CD or other multimedia format) of the submission package at the time a request for a clinical trial authorization is made.

Article 16-1: Submissions for a Clinical Trial Authorization or for a No Objection to conduct a clinical trial shall be organized in **3 P**arts;

- ✓ **Part 1:** Administrative.
- ✓ **Part 2:** Information about the Clinical Study Protocol and Related Documents.
- ✓ **Part 3**[2]**:** Information about the Investigational Product Manufacturing and Labeling (Phase II-III)

Article 16-2: NHRA has established specific requirements for each of the following:

a) Request for authorization (Phase II-III initial application) to conduct a clinical trial
b) Request for re-authorization and approval of amendments (substantial or major)
c) Notification of non-substantial (minor) amendments of an authorized clinical trial
d) Request for a no objection to conduct a Phase IV trial/study
e) Other important notifications

A summary table of applications content is located in Annex III.

Article 17: Sponsors-Applicants must include the following documents for the Initial request for authorization to conduct a Phase II-III clinical trial:

a) Cover Letter signed by an authorized Sponsor Manager which must include a statement of compliance with NHRA regulatory requirements
b) A completed and duly signed Application Form (Annex IV (d))
c) A clinical trial application package submission checklist
d) Proof of clinical trial registration in any WHO-approved clinical trial registries
e) Study Protocol with version number and date, and Clinical Trial Registration Number (the protocol must be signed by all individuals listed in the study team section of the protocol)
f) Protocol Synopsis
g) Investigator's Brochure (or SmPC for IPs registered in the EU or Prescribers Information for IPs registered in the USA).
h) Sample Informed Consent Form(s)[3] and Case Report Forms (data collection instruments)
i) Copy of the Clinical Trial Insurance[4] and Corporate Liability Insurance certificates
j) Information about the terms of payment or compensation to subjects who participate in clinical trial
k) CV's of Investigators and Sponsor's study monitor(s)
l) Financial Disclosure and conflict of interest's statements of Investigators
m) Product Manufacturing Dossier (IMPD for studies involving European Countries, CMC Section of the IND in studies involving the USA).
n) Profile IMP and Series certificate (certificate of analysis, certificate of quality)
o) Sample IMP/IP Labeling and Packaging.
p) Delegation / Letter of Authorization for a CRO registered in Bahrain (if any)
q) Copy of the processing fee Bank Cheque=BD. 500.
r) Copy NHRA-IREC letter (Approval/Rejection)
s) Data Protection document.

[2] Applications for a Phase IV Clinical trials/research are exempt from Part 3.
[3] Both English and Arabic versions of the ICF
[4] In some cases, NHRA may require sponsors-applicants to provide the terms of the insurance policy

Article 17-1: Where the data collected for clinical trial may be stored for use in further clinical trials, a separate application must be submitted to NHRA for review and authorization and the participants must provide full and informed consent.

Article 18: Sponsors-Applicants must include the following documents for the request for re-authorization and approval of substantial amendments of an approved clinical trial by the CT committee:

a) Cover letter requesting a re-authorization for a substantial amendment
b) Summary of the Proposed Amendment(s)
c) List of Modified Documents (document names, versions, dates)
d) Track of Changes of Amendment(s)
e) Signatures of Authorized representatives and/or Investigator of the Amended Document(s)
f) Supportive Information (when applicable)
g) Letter of NHRA-IRECs approval of the substantial amendment(s)
h) Copy of the processing fee Bank Cheque=BD. 350 (70%)

Article 18-1: No amendment to an approved and authorized research protocol may be implemented without consideration and approval by IREC.

Article 18-2: NHRA considers any changes/amendments that are not non-substantial to be substantial, and therefore applicants-sponsors must await NHRA re-authorization of the proposed changes prior to their implementation. Applicants-sponsor may still continue the clinical trial based on the ongoing approved clinical trial protocol and associated documents.

Minor amendments may be implemented as soon as the Investigator receives a letter from IREC confirming that the changes are minimal and non-substantial.

Article 18-3: IREC confirmation of minor amendments must be submitted by Sponsor-Applicant to NHRA along with the yearly progress reports.

Article 18-4: Definitions of what constitutes a substantial amendment can be found in Annex II (document title: Requirements for Independent Research Ethics Committee (IREC) involved in Clinical Trials in the kingdom of Bahrain)

Article 19: Sponsors-Applicants must include the following documents for the NHRA notification of non-substantial amendments of an approved clinical trial:

a) Summary of the minor amendment(s) (non-substantial)
b) List of Modified Documents (if any)
c) Signatures of Authorized representatives and Investigators of the Amended Document(s)
d) Letter of NHRA-IREC/ Chair at each institution acknowledging that the proposed amendment is non-substantial.

Article 19-1: NHRA will not issue a re-authorization or re-approval for non-substantial amendments of authorized clinical trials.

Article 19-2: Sponsors-Applicants may not commence implementing the minimally amended protocol until they receive a letter from the NHRA-IREC Chair/NHRA-CEO acknowledging that the amendment meets the criteria for non-substantial changes to the protocol. In case a clinical trial is conducted at more than one investigational site (institution), all IRECs must accept the changes as non-substantial.

Article 20: Sponsors-Applicants must notify in writing NHRA **within 15 working days following:**

a) First subject enrolled (in Bahrain)
b) Last subject last follows up visit
c) Safety measures, decision to halt/early termination of a trial taken by Sponsor or Investigator
d) Declaration of the end of the clinical trial

Article 20-1: In case of Safety Measures/Serious Event occurring during the conduct of the trial:

i. A sponsor-applicant or investigator must take appropriate urgent safety measures to protect subjects against any immediate hazard where new events relating to the conduct of the trial or the development of the investigational product are likely to affect the safety of the research subjects.
ii. The sponsor must inform NHRA and the Independent Research Ethics Committee concerned of the new events, the measures taken and their plan for further action as soon as possible.

