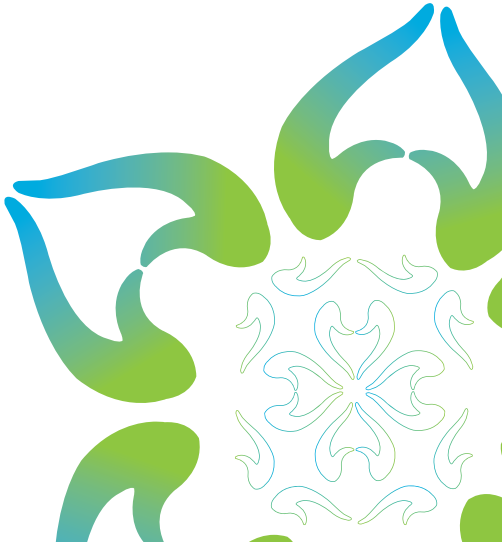
nhra BAHRAIN

مملكة البحرين
Kingdom of Bahrain

الهيئة الوطنية لتنظيم المهن والخدمات الصحية
NATIONAL HEALTH REGULATORY AUTHORITY

A SHORT GUIDE TO THE PROCEDURE FOR A CLINICAL TRIAL APPLICATION IN THE KINGDOM OF BAHRAIN

Version 1 - June 2017



DEFINITIONS

Clinical Trial (CT): 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 trial phases

Phase	Primary goal	Participants	Duration	Studies	Authorized in Kingdom of Bahrain (Yes/No)
Phase I	Testing of drug on healthy volunteers for dose-ranging	20-100 healthy volunteers	Several months	Safety & dosage	No
Phase II	Testing of drug on patients to assess efficacy and side effects	100-300	Months up to two years	Efficacy	Yes
Phase III	Testing of drug on patients to assess efficacy, effectiveness and safety	300-3,000	One to Four Years	Safety, efficacy & dosing	Yes
Phase IV	Post-marketing surveillance – watching drug use in public	1,000/s	One(1) Years +	Safety, efficacy, & cost effectiveness	Yes

A 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:

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

Intervention: includes both physical procedures by which data are gathered (for example, collection of blood) and manipulations of the subject or the subject's environment that are performed for research purposes.

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: 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.
Valid request: means that the application must contain all the documents and supporting information required for review.

IREC: Independent Research Ethics Committee: 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.

NHRA ECPH: NHRA Ethics Committee for Private Hospitals: is a 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 curries out in private hospital in Kingdom of Bahrain. Such NHRA ECPH 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.

INTRODUCTION

NHRA has established clinical trials/research regulatory requirements that 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).

This short guide demonstrates the Application process and procedures to authorize for conducting clinical trials in the Kingdom of Bahrain. For complete guide please visit our webpage: www.nhra.bh

LEGAL AUTHORITY

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.

THE APPLICATION PROCESS

Phase I clinical trials:

Currently Not Authorized in the Bahrain.

Phase II & III Clinical trials: Application Process

All required forms and documents shall be submitted directly or by mail to the office of the Chief Executive Officer (CEO); Sponsors must submit:

a. A cover letter to the office of the NHRA-CEO, along with a duly completed, dated and signed clinical trial application form; Sponsors-Applicants are responsible for ensuring that all requested information and supporting documents are submitted to NHRA.
(Form available on www.nhra.bh)

b. Two (02) hard copies (2 binders) 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.

c. Submissions for a Clinical Trial Authorization or for a no objection to conduct Phase II-III clinical trial shall be organized in 4 Parts;
Part 1: Administrative.
Part 2: Information about the Clinical Study Protocol and Related Documents.
Part 3: Information about the Investigational Product Manufacturing and Labeling (Phase II-III)
Part 4: Clinical Trial Agreement, Financial Disclosures, Investigator's Statement, Proforma Invoices for IP/IMP and study tools and supplies (if any)