Article 20-2: When the sponsor halts a clinical trial (stops recruitment of new subjects and/or interrupts the treatment of subjects already included in the trial), they shall notify NHRA and IREC within 15 days from the halt of the trial. They may not recommence the trial until IREC has given a favorable opinion/approval and NHRA has not raised grounds for non-acceptance of the restart of the study.

Article 20-3: The sponsor shall ensure that all relevant information about serious adverse reactions and new events likely to affect the safety of the subjects are reported to IREC and NHRA in accordance with the obligations outlined in the current regulation.

Article 20-4: In case of an early termination (premature end) of the trial by the sponsor-applicant, NHRA and IREC shall be notified as soon as possible but at least within 15 days of the early termination, and a detailed written explanation of the reasons for the termination shall be given.

Human Subject Protection:

Clinical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights. The interests of science can never take precedence over the rights and interests of individual research subjects

Article 21: Research involving human subjects must:

a) Be conducted only by individuals with appropriate scientific education, training and qualifications.
b) Be undertaken only if the importance of the objective (potential benefit) outweighs the risks and burdens to the research subjects. Furthermore, Investigators may not conduct a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.
c) Conform to sound scientific principles, adequate and accepted experimental designs, and must address ethical considerations set forth in the ICH/2017.
d) Be reviewed, approved and monitored and submit annually reports by Institution's IREC to NHRA-CTC unless more frequent reports are requested by NHRA depending on the nature of the clinical trial.
e) Be reviewed, approved and review the annually reports by NHRA-IREC.

Article 22: Vulnerable groups and individuals must receive specifically considered protection.

Article 23: Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information according to the Law #30 issue by his Majesty King of Kingdom of Bahrain (Annex I).

Article 24: Participation of research subjects in clinical research must be voluntary and given in a written informed consent. Written informed consent form used by investigators must be approved by both NHRA and IREC(s). No changes can be made to the approved informed consent forms unless both NHRA and IREC(s) approve the changes.

Article 25: Each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study.

Article 26: Potential subjects must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal nor denial to access of care.

International Conference on Harmonization

Article 27: Enrollment of participants should be solely based on the study inclusion criteria and away from any others consideration for race, gender, political orientations or spiritual belief.

Article 28: NHRA has adopted the full text of the ICH-GCP (E6) (full document in Annex V(a)) in its current version and any amended one and makes it a regulatory requirement.

Article 29: Sponsors-Applicants must ensure compliance with all ICH-GCP requirements and document their compliance with the guidelines. Unless specified otherwise in this Bahraini NHRA regulation, Sponsor-Applicants must fulfill their reporting requirements to NHRA-IREC and IREC in accordance to the ICH-GCP guidelines.

Specific reporting requirements and obligations (and timelines) are detailed in Sponsor's Reporting Requirements section of this regulation.

Article 30: Sponsors-Applicants must apply sound scientific principles, rigorous experimental methodology in the design of clinical trials, and take into account the following ICH documents:

a) General Considerations Clinical Trials (ICH E8) (Annex V(b))
b) Structure and Content of Clinical Study Reports (ICH E3)-2018 guidance (Annex V(c))
c) Clinical Trials in Geriatric (ICH E7) and Pediatrics Populations (ICH E11)-2017 (Annex V(d))

Responsibilities of Clinical Trial Sponsors-Applicants/CROs:

Article 31: Sponsors-Applicants must register clinical trial/research studies (all phases including non-interventional observational trials) in a WHO-approved Clinical trial registry portal, prior to commencing the clinical trial. Proof of registration (Universal Trial Number) must be submitted to both NHRA-CTC and NHRA-IREC, and direct link referenced in the Informed Consent Form, to allow research subjects to get access to status and the progress of the study.

Sponsors-applicants must submit to NHRA a printout of the updated webpage of the trial registry along with each annual progress report, reflecting changes that occurred in the clinical trial.

Clinical Trial Insurance

Article 32: Sponsors-Applicants must subscribe to a **clinical trial insurance** to cover research subject's injury or death that is be caused by investigational products and/or clinical trial procedures required by the study protocol.

a) The clinical trial insurance policy must carry adequate coverage and sufficient compensation amounts.
b) For International clinical trials in which research subjects from the Kingdom of Bahrain will be participating, NHRA requires clinical trial insurance compatible with international practice (EMA & FDA)
c) Insurance coverage is mandatory for all CT phases permitted in Kingdom of Bahrain (Phase II, III & IV).
d) As an alternative, a company indemnity in line with the Association of the British Pharmaceutical Industry Clinical Trial Guidelines may be accepted (subject to approval by the Healthcare Institution hosting the study)

Article 33: Sponsors-Applicants must notify NHRA within Ten (10) days of any adverse decision/opinion issued, at any time during the life of the clinical trial, by any regulatory/competent authority and/or Research Ethics Committee regarding the proposed clinical trial.

Article 33-1: For the purpose of Article 32; adverse decision/opinion means, rejection of the proposed clinical trial protocol, negative opinion, objection to the conduct of the proposed clinical trial, clinical holds, regulatory sanction(s), findings of misconduct and/or non-compliance, withdrawal of authorization or approval, suspension of the clinical trial, or any other decision described differently but meaning the same by other competent regulatory authority/ies.

Article 34: Sponsors-Applicants must appoint a monitor to oversee the conduct of the study, support the investigators, and ensure compliance with the study protocol, ICH-GCP and NHRA regulations. It is the obligation of the Sponsor-Applicant to monitor regularly the conduct of trial and to inform NHRA within 2 days of becoming aware of any suspicion of fraud, ethics violation, scientific misconduct, or utilization of the investigational product outside the scope of the study, or the inclusion of a subject without obtaining informed consent.

Article 34-1: The purpose of trial monitoring is to verify that:
a) The rights and well-being of human subjects are protected.
b) The reported trial data are accurate, complete, and verifiable from source documents.
c) The conduct of the investigator follows the approved protocol and all approved amendment(s), if any, in compliance with ICH-GCP, and NHRA regulatory requirement(s).

Article 34-2: The monitor must ensure that:
a) Investigational product(s) are supplied only to subjects who are eligible to receive it and as specified in the approved protocol.
b) Subjects are provided with necessary instructions on properly using, handling, storing, and returning the investigational product(s).
c) The receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
d) The disposition of unused investigational product(s) at the trial sites complies with applicable NHRA requirement(s) and is in accordance with the sponsor's authorized procedures.

Article 34-3: The Monitor must verify all aspects related to the performance of the investigator, during the conduct of the trial and that the investigator has provided all the required reports,

notifications, applications, and submissions, and that these documents are accurate, complete, timely, and legible, dated, and clearly identify the trial.

Article 35: Sponsor-Applicant must obtain a signed written clinical trial/research agreement with the investigator and the head of the healthcare facility/institution in which the clinical trial/study will be conducted. The agreement must be signed by all the parties involved and receiving financial incentives/payments (Principal Investigator, Head of the Institution or his/her authorized representative and the Sponsor-CRO-Sponsor's authorized representative).

a) Signatures of the Principal investigator leading his research team along with that of the head of the institution are sufficient for the validity of the Clinical Trial Agreement; however names of all individuals receiving payments or other financial incentives for their involvement in the proposed research must be listed in the Agreement.
b) Payments made by or on behalf of a sponsor-applicant or CRO to any party not listed in the clinical trial agreement including investigators, sub-investigators, research nurses, or any healthcare professional that may be involved in the clinical trial are strictly prohibited. This requirement does not extend to the normal salary that is paid to research staff.

Article 36: In case of early termination or suspension of a clinical trial, Sponsors-Applicants must fulfill their:

a) Regulatory and safety reporting obligation according to ICH-GCP guidelines until NHRA issues a letter acknowledging satisfactory reporting
b) Contractual obligations stipulated in the Clinical Trial Agreement, including provisions for the management of SAEs as well as Clinical Trial Files and Documents.
c) Accountability obligations regarding Investigational Products

Article 37: Sponsor-Applicant is responsible for implementing and maintaining quality assurance and quality control systems;

Article 37-1: Sponsor-Applicant must carefully select Investigators and Institutions participating in the clinical trial/research and ensure that foreseeable and serious adverse events or injury to research subjects can be adequately managed by the investigator or the participating institution.

Article 37-2: Written SOPs must be established by Sponsor-Applicant and/or CROs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, ICH-GCP, and the applicable regulatory requirement(s).

Article 37-3: Sponsor-Applicant must provide adequate training and support to Investigators and their research teams to enhance compliance with ICH-GCP, the study protocol and regulatory requirements. Training topics should include the protocol and Informed Consent process, IP storage, handling and administration; study specific procedures including any testing or interventions; recording and reporting of Adverse Events; recording and reporting of any issue that impacts on the benefit risk in the study.

Article 37-4: Sponsor-Applicant is responsible for conducting a comprehensive Risk Assessment of all study activities including the suitability of the Investigator, risks associated with the trial population, risks associated with the IP (adverse effects), risks associated with manufacture, packaging, labelling, transport, storage and use/reconstitution/administration of the IP and risks associated with the planned protocol (including any clinical testing or study-

associated interventions). The Risk Assessment should result in a comprehensive risk mitigation strategy. The Risk Assessment should be written and should be available for inspection.

Article 38: Sponsor-Applicant is responsible for securing agreement from all involved parties to ensure:

a. Direct access to all trial- related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by NHRA.
b. Retention of all trial specific essential documents (trial master file) pertaining to the trial for 25 years following the registration of the product in the Kingdom of Bahrain.
c. Notification of NHRA of any change in custody or transfer of ownership of clinical trial data, documents and files.

Responsibilities of Institutions:

Article 39: Healthcare facilities/Institutions planning to conduct Clinical Trial/Research studies regulated by NHRA must:

a) Comply with the current regulation
b) Guarantee that their IREC meet the requirements set forth by NHRA (Annex II document title: Requirements for Independent Research Ethics Committee (IREC) involved in Clinical Trials in the kingdom of Bahrain).
c) Establish quality systems and develop clinical research Standards Operating Procedures (SOPs) for research physicians (investigators) and healthcare professionals involved in research on human subjects. The institution should have SOPs in place which relate to research activity in general. The Sponsor-Applicant is responsible for ensuring that institutional SOPs are adequate for a particular study and for ensuring that any additional or study specific SOPs are in place prior to study start.
d) Possess adequate facilities to conduct the proposed research and are able to manage foreseeable serious adverse events or injuries to research subjects.
e) Manage injuries to research subjects and provide continuous care until subject return to a normal function.
f) Engage in clinical trial/research studies that are (1) authorized by NHRA, (2) approved by their respective IREC, and (3) have a written and signed agreement with the sponsor and investigator.
g) Ensure that the clinical trial insurance policy (when required) is properly endorsed, with adequate in coverage and with sufficient amounts.
h) Guarantee that research subjects are not charged for the cost of Investigational Products, tools or supplies used for the purpose of research. Compliance with Articles 53, 54 and 55 of this regulation is the direct responsibility of the head of institution.
i) Maintain clinical trial/research records for a duration of 25 (twenty-five) years in a facility accessible to NHRA inspectors.
j) Ensure that NHRA is informed within 02 (Two) business days of becoming aware of:
    1. Any occurrence of research misconduct, fraud or violation of NHRA regulations committed by the Principal Investigator or members of his research team. Such reporting could be performed directly by IREC on behalf of institution.
    2. Changes in the IREC composition or functions
    3. Major or repeat complains of research subjects regarding their safety, rights, dignity, privacy, wellbeing or denial of access to care.
k) Ensure that there is insurance or indemnity in place for medical malpractice for Investigators and research staff.