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

1. Cover Letter signed by an authorized Sponsor Manager which must include a statement of compliance with NHRA regulatory requirements.
2. A completed and duly signed Application Form
3. A clinical trial application package submission checklist
4. Proof of clinical trial registration in any WHO-approved clinical trial registries
5. 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)
6. Protocol Synopsis
7. Investigator's Brochure
8. Sample Informed Consent Form(s) and Case Report Forms (data collection instruments
9. Copy of the Clinical Trial Insurance and Corporate Liability Insurance certificates
10. Information about the terms of payment or compensation to subjects who participate in clinical trial
11. CV's of Investigators and Sponsor's study monitor(s)
12. Financial Disclosure and conflict of interests statements of Investigators
13. Product Manufacturing Dossier (IMPD for studies involving European Countries, CMC Section of the IND in studies involving the USA).
14. Profile IMP and Series certificate (certificate of analysis , certificate of quality)
15. Sample IMP/IP Labeling and Packaging.
16. Delegation / Letter of Authorization for a CRO registered in Bahrain (if any)
17. Copy the Clinical Trial Agreement with Investigators and Institutions

PHASE II &III CLINICAL TRIALS: DECISION PROCESS

Application decisions

Within 10 business days of receiving the application for a clinical trial authorization where contents assessment take a place, (NHRA will render its decisions based on recommendations of NHRA's Clinical Trial Committee(CTC)) and will either:

1. Accept the application and review process will be initiated,
2. Issue a letter of deficiency and put the application on-hold, until applicant complete the deficiencies, if acceptance is decided then review will take a place, Applicant must address deficiencies within 30 days before review start.
3. Refuse the application in case of an incomplete application, unqualified applicant or invalid documents)

Acceptance processes

No objection letter will be issue by NHRA. NHRA will render a final decision within:

1. 45 days for International Phase III study (which involve US FDA (under an approved IND) and/or EMA (under an approved European CTA),
2. 60 days for:
   (i) Phase II International Clinical Trials,
   (ii) Phase III International trials conducted in geographic areas other than USA or EU,
3. 90 days including studies conducted only in the Kingdom of Bahrain.

The process includes the following steps:

1. Applicant gets IREC/NHRA ECPH approval.
2. NHRA issue authorization for import license for CT Product after receiving IREC/NHRA ECPH approval letter. If IREC/NHRA ECPH rejects CT then applicant re-submit CTA to NHRA.
3. Applicant start subject recruitment.

Important Notes

- 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.
- Sponsors-Applicants must obtain an IREC/NHRA ECPH approval/favorable opinion from each institution in which they plan on conducting the clinical trial/research.
- Sponsors-Applicants planning to conduct a Phase II & III clinical studies and trials with healthcare professionals working in private practice must ensure that all participating investigators have obtained approvals from IREC/NHRA ECPH located in the Kingdom of Bahrain.
- 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.
- 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.

PHASE IV CLINICAL TRIALS: APPLICATION PROCESS

a. Applicant must submit request letter to the IREC/NHRA ECPH(via CTC Chairman) to obtain approval to conduct a Phase IV clinical trial/ clinical research study.

b. IREC/NHRA ECPH will either:

c. Accept the filing of a complete and valid application and initiate the review, approval is granted then applicant must get access to NHRA to get the no objection letter.

d. Issue a letter of deficiency and applicant must address IREC/NHRA ECPH concerns to NHRA when submit application.

e. Issue a letter of rejection, then no further action will be required.

f. In case approval granted by IREC/NHRA ECPH then applicant submit request letter to office of the National Health Regulatory Authority (NHRA)-CEO

g. Fill a valid application form; Sponsors-Applicants are responsible for ensuring that all requested supporting documents are submitted to NHRA.

h. Applications must be submitted/mailed: Sponsors-Applicants must submit two (02) hard copies (2 binders) 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.

i. Submissions for a Clinical Trial Authorization or for a No Objection to conduct a clinical trial shall be organized in 3 Parts;

Part 1: Administrative.

Part 2: Information about the Clinical Study Protocol and Related Documents.