Responsibilities of Investigators:

Article 40: The responsibility for the protection of research subjects must always rest with the research investigator and other health care professionals who are involved in the research, and never with the research subjects, even though they have given consent.

Article 41: It is the duty of the Principal Investigators (PI) who are involved in clinical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of each research subject.

Article 42: Principal Investigator must maintain at all times:

a. Current and valid license to practice in the Kingdom of Bahrain where applicable.
b. Current and valid GCP certification.
c. Current malpractice insurance providing coverage during the period of the clinical trial (Phase II, III and IV). Such insurance will cover any injury to the subject resulting from acts of omissions, errors or gross negligence. Injuries to subjects resulting from the clinical trial product or protocol required procedures are covered by the Sponsor-Applicant insurance.
d. Records of Training(s) provided by the Sponsor-Applicant-CRO.

Article 43: Principal Investigator must consider the ethical, legal and regulatory standards for research involving human subjects that are set in the Kingdom of Bahrain. Principal Investigator should ensure that both the Investigator and research staff are trained in GCP and study procedures before the study starts.

Article 44: Principal Investigator must submit to NHRA-IREC & Institutional IREC timely information, reports and findings provided to him by Sponsor-Applicant, including significant monitoring findings, periodic safety updates or information about serious adverse events occurring at other sites, protocol violations, changes in conflict of interest, non-compliance with regulations and misconduct.

At the end of the study, Principal Investigator must submit a final report to NHRA-IREC & Institutional IREC containing a summary of the study's findings and conclusions.

Article 45: Principal Investigators must disclose to relevant parties, including IREC, NHRA, funder, employer (institution), and sponsor, any perceived potential or actual conflict of interest they may have in relation with the research study.

Safety Reporting:

Article 46: Sponsor-Applicant-CRO and Investigator must inform NHRA IREC and Institutional IREC no within 48 hours or two (02) working days of any serious adverse event (SAE) occurring the clinical trial/research study, whether expected or unexpected.

Article 46-1: Sponsor-Applicant-CRO mandatory safety reporting requirement to NHRA to any SAE reported in any country participating in the clinical study;

i. The two(02) days reporting period applies to SAEs occurring in the Kingdom of Bahrain, and
ii. A 15-day period applies to SAEs occurring anywhere the study is conducted (other participating countries)

Article 46-2: Sponsor-Applicant-CRO must submit an initial report within the mandatory reporting period, and, subsequent interim SAE reports as more information becomes

available to them, until the research subject's SAE reaches a resolution or final status. At its discretion, NHRA may request different reporting timelines for interim reports of specific ongoing SAEs or may request further information on any aspect of the study.

Article 46-3: NHRA recommends the use of latest version of ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting of individual (ICH E2A guidance) (Annex V(e)), and the CIOMS SAE Form for individual case reports (template provided in (Annex V(f)). Other formats may be used by Sponsors-Applicants-CROs; however, the SAE report must include all information that must be captured in the safety report.

Article 46-4: Where clinical trials are blinded and NHRA deems it necessary to access preliminary data for the safety of the study participants, NHRA withholds the right to request a report from the independent data monitoring committee involved in the study.

Article 47: Sponsor-Applicants must compile a listing of serious adverse events (AEs), serious adverse drug reactions (ADRs), suspected adverse events or reactions, and submit to NHRA developmental safety update reports (PSUR), as they become available, and in accordance with ICH safety reporting guidelines (Annex V(e)). The frequency of PSURs must be established by the Sponsor-applicant prior to the commencement of the trial activities but is normally yearly (on the anniversary of the NHRA study approval date). The DSUR must present any issue that impacts on the benefit risk of the study (e.g. new safety issue identified in the study, new scientific data from another study run by the sponsor, new data published in the literature etc.) as well as a comprehensive assessment of the benefit risk.

Import of Investigational Products:

Article 48: Sponsors-Applicants must apply for an import license for Investigational Products (therapy or placebo being tested or used as a reference in a clinical trial), and study specific clinical trials supplies[5]. The application must include the following documents:

a) Status update of IRECs, and Competent Authorities in all countries and institutions in which the clinical trial is taking place. Any adverse response by any IREC or competent/regulatory authority must be addressed.
b) cGMP Certificate of the Manufacturer (if not provided in the initial submission)
c) Authorization of Manufacture issued by the Countries of manufacturer competent authority. If the original letter of Authorization is in a language other than Arabic or English, Applicant must submit a translation of the original with an authentication made by the Embassy of the Kingdom of Bahrain in the respective country.
d) Certificate of analysis/ QA documents
e) Proforma Invoice or Invoice for the Investigational Products and Clinical Trial Supplies (if any)

Exports of Clinical Trial Biological Samples:

Article 49: Clinical Research/Trials projects requiring Investigators to ship biological samples from the Kingdom of Bahrain to other countries for the purpose of analysis of clinical research/trial samples must obtain prior approval from the NHRA IREC & Institutional IREC.