Part 3: Clinical Trial Agreement, Financial Disclosures, Investigator's Statement, Proforma Invoices for IP/IMP and study tools and supplies (if any)

j. Sponsors-Applicants must include the following documents for the Initial request for authorization to conduct a Phase IV clinical trial:

1. Cover Letter signed by an authorized Sponsor Manager which must include a statement of compliance with NHRA regulatory requirements.
2. A completed and duly signed Application Form
3. A clinical trial application package submission checklist
4. Proof of clinical trial registration in any WHO-approved clinical trial registries
5. 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)
6. Sample Informed Consent Form (ICF) and Case Report Forms (CRF)data collection instruments)
7. Signature page of investigators and sponsors on protocol and IB
8. Copy of a valid license of investigator.
9. CV's of Investigators and Sponsor's study monitor(s)
10. Financial Disclosure and conflict of interests statements of Investigators
11. Delegation / Letter of Authorization for a CRO registered in Bahrain (if any)
12. IREC Letter of Approval
13. Copy the Clinical Trial Agreement with Investigators and Institutions

PHASE IV CLINICAL TRIALS: DECISION PROCESS

1. Within 10 business days of receiving the application for a clinical trial authorization where contents assessment take a place, NHRA(NHRA will render its decisions based on recommendations of NHRA's Clinical Trial Committee) and will either:
   - Accept the filing of a complete and valid application and review process will be initiated,
   - Issue a letter of deficiency and put the application on-hold, until applicant complete the deficiencies, if acceptance is decided then review will take a place,
   - Refuse the filing in case of an incomplete application, unqualified applicant or invalid documents); Applicant must address deficiencies within 30 days before review start.

2. No objection letter will be issue by NHRA. NHRA will render a final decision within:
   - 45 days for International Phase III study (which involve US FDA (under an approved IND) and/or EMA (under an approved European CTA),
   - 60 days for:
     -Phase II International Clinical Trials,
     -Phase III International trials conducted in geographic areas other than USA or EU,
   - 90 days including studies conducted only in the Kingdom of Bahrain.

3. NHRA issue no objection letter after receiving IREC/NHRAECPH approval letter. If IREC/NHRAECPH rejects CT then applicant re-submit CT Application to NHRA.

4. Applicant start subject recruitment.

AMENDMENTS APPLICATION FOR AN APPROVED CLINICAL TRIAL APPLICATION PROCESS

a. Applicant must submit request letter to the IREC/NHRAECPH to obtain approval for substantial amendment for an approved CT. IREC/NHRAE-CPH will either:
    1. accept filing and approved the substantial amendment,
    2. IREC/NHRAECPH issue a letter of rejection, then applicant must re-submit request to same IREC/ NHRAECPH for their re-review and approval.

AMENDMENTS: DECISION PROCESS

a. applicant submit request letter to office of the NHRA-Chief Executive Officer in NHRA, and Sponsors-Applicants must include the following documents for the request for re-authorization and approval of substantial amendments of an approved clinical trial:
    1. Cover letter requesting a re-authorization for a substantial amendment
    2. Summary of the Proposed Amendment(s)
    3. List of Modified Documents (document names, versions, dates)
    4. Track of Changes of Amendment(s)
    5. Signatures of Authorized representatives and/or Investigator of the Amended Document(s)
    6. Supportive Information (when applicable)
    7. Letter of IRECs/ NHRAECPH approval of the substantial amendment(s).

b. within thirty(30)business days of receiving the application for a clinical trial re-authorization following substantial amendments of approved clinical trials where contents assessment take a place, NHRA will render its decisions based on recommendations of NHRA's Clinical Trial Committee and will either:
    1. accept the filing of a complete and valid application and review process will be initiated,
    2. issue a letter of deficiency and put the application on-hold, until applicant complete the deficiencies, if acceptance is decided then review will take a place,
    3. refuse the filing in case of an incomplete application, unqualified applicant or invalid documents. Applicant must address deficiencies within 30 days to IRECs/NHRAECPH before review start.

c. Incase of acceptance and reviewing the content of the file, the re-authorization letter will be issued by NHRA.

d. NHRA will render a final decision within:
   1. 45 days for International Phase III study (which involve US FDA (under an approved IND) and/or EMA (under an approved European CTA),
   2. 60 days for:
   (i) Phase II International Clinical Trials,
   (ii) Phase III International trials conducted in geographic areas other than USA or EU,
   3. 90 days including studies conducted only in the Kingdom of Bahrain.

e. applicant start subject recruitment.