Article 50: NHRA IREC & Institutional IREC letter of approval to export biological samples and bio-specimens, must include specific information regarding the tests to be performed, the name of the

[5] Study supplies that are imported (unavailable in the Kingdom of Bahrain), which the Sponsor intends to provide to Investigators to complete the required study protocol tests and procedures.

foreign institution performing the analysis, and any specific conditions that investigators/institutions must comply with prior to shipping the samples. The receiving institution must give a written undertaking that the samples will only be used in accordance with the original protocol and study approvals and in accordance with the informed consent given by research subjects.

Article 51: No personal identifying information of research subjects can be used in the labeling of biological samples (bio-specimens) obtained from research subjects. Research subjects must have given informed consent for samples to be sent to other countries and for any planned analysis.

Investigational Product Management Policy

It is the process of storing, handling, and dispensing of any drug used for the purpose of research (Phase II and III only).

Article 52: Policy Summary

In order to ensure subject safety and the reliability and robustness of data from clinical trials, there should be clear arrangements for traceability, storage, return and destruction of investigational medicinal products, depending on the nature of the clinical trial.

- Investigational products shall be shipped, handled, stored and distributed to the investigational sites in compliance with NHRA requirements for Imports of Pharmaceutical Drugs, Medical and Devices, and in accordance with generally accepted good shipping, storage and distribution practices and standards.
- The sponsor must ensure that where possible, IMPs' stability data is easily accessible to guide and comply with storage requirements. To facilitate appropriate handling of temperature excursions, where IMPs are stored, a standardized form must exist which allows the investigators to document details of possible temperature excursions and deduce shelf-life expectancy, reliability and safety of the IMPs.
- Investigational products/drugs shall be used only under the direct supervision of the principal investigator and must have prior authorization and approval from both NHRA and IREC, respectively.
- Investigational medicinal products should be appropriately labelled in order to ensure subject safety and the reliability and robustness of data generated in clinical trials, and also to allow for the safe handling and distribution of those products to clinical trial sites. Where the investigational medicinal product has already been placed on the market as an authorised medicinal product, as a general rule no additional labelling should be required for clinical trials that do not involve the blinding of the label.
- Informed Consent shall be properly obtained, and the informed consent form shall be filled and signed in a manner that is compliant with this regulation.
- Institution's pharmacy shall stock and dispense investigational products/drugs in accordance with written directions submitted by the principal investigator and/or Sponsor of the study.
- The receipt, utilization and disposition of all investigational products shall be properly recorded.
- Unused/damaged Investigational products shall be returned to the Sponsor or destroyed in compliance with NHRA requirements.

Article 52-1: At the discretion of institution, a qualified NHRA pharmacist must be involved in the management of Investigational Medicinal Products.

Charging research subjects in clinical trials:

Charging for Investigational Products and clinical trial supplies-tools:

Article 53: Investigational products shall be provided to institutions and research subjects free of charge. Charging research subjects, for the use of unregistered products (Phase II and III) or registered in the Kingdom of Bahrain being investigated in a clinical trial (Phase IV trials) is considered an illegal sale of such product(s).

Article 54: NHRA IREC & Institution's IREC shall ensure that the:

(a) Sponsors-applicants of clinical trials requiring the use of study specific supplies or tools that are not part of the standard of care shall not charge institutions or research subjects for the tools or supplies necessary to conduct clinical trials.
(b) Already used by the research subject and
(c) Participation of the research subject is not conditioned by the purchase of any study specific tools or supplies.

Charging for tests and procedures:

Article 55: Sponsor-Applicants and/or Institutions-Investigators shall not charge research subjects for protocol required tests and procedures that are not part of the standard of care or routine practice.

Fraud, Violations and Misconduct

Article 56: Sponsors-Applicants, Principal Investigators, IRECs, and Institutions/Healthcare facilities managers shall upon becoming aware, report to NHRA within (02) days, any and all occurrences of serious deviations, serious and continuous non-compliance, fraud and misconduct.

Article 57: NHRA and/or NHRA IREC & Institutional IREC will suspend Investigators' research privileges at the institution/healthcare facility, in the event of deviations/ non-compliance / fraud and research misconduct till the investigation are completed.

Article 58: NHRA shall undertake all necessary regulatory sanctions and/or legal actions against Sponsor-Applicants, CROs, Investigators, IREC members, and Institutions/healthcare facilities who fail to comply with the reporting requirements to NHRA of ethical violations, fraud and misconduct.

Study/Activity Reports to NHRA:

Sponsors-Applicants-CROs Reports

Article 59: Sponsors-Applicants-CROs conducting Phase II-III / Phase IV trials must submit to NHRA annual progress reports, detailing the progress made in the conduct of the clinical trial. The goal is to inform NHRA about:

i. the conduct of the trial and the progress made of the trial at the investigational site(s)
ii. any potential changes in the ethical or safety considerations,
iii. regulatory changes that may have occurred at other participating countries, and
iv. any challenges the sponsor-applicant is facing while conducting the clinical trial/research.
v. level (screening and recruitment activities),
vi. the use of the IP/IMP, minor amendments, or
vii. changes that may have occurred in the Kingdom of Bahrain,
viii. protocol deviations,
ix. SAEs or Repeat Unanticipated AEs.
x. any new safety data related to the use of the registered product being investigated.

Article 59-1: When reporting protocol deviations to NHRA, Sponsors-Applicants-CROs must ensure the reports include, the investigation undertaken for the deviation, any comments from the investigators and the corrective/remedial measures implemented to prevent the reported deviations.

Article 60: Sponsors-Applicants-CROs must submit to NHRA within six (06) months of the end of the Phase II-III / Phase IV clinical trial activities a study final report. NHRA recommends the use of the latest version of ICH guidance on the Structure and Content of Study Reports (ICH E3 guidance) (Annex V(c)).

Article 61: Sponsors-Applicants-CROs conducting Phase IV studies may submit a less detailed report. However, the structure must be respected and preserved.

Institutions Reports

Article 62: IRECs of institutions and healthcare facilities conducting clinical trials/research studies regulated by NHRA must submit an annual activities report. The report must address the requirements set forth in Annex II, document title: Requirements for Independent Research Ethics Committee (IREC) involved in Clinical Trials in the kingdom of Bahrain.

Article 62-1: IRECs annual reports must list or discuss:

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.

Clinical Study Files and Records:

Article 63: Sponsors-Applicants, CROs and Investigators shall maintain any and all records, files, documents and data on NHRA regulated clinical trials/research in specific study files.

Article 63-1: The list of essential documents that must be maintained by Sponsors-Applicants-CROs, Investigators, and IRECs can be found in the ICH guidance document on Good Clinical Practice (ICH E6 Guidance) (Annex V(a)).

Article 63-2: Sponsors-Applicants, CROs and IRECs and Investigators shall maintain Study Files and IREC records of their activities for Twenty-Five (25) years from the date of the declaration of the end of Phase II-III and Phase IV clinical trials, and

Article 63-3: Institutions shall ensure that changes in IRECs' composition do not result in a loss of files, records or documents.

Article 63-4: IRECs' records, files and document must be transmitted in a timely manner to newly appointed IRECs' Chairs, and files transmittal records must be maintained.

Inspections

Article 64: NHRA may inspect Sponsors-Applicants-CROs, Investigators and IRECs facilities. Sponsors-Applicants-CROs, Investigators and IRECs must be inspection-ready at all times during the planning, conduct or close of an NHRA regulated clinical trial/research.

Article 64-1: NHRA's inspections of clinical trials/research can be conducted at any time during the conduct or after completion of the trial, with or without notice from NHRA.

Article 64-2: NHRA Inspectors shall present their credentials to representatives of Sponsors-Applicants-CROs, Investigators or IRECs, and fulfill their duties as determined and ordered by NHRA's CEO.

Article 64-3: Sponsors-Applicants-CROs, Investigators and IRECs' Chairs shall give NHRA inspectors access to their facilities and offices, and any document(s), file(s) or record(s) sought by Inspectors.

Article 65: NHRA shall issue an inspection report to Sponsors-Applicants-CROs, Investigators and/or IRECs highlighting key significant findings and follow up actions.

Article 66: Sponsors-Applicants-CROs, Investigators and/or IRECs shall provide NHRA with responses and comments to Inspectors' findings within Two weeks (02) weeks.

Article 67: if NHRA's inspection report result in findings requiring corrective or preventative actions, Sponsors-Applicants-CROs, Investigators and IRECs Chair shall provide NHRA within Five (05) working days a written commitment and a detailed plan to implement actions required by NHRA.

Article 68: Institutions must ensure compliance with Articles 01-67 of the current regulation, and document the arrangements with the Sponsor-application for the provisions of investigational products, study required tools and supplies as well as charges for protocol required tests and procedures in the clinical trial agreement.

Annex I: Law #30 issued by his Majesty the King of Kingdom of Bahrain

Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20I%20Law%20No.30%20issued%20by%20his%20Majesty%20King%20of%20Kingdom%20of%20Bahrain.pdf

Annex II: Standards & Requirements for Independent Research Ethics Committees

Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20II%20Standards%20and%20Requirements%20for%20IRECs.pdf

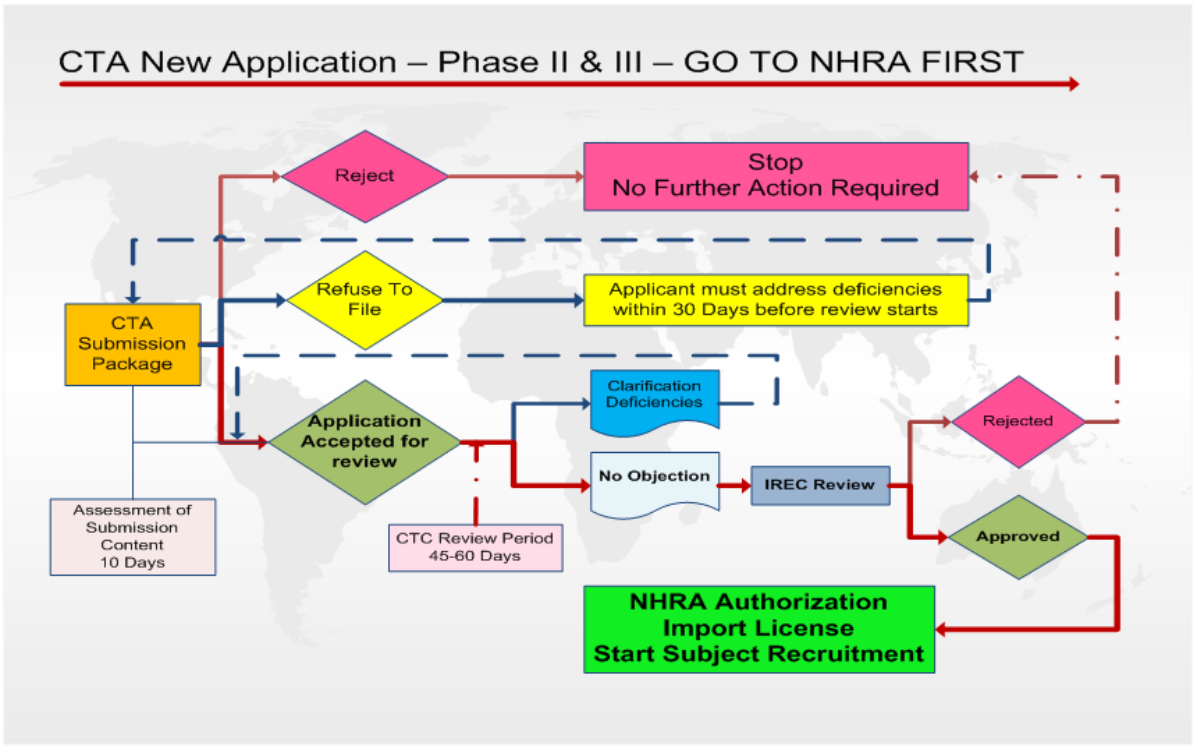
Annex III: Summary Clinical Trials Application Content