IMPORTANT NOTES

a. No amendment to an approved and authorized research protocol may be implemented without consideration and approval by IREC /NHRAE-CPH.

b. 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.

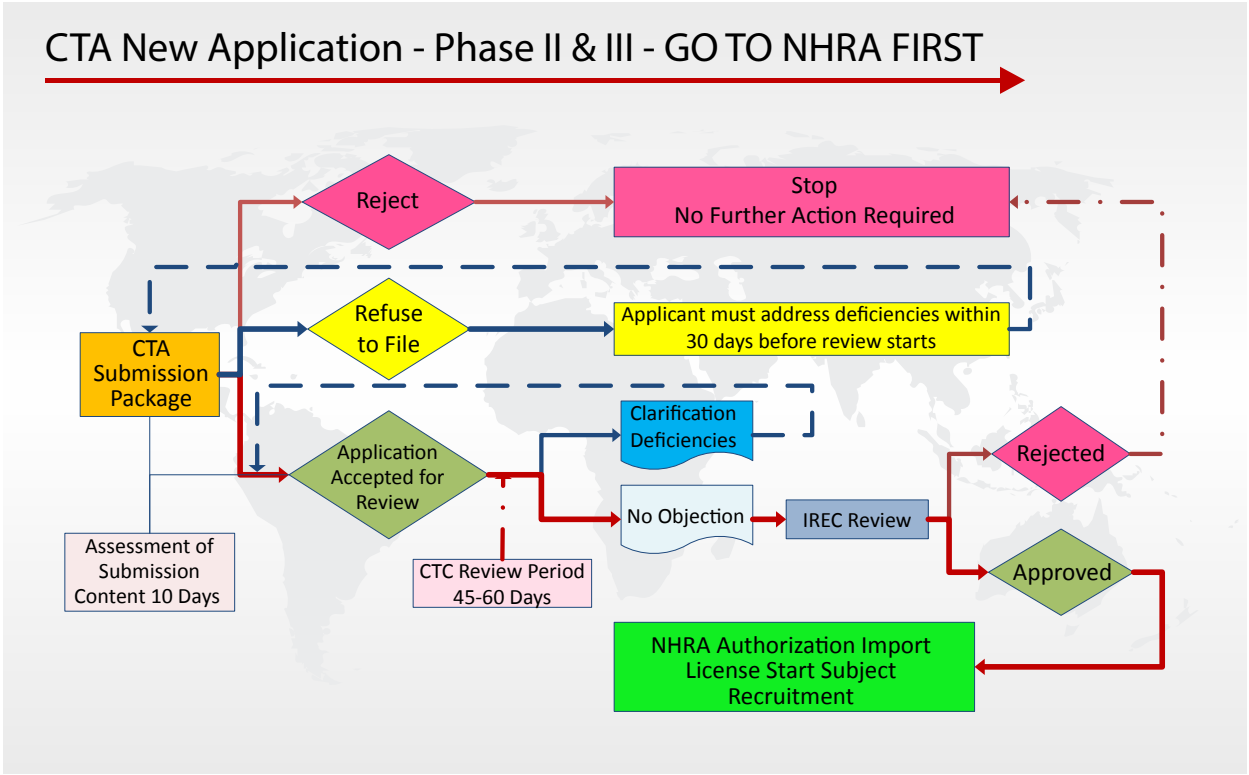
c. Minor amendments may be implemented as soon as the Investigator receives a letter from IREC/ NHRAECPH confirming that the changes are minimal and non-substantial.

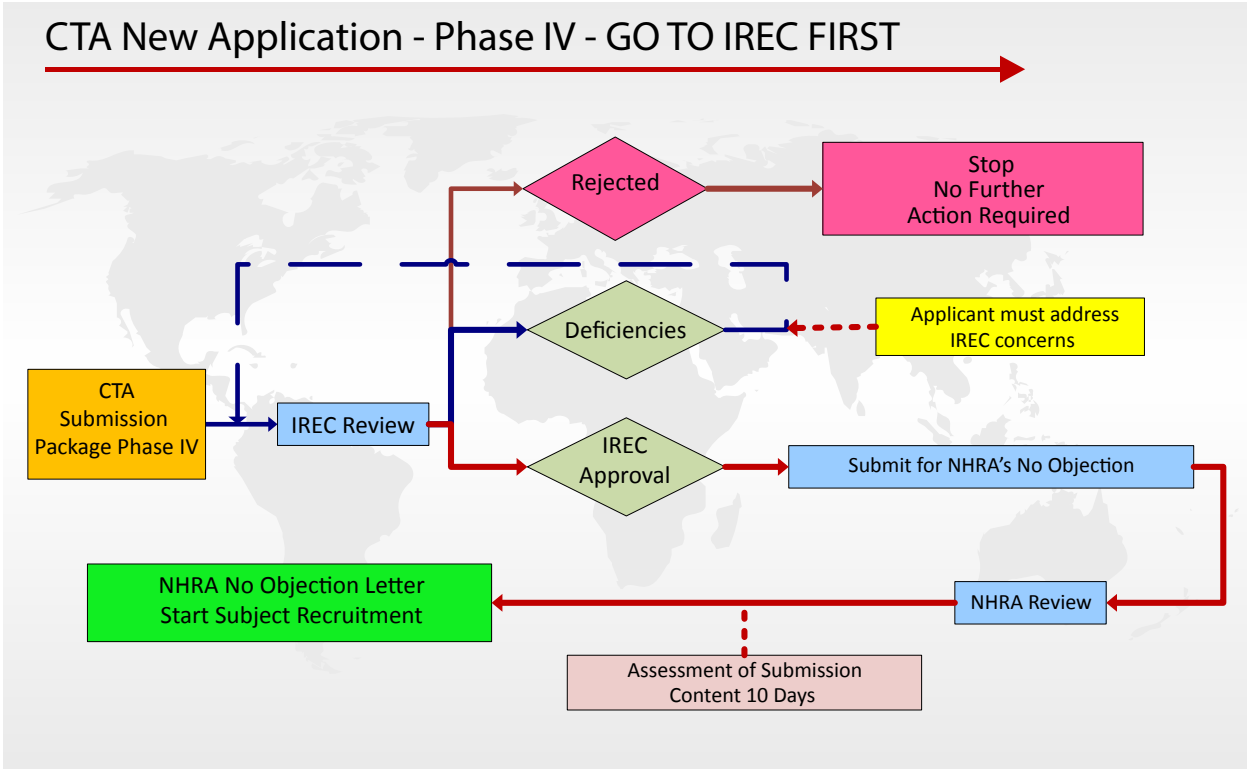
d. IREC/NHRAECPH confirmation of minor amendments must be submitted by Sponsor-Applicant to NHRA along with the yearly progress re-ports.