Accessible via:

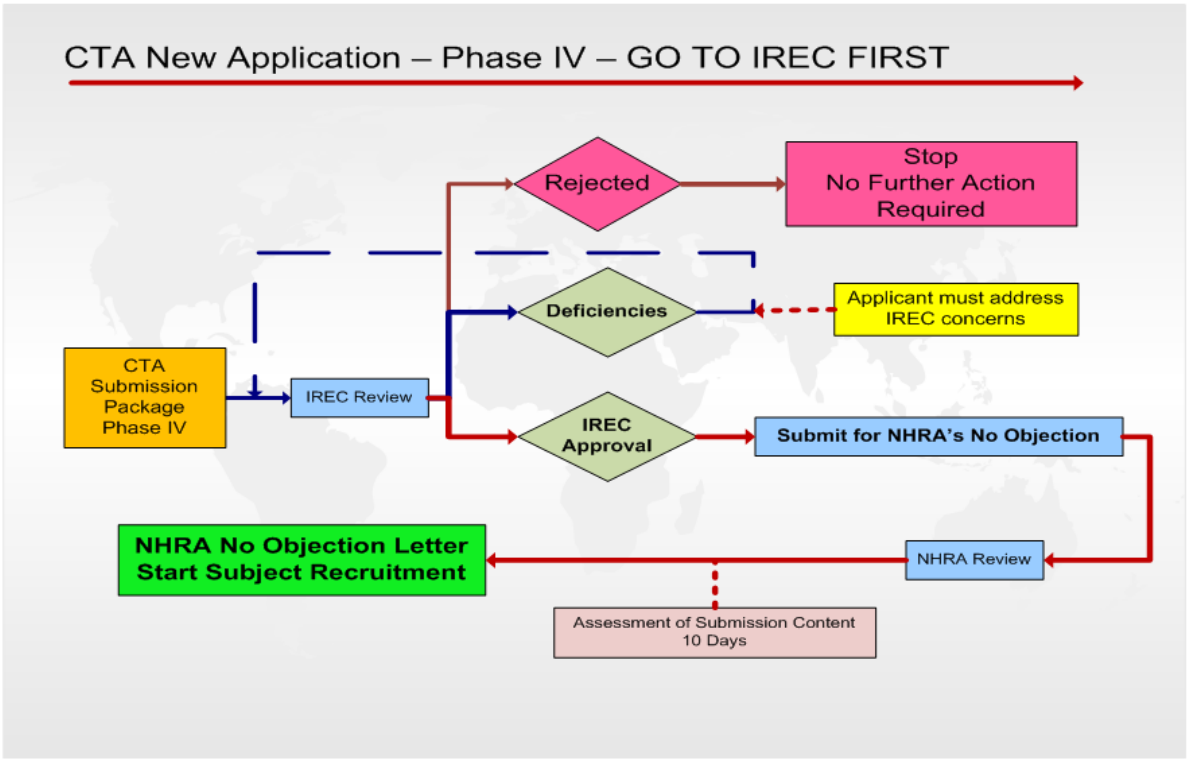
https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20III%20Summary%20Clinical%20Trials%20Application%20Content.pdf

Annex IV

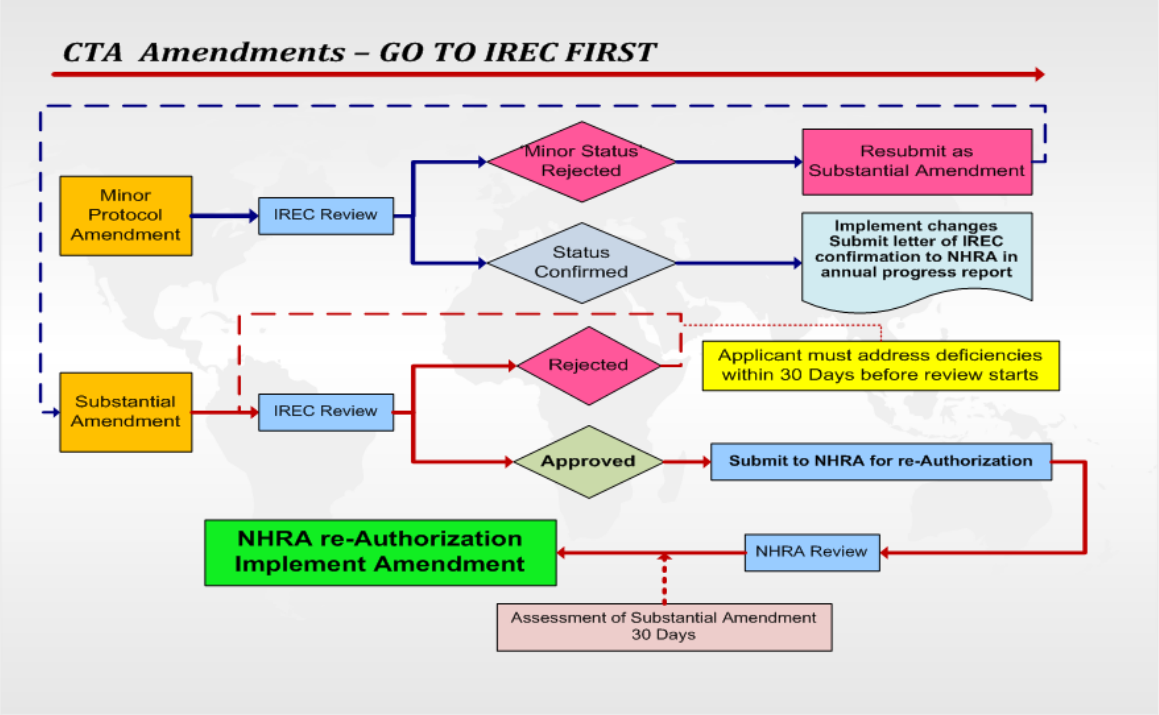
a) CTA Process Flow Chart (Phase II-III)