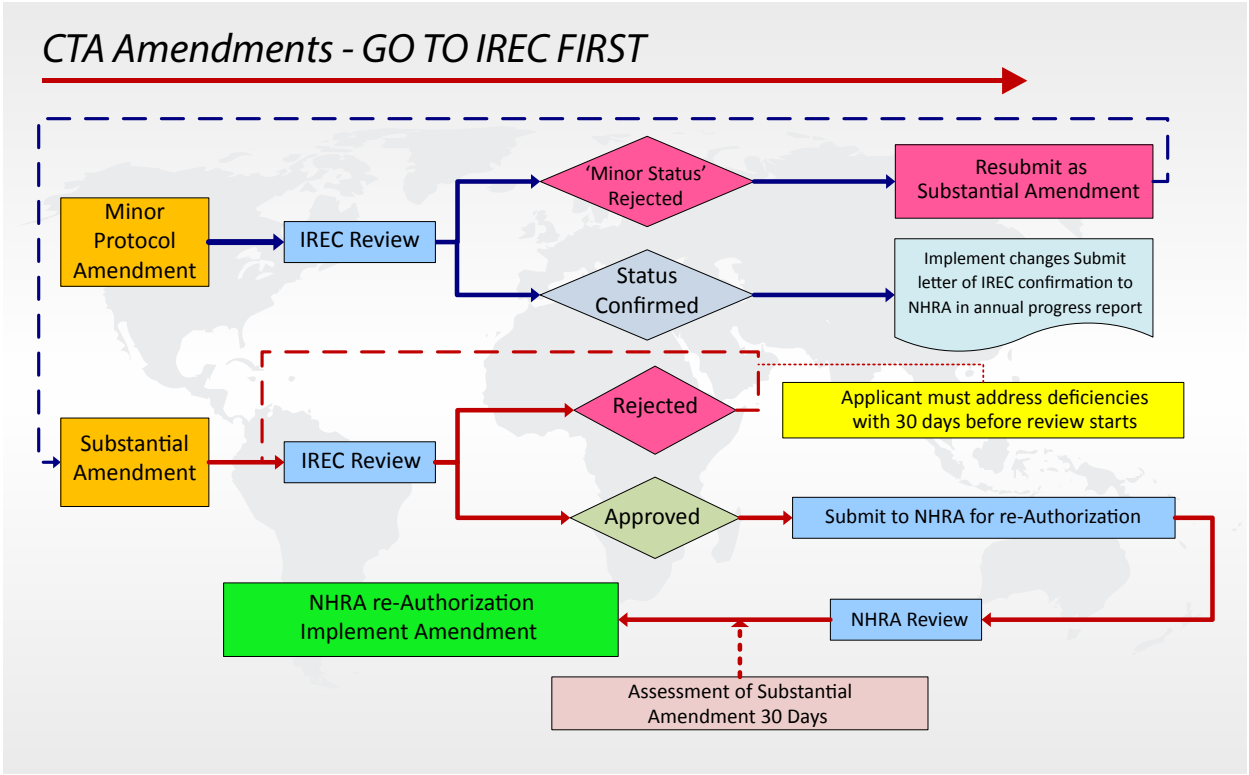
e. Sponsors-Applicants must include the following documents for the NHRA notification of non-substantial amendments of an approved clinical trial:

    1. Summary of the minor amendment(s) (non-substantial)
    2. List of Modified Documents (if any)
    3. Signatures of Authorized representatives and Investigators of the Amended Document(s)
    4. Letter of IREC/ NHRAECPH Chair at each institution acknowledging that the proposed amendment is non-substantial.

f. 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.


CTA New Application - Phase II & III - GO TO NHRA FIRST
Reject
Stop
No Further Action Required
Refuse
to File
Applicant must address deficiencies within
30 days before review starts
CTA
Submission
Package
Clarification
Deficiencies
Application
Accepted for
Review
Rejected
No Objection
IREC Review
Approved
Assessment of
Submission
Content 10 Days
CTC Review Period
45-60 Days
NHRA Authorization Import
License Start Subject
Recruitment


CTA New Application - Phase IV - GO TO IREC FIRST
Rejected
Stop
No Further
Action Required
Deficiencies
Applicant must address
IREC concerns
CTA
Submission
Package Phase IV
IREC Review
IREC
Approval
Submit for NHRA's No Objection
NHRA No Objection Letter
Start Subject Recruitment
NHRA Review
Assessment of Submission
Content 10 Days


CTA Amendments - GO TO IREC FIRST
Minor Protocol Amendment
IREC Review
'Minor Status' Rejected
Resubmit as Substantial Amendment
Status Confirmed
Implement changes Submit letter of IREC confirmation to NHRA in annual progress report
Substantial Amendment
IREC Review
Rejected
Applicant must address deficiencies with 30 days before review starts
Approved
Submit to NHRA for re-Authorization
NHRA re-Authorization Implement Amendment
NHRA Review
Assessment of Substantial Amendment 30 Days

With Complement

Clinical Trial Committee

1st Edition – 2017

Kingdom of Bahrain

National Health Regulatory Authority
Building No. 2420 , Road No. 2831, Block No. 428
Al-Seef District, P.O. Box 11464
Manama, Kingdom of Bahrain
Tel: +973 17 113 333
Fax: +973 17 113 270

www.nhra.bh