b) CTA Process Flow Chart (Phase IV)



c) CTA Process amendments of approved trials



d) CT Application Form

Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20IVd%20NHRA%20CT%20Application%20Form.pdf

Annex V: Important ICH Documents

a) Good Clinical Practice (ICH E6)

ICH E6 Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Va%20Good%20Clinical%20Practice%20(ICH%20E6)(R2).pdf

b) General Considerations for Clinical Trials (ICH E8)

ICH E8 Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Vb%20General%20considerations%20for%20Clinical%20Trials%20(ICH%20E8).pdf

c) Structure and Content of Clinical Study Reports (ICH E3)

ICH E3 Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Vc%20Structure%20and%20Content%20of%20Clinical%20Study%20Reports%20(ICH%20E3).pdf

d) Clinical Trials in Geriatric (ICH E7) and Pediatric Populations (ICH E11)

ICH E7 Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Vd%20Studies%20in%20support%20of%20special%20populations%20-%20Geriatrics%20(ICH%20E7).pdf

ICH E11 Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Vd%20Clinical%20Investigation%20of%20Medicinal%20Products%20in%20Pediatric%20Population%20(ICH%20E11)(R1).pdf

e) ICH Guidelines for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (E2A)

ICH E2A Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Ve%20Guidelines%20for%20Clinical%20Safety%20Data%20Management%20-%20Definitions%20and%20Standards%20for%20Expedited%20Reporting%20(ICH%20E2A).pdf

f) CIOMS Safety Reporting Form

Accessible via:

https://www.nhra.bh/Departments/CPD/ct/MediaHandler/GenericHandler/documents/departments/CT/Regulation/Annex%20Vf%20CIOMS%20Safety%20Reporting%20Form.pdf

Appendix 1: Clinical Trials Algorithm

IS IT A CLINICAL TRIAL TO BE CONSIDERED BY NHRA?

This algorithm and its endnotes will help you answer that question. Please start in column A and follow the instructions. Additional information is provided in the notes at the end of the table. If you have doubts about the answer to any of the questions contact the NHRA clinical trials unit azhar.naseeb@nhra.bh.

A	B	C	D	E
A CLINICAL TRIAL OF A MEDICINAL PRODUCT?				**A NON-INTERVENTIONAL CLINICAL TRIAL?**
Is it an intervention or a medicinal product (MP)?	**Is it not a medicinal product?**	**What effects of the treatment/ medicine**	**Why are you looking for those effects?**	**How are you looking for those effects?**
If you answer no to all the questions in column A, the activity is not a clinical trial on a MP. If you answer yes to any of the questions below go to column B.	If you answer yes to the question below in column B the activity is not a clinical trial on a MP. If you answer no to this question below go to column C.	If you answer no to all the questions in column C the activity is not a clinical trial under the scope of NHRA guidelines. If you answer yes to any of the questions below go to column D.	If you answer no to all the questions in column D the activity is not a clinical trial under the scope of NHRA guidelines. If you answer yes to any of the questions below go to column E.	If you answer yes to all these questions the activity is a non-interventional trial which is outside the scope of of NHRA guidelines. If your answers in columns A,B,C & D brought you to column E and you answer no to any of these questions the activity is a clinical trial within the scope of the of NHRA guidelines. .
A.1 Is it a substance[i] or combination of substances presented as having properties for treating or preventing disease in human beings? A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose? A.3 Is it an active substance in a pharmaceutical form?	B.1 Are you only administering any of the following substances? • Human whole blood[ii]; • Human blood cells; • Human plasma[iii]; • Tissues except a somatic cell therapy medicinal product[iv]; • A food product[v] (including dietary supplements) not presented as a medicine; • A cosmetic product[vi] • A medical device	C.1 To discover or verify/compare its clinical effects? C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics? C.3 To identify or verify/compare its adverse reactions? C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?	D.1 To ascertain or verify/compare the efficacy[vii] of the medicine? D.2 To ascertain or verify/compare the safety of the medicine?	E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in Bahrain? E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation? E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol[viii]? E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study? E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice? E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

[i] Substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being
[ii] This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process
[iii] This does not include human plasma being used as a disease modifying
[iv] Somatic cell therapy medicinal products use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means.
[v] Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.
[vi] The Cosmetic Directive 76/768/EC, as amended harmonises the requirements for cosmetics in the European Community. A "cosmetic product "means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.
[vii] Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.
[viii] Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice.