DRAFT GUIDELINES FOR CONDUCT OF CLINICAL RESEARCH IN PAKISTAN.

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Drug Regulatory Authority of Pakistan
Islamabad - Pakistan

1. HISTORY

This is the second edition of these guidelines.

2. APPLICATION

These guidelines are applicable on the Sponsors, Researchers, Investigators, Contract Research Organization (CROs) and Bio-Analytical Laboratories, who intends to submit a new application or involved in conduct of Clinical Trial/Research or its subsequent submissions under the regulatory scope of the Bio-Study Rules, 2017.

3. PURPOSE

This document is intended to provide general guidance to applicants in making new applications for Clinical Trials/Research on therapeutic goods, or any subsequent submissions to the Drug Regulatory Authority of Pakistan (DRAP). The current guideline describes the regulatory requirements, procedure for submission, review, evaluation and approval of applications for the conduct of Clinical Trial/Research, and all other process related to Clinical Research from its start till completion.

These guidelines are drawn in conformity with the legal requirements of the Bio-Study Rules 2017, Drug Act 1976, DRAP Act, 2012 and the latest ICH-GCP Guidelines. In the event of any contradiction between the contents of this document and any written law, the latter should take precedence. The Authority accepts no liability for any errors or omissions in this guidance document, or for any action / decision taken as a result of using this document. The Authority reserves the right to amend any part of these guidelines whenever it deems fit.

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4. INTRODUCTION

The Drug Regulatory Authority of Pakistan (DRAP) regulates the conduct of clinical trials of therapeutic goods in Pakistan under the Bio-Study Rules, 2017. Clinical trials include investigational studies in humans intended to discover or verify the clinical, pharmacological, or other pharmacodynamics effects of an investigational product, or to identify any adverse reactions to an investigational product, (i.e. Phase I to Phase IV studies), or to study absorption, distribution, metabolism and excretion of an investigational product with the object of ascertaining its safety and efficacy.

Investigational products also include registered or enlisted product, placebo, or unauthorized therapeutic goods with any type of active substance, including pharmaceutical, biological, herbal and homeopathic products, and medical devices, etc. Authorized products (registered / enlisted) may be used in accordance with the terms of the registration or enlistment as applicable, or used in a different way, e.g., at a higher dose, for a new indication or when packaged in a different container closure system.

These guidelines will assist researchers / investigators on the procedures for filing applications of clinical trials and will provide an insight on the steps to be followed by the applicants who wish to conduct Clinical Trials/Research in Pakistan. It is required that all the therapeutic goods and health products used in Pakistan are registered with the Drug Regulatory Authority of Pakistan (DRAP) and any Clinical Research using such registered or unregistered products must receive written approval (i.e. license for Clinical Trial Site, CRO or BA/BE Center & registration for Clinical Research) from DRAP, under the Bio-Study Rules 2017 for that purpose.

Approval of Clinical Research application by the DRAP for conduct of the Clinical Research does not absolve the applicant from compliance with another applicable law or regulation of the country. Furthermore, assessment of a Clinical Research application and assessment of registration dossier for the same products are two distinct processes. **Approval** of a Clinical Research does not determine the acceptability or otherwise of a marketing authorization / registration application.

5. LEGAL FRAMEWORK

DRAP regulates issues related to safety, quality, efficacy, handling and use of investigational products in clinical trials under Section 3 and 7 of the Bio-Study Rules 2017 and subsection (c) (ix) of section 7 of Drug Regulatory Authority of Pakistan Act, 2012. The Authority may issue an authorization on Form-V and Form-VI of the Bio-Study Rules 2017, to any applicant, for carrying out clinical trials in respect of an investigational medicinal product that may be specified in the certificate.

GLOSSARY

Acronyms

ADR	Adverse Drug Reaction
AE	Adverse Event
BA/BE	Bioavailability / Bioequivalence
BAL	Bio-Analytical Laboratory
CIOMS	Council of International Organization for Medical Science
CoA	Certificate of Analysis
CRO	Contract Research Organization
CR	Clinical Research (pertains to Clinical Trial or BA/BE Study)
CRA	Clinical Research Application
CRF	Case Report Form
CSC	Clinical Studies Committee
CSR	Clinical Study Report
CTRP	Clinical Trial Registry of Pakistan
DLP	Data Lock Point
DRAP	Drug Regulatory Authority of Pakistan
DSUR	Development Safety Update Report
DSMB	Data Safety Monitoring Board
ERC	Ethics Review Committee
FIFO	First In First Out
GCP	Good Clinical Practice
GLP	Good laboratory Practice
GMP	Good Manufacturing Practice
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB	Institutional Review Board
IRC	Institutional Review Committee
ISCTN	International Serial Clinical Trial Number

LPLV	Last Patient Last Visit
LSO	Last Subject Out
MRCT	Multi-Regional Clinical Trial
MCCT	Multi Countries Clinical Trial
NBC	National Bio-ethics Committee
PI	Principal Investigators
PBRER	Periodic Benefits-Risk Evaluation Report
SAE	Serious Adverse Events
SER	Summary Evaluation Report
TRS	Technical Review Series
WHO	World Health Organization

Definitions

Adverse Drug Reaction	"Adverse drug reaction" or "ADR" means response to medicines or therapeutic good which is noxious and unintended that occurs at doses normally used for the prophylaxis, diagnosis, or therapy of disease or for the restoration, correction or modification of physiological function. A response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected; ***OR*** In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out. Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline) for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).
Adverse Event	"Adverse event" or "AE" means any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or therapeutic good and which does not necessarily have a causal relationship with this treatment; OR Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).
Amendment (to the protocol)	See Protocol Amendment.
Applicable Regulatory Requirement(s)	Drug Regulatory Authority of Pakistan, law(s) and regulation(s) addressing the conduct of clinical trials/research of investigational products.
Approval (In relation to Institutional Review Boards)	The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.
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), Good

	Clinical Practice (GCP), and the applicable regulatory requirement(s).
Audit Certificate	A declaration of confirmation by the auditor that an audit has taken place.
Audit Report	A written evaluation by the Sponsor's or Regulatory Authority's auditor of the results of the audit.
Audit Trail	Documentation that allows reconstruction of the course of Audit.
Blinding/Masking	A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).
Case Report Form (CRF)	A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.
Certified Copy	A copy (irrespective of the type of media used) of the original record that has been verified (i.e. by a dated signature or by generation through a validated process) to have the same information, including data that describe the context, content, and structure, as the original.
Clinical Research	Any type of research involving Human Subjects with Clinical Intervention. e.g. Clinical Trial(s) and/or BA/BE Study.
Clinical Trial / Research Application	The Clinical Trial/Research application is the dossier that includes all documentation pertaining to the conduct of clinical trial/research in country according to the regulation. The dossier includes a cover letter, CV's of investigators, protocol and an investigator's brochure or product information etc. (Protocol and Investigator's brochure should be in accordance with ICH- GCP guidelines).
IMPs/Drug Import License (DIL)	DRAP, authorizing the licensee to import any product for purposes of clinical trials, notwithstanding that the product is not a registered product, or a license issued by DRAP authorizing the licensee to import any registered or unregistered product for purposes of clinical trials.
Clinical Trial/ Study Report	A written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).
Clinical Trial/Study	Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other Pharmacodynamics effects of an investigational product(s) and/or to identify any adverse reactions to an investigational product(s) and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.
Clinical Trials (Phase)	A systematic study on pharmaceutical products in human subjects (including patients and other volunteers) in order to discover or verify the effects of and/or identify any adverse reaction to investigational products, and/or to study the absorption, distribution, metabolism and excretion of the products with the object of ascertaining their efficacy and safety. Clinical trials are generally classified into Phases I to IV. It is not possible to draw distinct lines between the phases, and diverging opinions about details and methodology do exist. Brief descriptions of the individual phases, based on their purposes as related to clinical development of pharmaceutical products, are given below:
Comparator Product	An investigational or marketed product (i.e. active control) or placebo, used as a reference in a Clinical Trial or BA/BE Study.

Compliance (in relation to trials)	Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
Confidentiality	Prevention of disclosure, to other than authorized individuals, of a Sponsor's proprietary information or of a subject's identity.
Contract	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.
Contract Research Organization (CRO)	A person 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.
Coordinating Investigator	An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.
Direct Access	Permission to examine, analyze, verify, and reproduce any records and reports that are important for evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's 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.
Documentation	All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.
Drug Regulatory Authority of Pakistan (DRAP)	Regulatory authority established in Pakistan for the purpose of regulating the Control of Therapeutic Goods. Regulates all activities related to import, procurement of raw and packing materials, production and import of finished drugs, export, sales, pricing, etc.
Essential Documents	Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. (See Section 12 of these guidelines)
Good Clinical Practice (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 the rights, integrity, and confidentiality of trial subjects are protected.
Impartial Witness	A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
Independent Data-Monitoring Committee (IDMC) /Data and Safety Monitoring Board (DSMB)	Independent data-monitoring committees that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.
Impartial Witness	A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.
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(IDMC) / Data and Safety Monitoring Board (DSMB)	the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.
Informed Consent	A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form. Informed consent should be in accordance with Section 4.8 of the ICH-GCP Guidelines, and should be in English, National (Urdu) & Local language. (See **Annexure-VII** for ICF contents).
Inspection	The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial that may be located at the site of the trial, at the sponsor's and/or contract research organizations (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).
Institution (Medical)	Any public or private entity or agency or medical or dental facility where clinical trials are conducted.
Institutional Review Committee (IRC) or Institutional Review Board (IRB)	An independent body constituted of medical, scientific, and non- scientific members whose responsibility is to ensure the protection of the rights, safety and well–being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects and providing continuing review of trial protocol and amendments and of the methods and material to be used.
Interim Clinical Trial/ Study Report	A report of intermediate results and their evaluation based on analyses performed during the course of a trial.
Investigational Medicinal Products (IMPs)	A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a registered product when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication or when used to gain further information about an approved use.
Investigator	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. Principle Investigator will be responsible for whole Clinical Studies / Trial.
Investigator Institution	A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.
Investigator's Brochure	A compilation of the available clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects or animals. Investigator brochure should be in accordance with Section 7 of ICH-GCP guidelines, as per Rule 15 of the Bio-Study Rules 2017. (See **Annexure-V** of these guidelines for IB contents).
Manufacture	All operations that include purchase of materials and products production, quality control, release, storage, shipment (from storage related to manufacturing site) of finished products, and related controls.
Manufacturer	A company that carries out at least one step of production as well as the final

	release of the finished product.
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), Good Clinical Practice (GCP), the Bio-Study Rules 2017, DRAP Act 2012 and the rules made under.
Monitoring Plan	A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.
Monitoring Report	A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.
Multi-center Trial	A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.
Opinion (in relation to Independent Ethics Committee)	The judgment and/or the advice provided by an Independent Ethics Committee (IEC).
Phase I	These are the first trials of a new active ingredient or new formulation in humans/animals often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of the safety and the pharmacokinetic, and where possible the pharmacodynamics profile of the active ingredient(s) in humans/animals
Phase II	These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationships in order to provide an optimal background for the design of extensive therapeutic trials.
Phase III	Trials in larger (and possibly varied) patient groups with the purpose of determining the short-and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.
Phase IV	Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted and are normally in the form of post-marketing surveillance, or assessment of therapeutic value or treatment strategies. Although methods may differ, these studies should use the same scientific and ethical standard as applied in premarketing studies. After a product has been placed on market, clinical trials designed to explore new indications, new methods of administration or new combinations, etc. are normally considered as trials for new pharmaceutical products.
Product (synonym : medical product)	A drug in a pharmaceutical dosage form, a medical device or a cosmetic, having a singular identity, composition, characteristics and origin.
Protocol	A document that describes the objective(s), design, methodology, statistical considerations, and organization of a clinical trial. The protocol usually also

	gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout these Guideline the term protocol refers to protocol and protocol amendments. The protocol should be in accordance with section 6 of the ICH-GCP guidelines. (See **Annexure-VI** of these guidelines for IB contents).
Protocol Amendment	A written description of a change(s) to or formal clarification of a clinical trial protocol.
Quality Assurance (QA)	All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported incompliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
Quality Control (QC)	The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial- related activities have been fulfilled.
Randomization	The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.
Registered Product	Any product approved or permitted to be marketed in the country by DRAP
Serious Adverse Event or Serious Adverse Drug Reaction	Any untoward medical occurrence that at any dose: - Results in death. -Is life –threatening. -requires inpatient hospitalization or prolongation of existing hospitalization -results in persistent or significant disability/in capacity, or -Results in a congenital anomaly/birth defect.
Side effect	Unintended effect occurring at normal dose related to the pharmacological properties of a drug.
Source Documents	Original documents, data, and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).
Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Sponsor-Investigator	An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor- investigator include both those of a sponsor and those of an investigator.
Sub investigator	Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial- related procedures and/or to make important trial-related decisions, (e.g., associates, residents, research fellows). See also Investigator.
Subject Identification Code	A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.
Subject/ Trial	In this guideline, subject means animal and/or human participants in a clinical trial. An individual who participates in a clinical trial, either as a recipient of the

Subject	investigational product(s) or as a control.
Trial Site	The location(s) where trial-related activities are actually conducted.
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
Unregistered Product	Any product that is not registered or permitted to be marketed in the country by the DRAP.
Well-being (of the trial subjects)	The physical and mental integrity of the subjects in a clinical trial.

6. REQUIREMENT FOR CONDUCT OF CLINICAL TRIALS/RESAERCH OR BA/BE STUDIES: -

According to Bio-Study Rules, 2017, a Clinical Trial or BA/BE Study may only be started or conducted in the Pakistan if:

- the Clinical Trial Site or BA/BE Study Center is licensed by the Clinical Studies Committee of the DRAP;
- the Institutional Review Board (IRB) and National Bioethics Committee (NBC) have granted a favorable opinion to the Clinical Trial / BA/BE Study;
- the Clinical Trial / BA/BE Study is approved /registered by the Clinical Studies Committee of the DRAP.

7. KEY RESPONSIBILITIES OF INSTITUTIONS AND STAKEHOLDERS IN THE CLINICAL RESEARCH: -

7.1. Drug Regulatory Authority of Pakistan (DRAP):

Drug Regulatory Authority of Pakistan being the National Regulatory body for therapeutic goods is responsible for the issues related to safety, quality, efficacy, handling and use of investigational products in the Clinical Research under Rule 3 and 7 of the Bio-Study Rules 2017 and sub-section (c) (ix) of section 7 of Drug Regulatory Authority of Pakistan Act, 2012.

No person may carry out any Clinical Research in Pakistan, in respect of any therapeutic good unless he or she is in possession of a registration certificate and/or Site/Center license issued by the DRAP.

7.2. National Bio Ethics Committee (NBC):

National Bioethics Committee is responsible for ethical approval of all Clinical Research to be conducted in Pakistan, prior approval from NBC, is mandatory for submission of Clinical Research application to DRAP, as per Rule 9(1) of the Bio-Study Rules 2017.

7.2.1. Public or Private Health Institution's IRB / ERC / IRC:

As per Rule 9 (1) & (3) of the Bio-Study Rules 2017. IRB / ERC / IRC of the Public or Private Health Institutions shall be responsible for ethical clearance & periodic review of the Clinical

Research, being carried out in the institution, and submission of their reports to the CSC.

7.3. Sponsor:

The Sponsor is the person who takes responsibility for the initiation, management and/or financing of a Clinical Research. The Sponsor may delegate any or all of his/her research-related duties and functions to another person / organization (i.e. Contract Research Organization). Any duties or functions that are delegated to a third party must be documented and specified in writing in the application form. The Sponsor remains ultimately responsible for ensuring that the conduct of the trial/research and the data generated complies with the applicable regulatory requirements and the ICH-GCP guidelines.

7.4. Principal Investigator:

Principal Investigator (PI) is the researcher, usually a doctor or other medical professional, who assumes full responsibility for a research study, including but not limited to, the oversight and training of research assistants, administration of informed consent, and protecting participant confidentiality and leads the clinical research along with the other members of the research team, regularly monitors study participants' health to determine the study's safety and effectiveness. A PI is primarily responsible for the preparation, conduct, and administration of a research grant, cooperative agreement, or other sponsored project in compliance with applicable laws and regulations and institutional policy governing the conduct of clinical research.

7.5. Co-Principal Investigator(s):

Co-Principal Investigator (Co-PI) is a term refer to an investigator who shares scientific and administrative leadership responsibilities (granted in writing by the PI) for a trial/study with the PI.

7.6. Site Investigator(s):

Site Investigator or Site PI is a term refer to an investigator who is responsible for to take primary responsibility for the conduct of the Clinical Study at the Study Site under leadership of Principal Investigator.

7.7. National Pharmaceutical Association (e.g. PPMA and Pharma Bureau):

As per rule 13 (1) sub-rule (i), one representative of Pakistan Pharmaceutical Manufacturer Association and the Pharma Bureau, each having fifteen years of experience and expertise of conducting Clinical Trials and BA or BE studies, to be nominated by the Authority as observer for the CSC.

7.7.1. Role of observers in the Committee:

The role of observers in the Committee's meeting is restricted to observing; they can attend the meeting and listen to the conversation and can share their observations with the permission of Chairman CSC and cannot vote or otherwise officially take part in decision making. Further, they are bound to keep meeting content (agenda and other information) confidential. However, they can prepare a report regarding conduct of meeting proceedings and may submit suggestions in writing to the Chairman CSC for advancement and ease in development of research culture in Pakistan.

8. APPLICATION FOR CROs, BA/BE STUDY CENTER, BIO-ANALYTICAL LABORATORY, CLINICAL TRIAL SITE(s) AND / OR CLINICAL RESEARCH: -

8.1. Who can apply:

The application for licensing / approval of CROs, BA/BE Study Center or Bio-Analytical Laboratory should be submitted by Head of institution or other expert person having at least equal or higher educational qualification in field of medicine/pharmaceuticals sciences and application for approval/licensing of Clinical Trial Site(s) (CTS) should be from Principal Investigator (PI) or Co-Principal Investigator (Co-PI) or by Head of institution or other expert person having at least equal or higher educational qualification in field of medicine and should be working at the applied site. Whereas, for registration of Clinical Trial(s), the Sponsor of the trial/study (may apply if situated in the Country) or the nominated Principal Investigator of the study may apply to the CSC through its Chairman / Secretary for conduct of a Clinical Research in Pakistan.

8.2. Where to Apply:

The application for licensing / approval of CROs, BA/BE Study Center or Bio-Analytical Laboratory and/or Clinical Trial Site(s) and for registration of Clinical Research in Pakistan shall be submitted to:

The Chairman CSC / Director,
Division of Pharmacy Services,
Drug Regulatory Authority of Pakistan
3rd Floor, T.F Complex,7 – Mauve Area,
G-9/4, Islamabad

OR

The Secretary CSC (Additional / Deputy Director),
Division of Pharmacy Services,
Drug Regulatory Authority of Pakistan
3rd Floor, T.F Complex, 7 – Mauve Area,
G-9/4, Islamabad.

8.3. Processing fee for application(s):

Every application for licensing / approval of CROs, BA/BE Study Center or Bio-Analytical Laboratory or Clinical Trial Site or for registration of Clinical Trial / BA/BE Study, shall be accompanied with a non- refundable processing fee, as approved and notified by the

Authority vide S.R.O. 496(I)/2023, dated 17th April 2023. Login and afterwards fee challan can be generated online using following link:

https://fee.dra.gov.pk/login

After generating fee challan using above mentioned link, it needs to be paid in the nearest branch of Allied Bank of Pakistan, in the bank account of Drug Regulatory Authority of Pakistan, within due date of expiry of the challan. In case the generated challan expires, applicant may generate a new challan using same directions as previously followed.

8.4. Application for Licensing of Site/Center & Clinical Research

i. Application for licensing / approval of CROs, BA/BE Study Center or Bio-Analytical Laboratory or Clinical Trial Site shall be made on prescribed Form-I of the Bio-Study Rules, 2017. The **Form-I** along with guidance/explanatory notes attached as **Annexure-I.**

ii. Application for registration of the Clinical Trial shall be made on prescribed **Form-II** of the Bio-Study Rules, 2017. The Form-II along with guidance/explanatory notes attached as **Annexure-II.**

iii. Application for registration of the BA/BE Study shall be made on prescribed **Form-IIA (Amended)** of the Bio-Study Rules, 2017. The **Form-IIA (Amended)** along with guidance/explanatory notes attached as **Annexure-III.**

iv. Application for Renewal of License of the CROs, BA/BE Study Center or Bio-Analytical Laboratory or Clinical Trial Site, shall be made on prescribed **Form-III** of the Bio-Study Rules, 2017. The **Form-III** along with guidance/explanatory notes attached as **Annexure-IV**

v. All Application forms are available online at the DRAP's official website (www.dra.gov.pk) and could be download using link (https://www.dra.gov.pk/publications/application-forms/#CT) or can be obtained from the Pharmacy Services Division-DRAP.

vi. Only one copy of completely filled form shall be submitted for each application.

vii. The application should be submitted in writing, in the format and numbering as set out in the Application Forms. The text and diagrams must be clear and legible (use 12 pt. Times New Roman font).

viii. The details requested in the application form should be completed briefly but in full, to enable quick review of studies. However, each section should be cross-referenced to the detail in the Trial Protocol, Investigators Brochure, and other appended documentation. Trial Protocol & Investigator Brochure should be in accordance with Section 6 & Section 7 of the latest ICH-GCP Guidelines respectively.

8.5. Presentation of the Application:

The application should be bound in a single volume (or series of volumes) and the pages of the application should be numbered sequentially. The appended documents should be bound

together with the application, with tabbed sections identifying each appended document.

8.6. Supporting Documentations:

Complete, legible copies of key (peer reviewed) publications (where applicable) supporting the information in the application should be attached. They should be cross-referenced from within the CTA text. Additional data will be requested as and when necessary.

8.7. Electronic/Scanned Format:

It is advised that after preparation of application dossier and sequential page numbering, scan the complete application at 300-dpi and make a softcopy on PDF-OCR (Portable Document Format-Optical Character Recognition) format and should also be supplied on appropriate data storage device or may be communicated through official email. It should be noted that along with a complete dossier, a separate folder containing a copy of separate technical documents (i.e. Protocol, IB, ICF, Pre-Clinical/Clinical Data etc.) need to be provided.

8.8. Language:

Application for Licensing of site or registration of Clinical Research must be in English. All other data, particulars supporting documentations, labels and package inserts must also be in English.

When supporting documentation is not originally in English, a copy of the document in its original language, accompanied by authenticated translation in English shall be submitted.

8.9. Confidentiality:

The Drug Regulatory Authority of Pakistan commits to maintain the confidentiality of any information submitted as part of a clinical trial application, supporting documents or associated correspondence.

9. REVIEW AND APPROVAL OF CLINICAL TRIAL APPLICATIONS: -

9.1. Completeness of Application Form and Supporting Documentation:

Applicant should submit complete application, on receipt, Division of Pharmacy Services, DRAP will screen the application within 30 working days for its completeness. Application for licensing of CROs, BA/BE Study Center or Bio-Analytical Laboratory or Clinical Trial Site(s) & registration of Clinical Trials or BA/BE Studies shall essentially be complete in the first instance

if it includes all documents (as specified in Form-I, Form-II & Form-IIA (Amended) & Form-III of the Bio-Study Rules, 2017).

Applications for licensing / approval CROs, BA/BE Study Center or Bio-Analytical Laboratory or of Clinical Trial Site(s) are thoroughly reviewed and evaluated by the Pharmacy Services Division & if there are any shortcomings observed or clarification required then a letter of shortcoming issued / shared with applicant for fulfilment & if the applications found complete then forwarded to the Chairman CSC / the CSC for constitution of inspection panel. The nominated inspection panel after inspection submit report on approved inspection checklist(s) (**Annexure-VII to X**), which is reviewed by the Pharmacy Services Division. The Division then prepare an agenda item for the application in view of inspection panel report and its recommendations and shall be placed before the CSC for its consideration & final decision.

Note: - *It should be noted that, the complete procedure for Form-I application will be completed within 90 working days (from the date of receipt of application(s)) including issuance of licence or rejection of the application.*

Whereas, all applications of Clinical Trials or BA/BE Studies are thoroughly reviewed and evaluated by the Pharmacy Services Division within 30 working days for its completeness, and if any sort of shortcomings observed or any clarification required then a letter of shortcoming issued / shared with applicant for fulfilment, and if the application(s) found complete then its **Summary Evaluation Report** (**Annexure-VI**) prepared and all technical documents (Non-Clinical / Clinical Data, Investigator's Brochure, Study Protocol, Informed Consent Form & other related documents) with SER are shared with expert members of CSC for technical evaluation & comments if any. Thereafter, agenda items (i.e. Summary Evaluation Report with Review Report of Experts) of applications shall be placed before the CSC in its upcoming meeting for the consideration and final decision.

Note: - *It should be noted that, the complete procedure for Form-II & Form-IIA (Amended) application(s) will be completed within 90 working days (from the date of receipt of application(s)) including grant of registration or rejection of the application.*

9.2. Application Reference Number:

When an application is received, an acknowledgement of receipt/file number may be issued with a reference number for each application. This reference number must be stated in all correspondence concerning the application.

9.3. Supplementary Information and Updates:

Any new information available for the product such as adverse effects, changes in formulation or manufacturer for the active ingredients or finished products must be reported

to the DRAP. If changes such as protocol amendments, informed consent form updates and additional trial sites are made, DRAP must be immediately informed. The DRAP may request for further supplementary data or documentation whenever appropriate.

In case additional quantity of study medication(s), additional trial site(s), additional new product, additional manufacturing site/re-packer, additional port of entry, and change of applicant, extension of product's shelf life or a new protocol, that should be in accordance with Section 6 of the ICH-GCP guidelines, is required. An application for amendments along with prescribed processing fee must be made where the Sponsor/PI will need to fill in the relevant section where changes applied.

9.4. Expert's Review:

Technical documents (Non-Clinical / Clinical Data, Investigator's Brochure & Study Protocol or any other related document(s)) of every Clinical Research application along with Summary Evaluation Report will be shared electronically (through email) for technical evaluation / review.

The initial review by the CSC members or designated/nominated experts may result in queries that need to be answered by the applicant. The CSC member's / expert reviewers will not have direct contact with the applicant and all correspondence should be directed through Pharmacy Services Division, DRAP only.

After evaluation each expert member will submit a review report regarding their relevant expertise. After receipt of review reports / comments (if any) from all experts the Summary Evaluation Reports (**Annexure-X**) prepared by the Division according to expert's review report and placed before CSC for deliberations, discussion and final decision.

The Clinical Research application(s) if required, may be sent for review to the experts designated / nominated / Co-Opted by the Clinical Studies Committee (CSC) or by the Authority. There will be confidentiality agreement with the reviewers and the Committee members to ensure that the content of the research application(s) remains confidential.

The CSC member's / expert reviewers will generate a review report that shall be placed before the CSC in its very next meeting for the consideration along with Summary Evaluation Report as an agenda item.

9.5. Approval of Clinical Research Applications:

The Clinical Studies Committee (CSC) will be responsible for evaluation and approval of the application, if the application is complete and deems fit.

The Clinical Studies Committee (CSC) may approve or may reject the application and specify the reasons for rejection. Approval will be dependent on completeness of application and its prior approval by ERC/IRB and the National Bio-ethics Committee.

The decisions of the Clinical Studies Committee (CSC) will be communicated to the applicants in writing, by the Secretary CSC or its nominated officer(s) after finalization and approval of minutes of the CSC meeting.

In case of rejection, the applicant may appeal before Appellate Authority and provide additional information where applicable and whenever required.

9.6. Reliance in Clinical Research decisions, reports or information from other NRAs or SRAs: -

As per Rule 13 (8), the CSC shall also consider relevant clinical trial decisions, reports or other information from Stringent Regulatory Authorities (SRAs) and regional or international bodies like WHO, ICH and others. Any application for approval or registration of Clinical Research will not undergo in the assessment process, if the same at any stage, has already been rejected, suspended or put on hold due to any reason, in ICH member countries or stringent regulatory authorities and shall be rejected during the process of screening.

Further, if applicant support or produce favorable decisions of Stringent Regulatory Authorities (SRAs) and regional or international bodies like WHO, ICH and others, for submitted application for Clinical Research, it will benefit the approval process of the application.

The DRAP developed guidelines "*Reliance Mechanism in Regulatory Processes*" for reliance & consideration of relevant decisions for Clinical Research, reports or other information as provided under Rule 13 (8) of the Bio-Study Rules 2017. The guidelines available online on DRAP's official website: https://www.dra.gov.pk/publications/guidelines/pharmacy-services/

List of approved Stringent Regulatory Authorities (SRAs) is as follows:

Sr. No.	Country	Reference Regulatory Authority
i.	USA	Food & Drug Administration (FDA)
ii.	Canada	Health Canada
iii.	Australia	Therapeutic Goods Administration (TGA)
iv.	Japan	Pharmaceuticals and Medical Devices Agency (PMDA)
v.	UK	Medicines and Healthcare Regulatory Agency (MHRA)
vi.	France	National Agency for the Safety of Medicine and Health Products (ANSM)
vii.	Germany	Federal Institute for Drugs and Medical Devices
viii.	Netherlands	Medicines Evaluation Board

ix.	Switzerland	Swiss medic
x.	Austria	Austrian Agency for Health and Food Safety
xi.	Denmark	Danish Medicines Agency
xii.	Sweden	Swedish Medical Products Agency
xiii.	Norway	Norwegian Medicines Agency
xiv.	Belgium	Federal Agency for Medicines and Health Products
xv.	Finland	Finnish Medicine Agency
xvi.	Italy	Italian Medicine Agency (AIFA)
xvii.	Ireland	Health Products Regulatory Authority (HPRA)
xviii.	Iceland	Icelandic Medicine Agency
xix.	Spain	Spanish Agency for Medicines and Health Products
xx.	Europe	European Medicines Agency (EMA)
xxi.	WHO	World Health Organization

If applicant has any information regarding relevant CT decisions, reports or information from other NRAs or SRAs, so it may be attached with application, so, may be considered by the CSC.

9.7. Import of Investigational Medicinal Products (IMPs)

Applicants after getting approval for applied Clinical Research may apply for an import license (for same quantities as mentioned in the Clinical Research application) on Form-4 of the Drugs (Import & Export) Rules 1976 if importation of IMPs is required for the research. The Form-4 along with all required documents & prescribed fee may be submitted to respective field offices of the DRAP.

The Approval for importation of Investigational Medicinal Products (IMPs) will be dealt / approved by Quality Assurance and Lab Testing (QA & LT) Division of DRAP, after registration / approval of the Clinical Research, under the Bio-Study Rules 2017.

After fulfilment of all codal formalities of Form-4 of the Drugs (Import & Export) Rules 1976, import license on Form-6 of the Drugs (Import & Export) Rules 1976 will be issued with a two (02) years validity.

If duration of Clinical Research is more than two (02) years, then applicant may renew import license by submitting Form-4 under the Drugs (Import & Export) Rules 1976, to respective field offices of the DRAP.

9.8. Post-trial review

It is mandatory under the section 8 (3) & (6) of the Bio-Study Rules 2017, that the Final Report/Clinical Study Report for each Clinical Research conducted in Pakistan should be submitted to the DRAP. Following review of submitted Final Reports/Clinical Study Report, DRAP will then pronounce itself on the conduct of that Clinical Research.

10. NON-ROUTINE PROCEDURES FOR CLINICAL TRIALS IN PUBLIC HEALTH EMERGENCY

In Situation of public health emergency, routine procedures for Clinical Trial application may not be followed. Public Health Emergencies is defined as "an emergency need for health care [medical] services to respond to a disaster, significant outbreak of an infectious disease, bioterrorist attack or other significant or catastrophic event".

In case of Clinical Research, as per Rule 7(10) of the Bio-Study Rules 2017, the CSC may process the application of a Clinical Research on fast-track basis if it deems necessary to do so in the best public interest or in public health emergency cases (e.g. COVID-19 pandemic etc.), to save the precious lives of human subjects, after recording the reason therefore.

In any health emergency condition as mentioned above (e.g. COVID-19 pandemic etc.) or in the best of public interest, the Chairman CSC may call CSC meeting exercising his power conferred in Rule 13(7) of the Bio-Study Rules 2017, for fast track processing of the application without initial scrutiny and Summary Evaluation Report by the Pharmacy Services Division & the CSC may waive the requirement for auxiliary documents (i.e. non clinical data, details regarding participating countries, sample label of investigational product or undertaking on affidavit), if CSC feels it deems fit.

If applicant want to apply a Clinical Research for non-routine/health emergency, so may inform accordingly in the application cover letter, along with reasoning/justification letter for fast track consideration of application by the CSC.

11. PROCEDURES FOR PARALLEL PROCESSING OF APPROVAL OF SITE(S) / CENTERS AND CLINICAL RESEARCH

If applicant want to apply a Clinical Research along with new Site(s) (which are not yet approved by the DRAP), so, may submit separate application(s) for Site(s)/Center(s) and Clinical Research mentioning the reasons in research application and a request for parallel processing of research and site(s) applications. All other prerequisites and processing will be the same as mentioned above. Whereas, in parallel processing case research approval will be subject to the approval of applied site(s) remaining procedures will be same for both applications.

12. TIMELINES & PROCESS FLOW FOR ROUTINE, NON-ROUTINE &

PARALLEL PROCESSING OF APPLICATIONS

It is for information that; all applications received under the Bio-Study Rules, 2017 are processed on the basis of FIFO. Upon receipt of an application, it is initially scrutinized/evaluated within 30 working days and if there are any deficiencies / shortcoming in the application, so, a shortcoming / clarification letter shall be communicated to the applicant for fulfilment, within 05 working days after getting approval from the Chairman CSC.

Upon receipt of shortcoming application again evaluated by the Pharmacy Services Division as per approved SOPs within stipulated timelines (i.e. 15-20 working days).

After consideration, decision and finalization of the CSC meeting minutes, the CSC decisions (Licenses, Registration letter, Rejection letter or any other decisions) communicated to applicants within 10-15 working days.

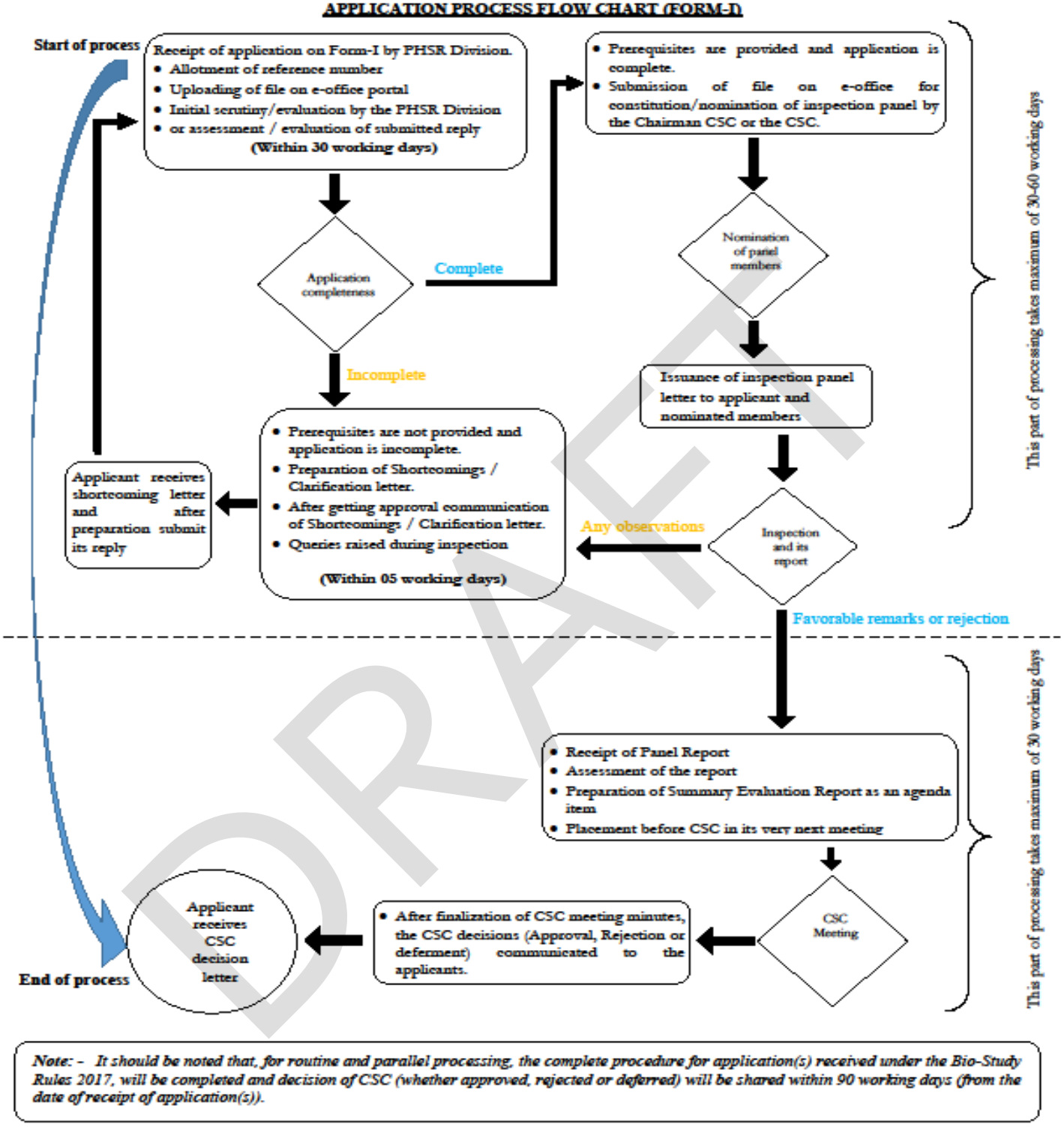
> ***Note: -*** *It should be noted that, for routine and parallel processing, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 90 working days (from the date of receipt of application(s)).*

In case of any non-routine or Public Health Emergencies (e.g. COVID-19 pandemic etc.), all application related to the Public Health Emergencies will be processed as soon as possible or within seven (07) working days & if there are deficiencies / shortcomings in the application will be communicated to applicant within 03 days & also shared electronically to save the time. After fulfilment / completion of application, the Chairman CSC may call meeting (in-person or virtual) of the CSC for urgent disposal of applications related to health emergencies. After consideration, decision and finalization of the CSC meeting minutes, the CSC decisions (Licenses, Registration letter, Rejection letter or any other decisions) communicated to applicants within 07 working days.

> ***Note: -*** *It should be noted that, for non-routine/Public Health Emergencies, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 40 working days (from the date of receipt of application(s)).*

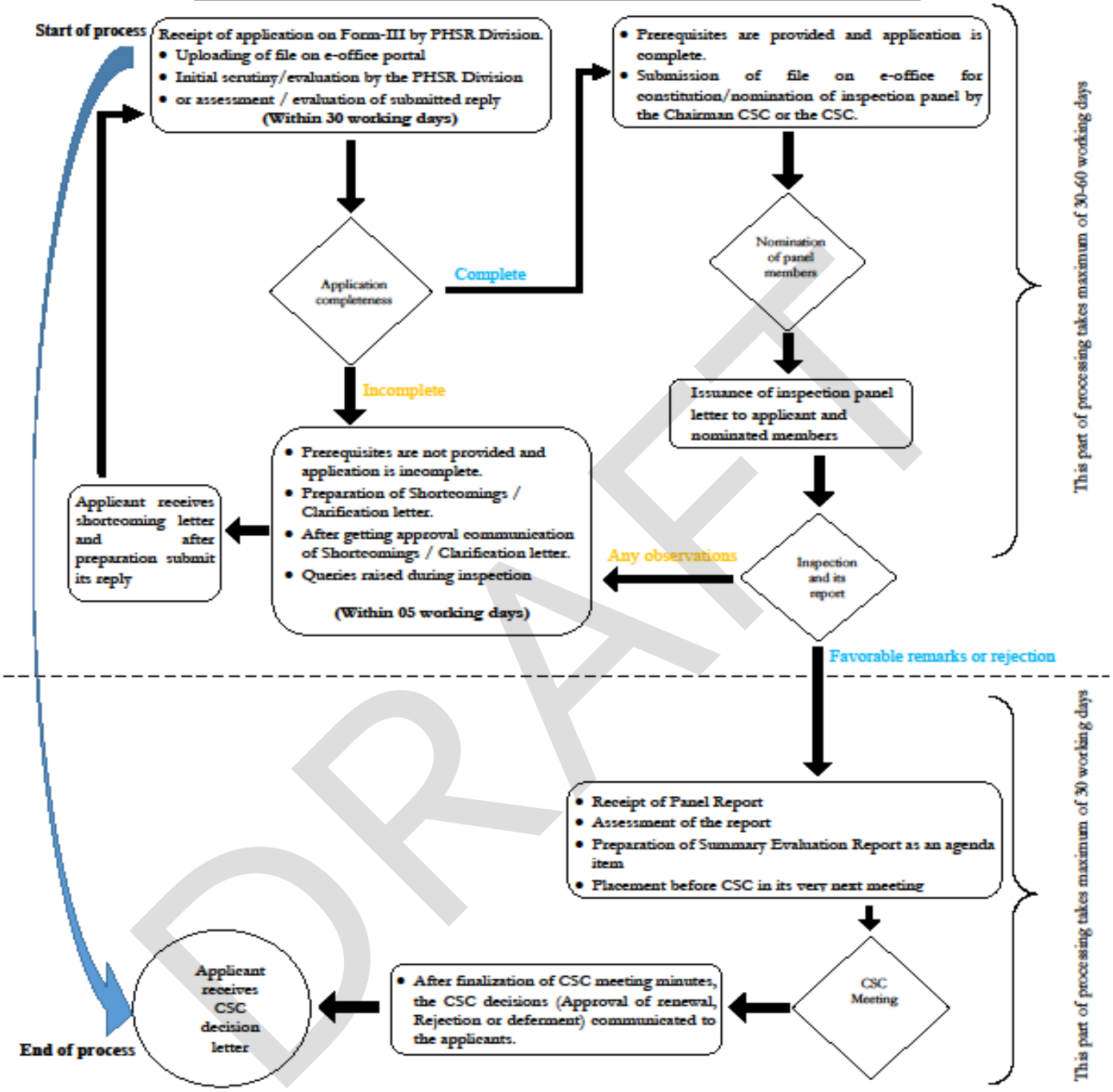
Application wise Process Flow Charts in PDF format are given below and can be maximize by double click on it:

APPLICATION PROCESS FLOW CHART (FORM-I)



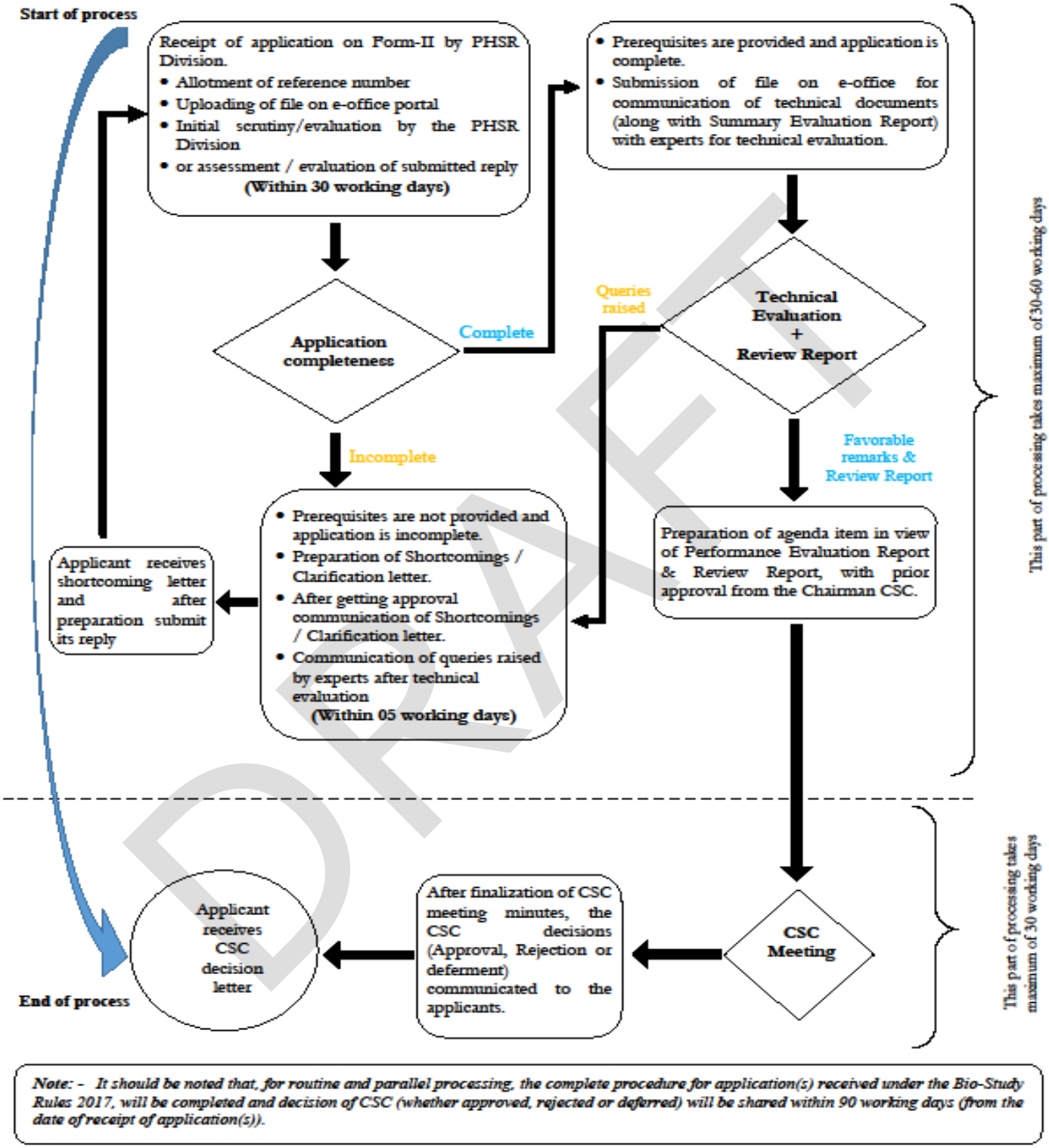
Note: - It should be noted that, for routine and parallel processing, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 90 working days (from the date of receipt of application(s)).

APPLICATION PROCESS FLOW CHART (FORM-III) FOR RENEWAL OF LICENCES



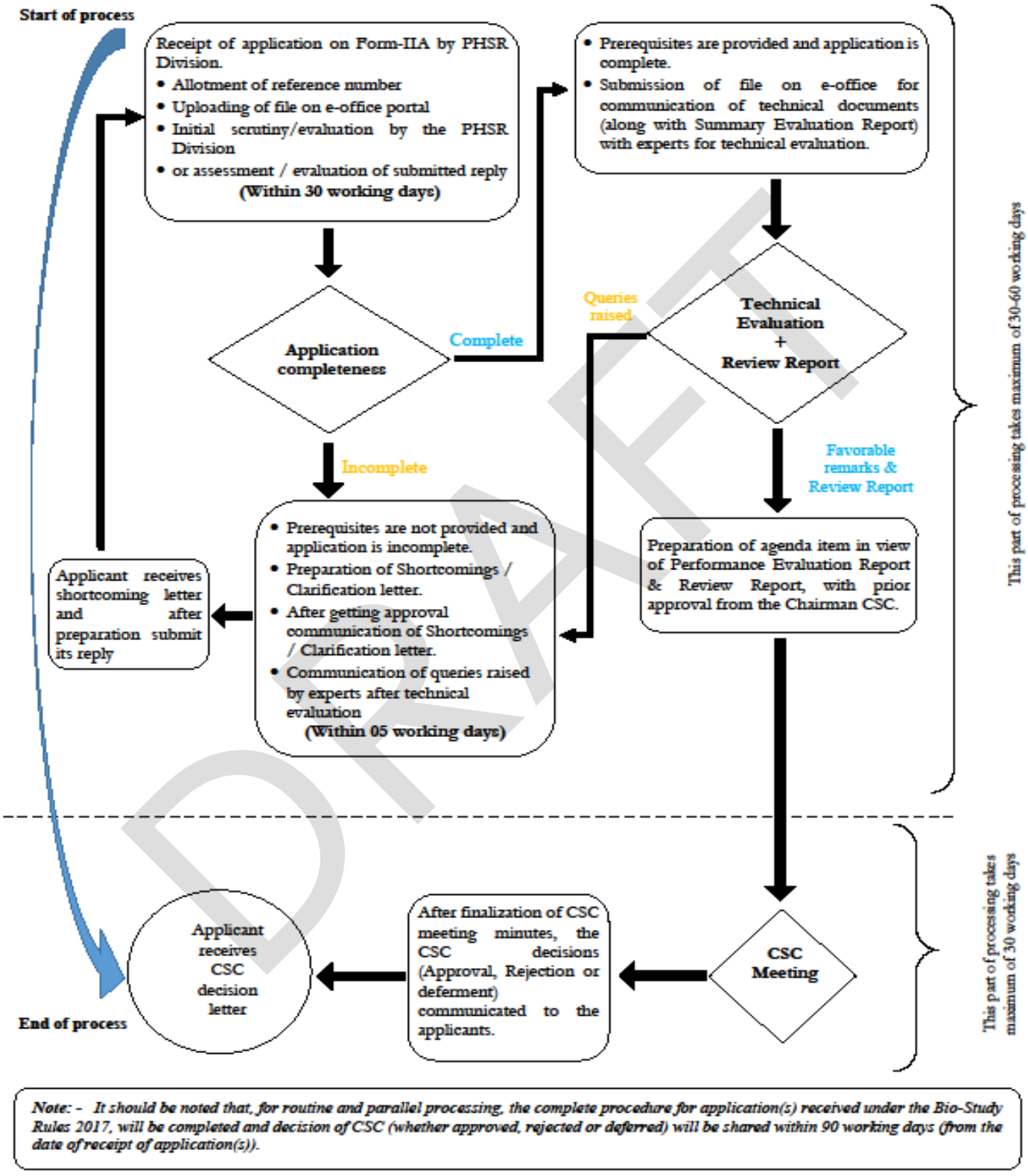
Note: - It should be noted that, for routine and parallel processing, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 90 working days (from the date of receipt of application(s)).

APPLICATION PROCESS FLOW CHART (FORM-II) (REGISTRATION OF CLINICAL RESEARCH)



Note: - It should be noted that, for routine and parallel processing, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 90 working days (from the date of receipt of application(s)).

APPLICATION PROCESS FLOW CHART (FORM-IIA) (REGISTRATION OF BA/BE STUDY)



Note: - It should be noted that, for routine and parallel processing, the complete procedure for application(s) received under the Bio-Study Rules 2017, will be completed and decision of CSC (whether approved, rejected or deferred) will be shared within 90 working days (from the date of receipt of application(s)).

13. ETHICAL APPROVAL OF THE CLINICAL RESEARCH: -

All applicants need to attach ethical clearance certificate(s) as it is mandatory under rule 9 of the Bio-Study Rule 2017, So, ethical approval of the Clinical Research/Studies Protocol, Protocol Amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects, is required to be sought from Institutional Review Committee (IRC), Ethics Review Committee (ERC) or Institutional Review Board (IRB), and National Bio-Ethics Committee (NBC), Islamabad.

13.1. Institutional Review Committee (IRC), Ethics Review Committee (ERC) or Institutional Review Board (IRB):

As per rule 9 of the Bio-Study Rules 2017, IRC, ERC or IRB is an independent body, constituted by medical professionals and non-medical members, whose responsibility is to verify that the safety, integrity and human rights of the subjects participating in a particular trial are protected, thereby providing public reassurance. IRC, ERC o r IRB should be constituted and operated so that the suitability of the investigators, facilities, protocols, the eligibility of trial subject groups, and the adequacy of confidentiality safeguards may be objectively and impartially reviewed independently of the investigator, sponsor, and relevant authorities.

The IRB should consist of following number of members, who collectively have the qualifications and experience to review and evaluate the science, medical, legal aspects and ethics of the proposed trial. The IRB should include: -

(a) At least five members;

(b) At least one member whose primary area of interest is in a non-scientific area; and

(c) At least one member who is independent of the institution or trial site.

No person involved in a clinical trial study should be part of IRB and independent ethics committee or NBC. The funding and source of funding of IRB and its members be clearly defined and documented.

The IRB shall be responsible for the periodic review of the clinical trial study, and submission of their reports to the CSC. All Clinical Trial Site(s) should have their own independent Institutional Review Committee (IRC), Ethics Review Committee (ERC) or

Institutional Review Board (IRB)

13.2. National Bio-Ethics Committee (NBC)

NBC is the major & only official body to uphold the bioethical principles in all sectors of health-care in the country. The purpose of NBC is to safeguarding the dignity, rights, safety and well-being of subjects who seek assistance to safeguard their health, be their treatment, as the participants in research projects in the country, as teachers and the taught, and publications in the medical field. NBC is expected to take care of the principle of justice in the equitable distribution of resources for health delivery.

As per rule 9 of the Bio-Study Rules 2017, it is mandatory for the applicants who are willing to conduct clinical trials or studies, to seek prior approval from National Bioethics Committee (NBC) of Pakistan.

14. AMENDMENTS AND URGENT SAFTY MEASURES: -

After approval of a Clinical Research by the CSC, the Sponsor itself or through its Principal Investigator may contact and apply for approval of amendments as needed to ensure that the clinical investigations conducted according to protocols included in the research application. Sponsors/PIs are directed to submit protocol amendments for new protocols or changes to existing protocols **before** implementation of the respective changes. When several submissions with minor amendments are expected within a short period, Sponsors/PIs are encouraged, to the extent feasible, to include all amendments in a single submission.

As per Rule 8 (10), no amendments in the approved protocol of Clinical Research can be made without seeking prior approval from the CSC or the Chairman CSC. All amendment applications should be in accordance with Section 6 of the ICH-GCP guidelines as the DRAP adopted ICH-GCP Guidelines under Rule 15 of the Bio-Study Rules 2017.

If the amendment is judged (by Principal Investigator) as urgently necessary to protect life or well-being of trial participants or the community, the change may be effected immediately, and the investigator must inform the IRB / IRC, NBC-PHRC DRAP within 48 hours- by telephone followed by a written full explanation and the information as mentioned below,

If the amendment may affect the safety of the trial participants (e.g. changes to dose, regimen, concomitant medication, monitoring, etc.) the amendment must be submitted in full, and approval from DRAP, NBC-PHRC, and IRB / IRC obtained prior to implementation.

If the amendment is unlikely to impact on participant safety (e.g. change of investigator (except

Principle Investigator), end point assay, laboratory, statistical analysis, etc.) the full detail of the change must be submitted in writing, and the change may be implemented 30 working days after receipt of the amendment by the DRAP, if no notification to the contrary is received by the applicant within that period.

Any specific technical information referenced in amendment application as already submitted to the DRAP in the original research application is expected to be identified by name, reference number, volume, page number, and date of submission. The amendments are generally classified into two categories "Major/Substantial" & "Minor/Non-Substantial" amendments.

14.1. CLASSIFICATION/CATEGORIZATION OF AMENDMENTS:

Classification/Categorization of Amendments for Clinical Research	Major / Substantial	Minor / Non-Substantial
Change of main objective	X	
Change of primary or secondary endpoint	X	
Use of new measurements (methods) for the primary endpoint	X	
Change in the definition of the end of the trial	X	
Addition of a trial arm or placebo group	X	
Change of inclusion / exclusion criteria	X	
Changes in Informed Consent Forms		
Reducing number of monitoring visits	X	
Change of study designs with impact on statistical analysis or the risk/benefit assessment	X	
Change of Sponsor or the Sponsor's legal representative	X	
Change of IMPs source	X	
Change of dosing of IMPs	X	
Change of mode of administration of IMPs	X	
Revocation or suspension of the IMP's Marketing Authorization	X	
Changes in the manufacturing process and/or specifications of an active substance /IMPs	X	
Change of the Reference Safety Information (RSI) during the conduct of a clinical research.	X	
Change of PIs	X	
Change of Co-PIs		X
Change of Site Investigator		X
Change/updates of the investigator's brochure (unless there is a change to the risk/benefit assessment for the trial);		X
Changes to the patient information (CRF, Pamphlets etc.)		X
Addition of a CSC approved study site and investigators		X
Change of contact details of the applicant		X
Change of CRA (Clinical Research Associate) for monitoring		X
Change of CRO by Sponsor		X
Closing of a Study Site (Due to inactivity)		X
Changes in Case Report Forms		X
Increase or decrease in duration of the research, provided that:		X

i. the exposure to treatment with the IMP is not extended, ii. the definition of the end of the trial is unchanged, and iii. monitoring arrangements are unchanged		
Change in the number of clinical trial participants distribution per trial site (if the total number of participants in the Country concerned is identical/same)		**X**
Insignificant increase/ decrease in view of the absolute number of participants		**X**
Minor clarifications to the protocol		**X**
Correction of typographical errors		**X**
Shelf life extensions of IMP according to protocol		**X**
Changes in funding arrangements		**X**
Changes in the logistical arrangements for storing or transporting samples		**X**

All amendment applications should be accompanied with all following requisite documents/information:

i. Application on Sponsor/PIs institution/organizational letter head.
ii. Details of amendment types for which applied.
iii. A table in a covering letter with detail o f all amended parts and its justification.
iv. The reasons for the amendments must be provided.
v. The possible consequences for participants already enrolled must be described (if any).
vi. Where an amendment applied for Protocol, Informed Consent Form or Investigator's Brochure its amended copy along with change control copy need to be attached.
vii. IRB/ERC approval for applied amendments.
viii. NBC approval for applied amendments.
ix. Prescribed processing fee in amendment/miscellaneous head as applicable.

The Pharmacy Services Division, DRAP will review the amendment application together with supporting approval. All Major/substantial amendments will be referred to Clinical Studies Committee (CSC) for expert review and consideration for approval/notification of the amendment(s) whereas, all Minor / Non-Substantial amendments shall be forwarded to the Chairman CSC for its consideration and notification.

15. AUDIT OR INSPECTION FOR LICENSING OF CRO, CTS, BIO-ANALYTICAL LABORATORY OR BA/BE STUDIES CENTERS: -

An inspection or audit of CROs, CTS, Bio-Analytical Laboratory or BA/BE Studies Center may be conducted by the Experts nominated by the Chairman CSC or by the Clinical Studies Committee (CSC). The aim is to evaluate the suitability and acceptability of research related facility.

The CSC developed and approved its inspection checklists for each (CROs, CTS, Bio-Analytical Laboratory or BA/BE Studies Center) type of license application.

i.	Inspection Checklist for CROs	Annexure-VII
ii.	Inspection Checklist for Clinical Trial Sites	Annexure-VIII
iii.	Inspection Checklist for Bio-Analytical Laboratory	Annexure-IX
iv.	Inspection Checklist for BA/BE Studies Center	Annexure-X

16. AUDIT OR INSPECTION FOR GCP COMPLAINCE: -

An inspection or audit of Clinical Research may be conducted (Before, During and/or After research) by the Experts nominated by the Chairman CSC, Clinical Studies Committee (CSC) or the DRAP (GCP Inspectors). The aim is to evaluate the suitability of research facility and verification of adherence and compliance to the approved research protocol, legislation, Good Clinical Practice (GCP) principles and practices as elaborated in the latest version of ICH-GCP Guidelines, the Bio-Study Rules, 2017 and its guidelines. Further, acceptability of clinical data submitted to DRAP. The nominated experts or GCP inspectors of the Authority may contact the PI/Site PI or Sponsor (as required) for the finalization of schedule of inspection when required, an official letter for GCP inspection by nominated experts/inspectors shall also be communicated by the Pharmacy Services Division in this regard.

i. Inspection of Clinical Research at its approved site(s) may be conducted by panel or team nominated by the Chairman CSC or by the CSC before and after approval of the site.
ii. Such inspections may be before commencement of the trial, or at predetermined intervals, or may be on the direction of the Clinical Studies Committee (CSC), responsible for clinical trial review.
iii. However, in the case of complaints or reports of unexpected adverse reactions, inspections may take place at short notice and may be unannounced.

The Inspections will include - but not be limited to:

i. The facilities and staff used for the trial: as approved by the Clinical Studies Committee (CSC) under the Bio-Study Rules 2017.
ii. Compliance with the approved Protocol.
iii. All amendments to the Protocol, which may have been approved.
iv. Accurate, complete and current records according to the Protocol.
v. Verifying that Serious Adverse Events are reported as required by the Protocol.
vi. Verifying those inspections intended to monitor and audit the trials are conducted as required by the Protocol and the reports are available for inspection.

The CSC/DRAP conduct all GCP inspections as per "***Guidelines for Conduct and Reporting of GCP Inspections",*** available online on DRAP official website for preparation and guidance.

All GCP Compliance inspection reports shall be placed before CSC for review, consideration and issuance of guidance, directions or decision if any.

17. REPORTS AND FINAL REVIEW: -

17.1. Reports of Serious Adverse Events:

All applicants informed that, as per Rule 8(5) any adverse reaction shall be reported immediately to the concerned section, The PI shall report to IRB / IRCs and the Sponsor with copies to Pharmacy Services Division, DRAP all serious adverse events (SAEs), both expected or unexpected, as soon as possible but not later than seven (07) calendar days upon receiving notice of such event.

The Sponsor shall bound the Principal Investigator to report all Serious Adverse Events (SAEs) immediately to him except for those the research protocol identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter.

Adverse events and laboratory abnormalities identified in the protocol as critical to safety evaluations shall be reported to the Sponsor according to the reporting requirements and within the time periods specified in the protocol.

For reported deaths of a subject, the Principal Investigator shall supply the Sponsor and the Ethics Committee and the Authority with any additional information requested.

The Sponsor shall keep detailed records of all adverse events which are reported to him by the PIs or Site-Investigators. These records shall be submitted to the Pharmacy Services Division/CSC addressing the Chairman CSC / Secretary CSC in connection to the Clinical Research report.

The Sponsor shall report domestic adverse drug reactions and adverse events occurring during the Clinical Trials/Research to the Pharmacy Services Division / CSC as per following timelines, namely; -

(a) the Sponsor shall ensure that all relevant information about domestic Suspected Unexpected Serious Adverse Reactions (SUSAR) occurring in clinical investigation, that are fatal or life-threatening are recorded and reported as soon as possible, and in any case no later than seven (07) calendar days after knowledge by the Sponsor of such a case, and the relevant follow-up information is subsequently communicated within additional eight (08) calendar days;

(b) all other domestic suspected unexpected serious adverse reactions (SUSARs) that are

not fatal life-threatening shall be reported as soon as possible but within a maximum of fifteen calendar days of first knowledge by the sponsor; and

(c) Non-serious AEs or ADRs shall not be reported on expedite basis but shall be included in the periodic reports.

The Sponsor shall submit DSUR as per International Council on Harmonization (ICH) format for as long as the Sponsor conducts clinical trials/research in Pakistan with the investigational drug. For the ease of manufacturer or drug registration holder or sponsor, the DSUR shall be submitted for all ongoing clinical trials.

The sponsor is conducting or has completed during the review period including, -

(a) Clinical Trials conducted using an investigational drug i.e., human pharmacology, therapeutic exploratory and therapeutic confirmatory trials (Phase I – III);

(b) Clinical Trials conducted using marketed or registered drugs / therapeutic goods in approved indications, i.e., therapeutic use trials (Phase IV);

(c) Other therapeutic use of an investigational drug (e.g., expanded access programs, compassionate use programs, particular patient use, single patient investigational new drugs / therapeutic goods, and treatment investigational new drugs / therapeutic goods); and

(d) Comparability trials conducted to support changes in the manufacturing process of the drug.

The DSUR shall be submitted annually no later than sixty calendar days from the DSUR's DLP. The DLP of the DSUR should be based on Initial Blinding Date (IBD).

If the investigational drug has received accelerated approval or registration, and clinical trials continue or are initiated, both a PBRER and a DSUR should be prepared in accordance with ICH-GCP Guidelines. The Sponsor shall change the DSUR's, DLP to coincide with the IBD so that the DSUR and the PBRER can be synchronized. In synchronizing the DLP for the DSUR and PBRER, the period covered by the next DSUR should be no longer than one year.

When submission of an annual DSUR report is no longer required, the sponsor should indicate that the final DSUR serves as the last annual report for the investigational drug. The sponsor should also indicate whether or not clinical trials are continuing elsewhere.

Additional follow up information should be made available to Pharmacy Services Division, DRAP as soon as possible, but in any case, not later than fifteen (15) calendar days.

17.2. Progress and Final Trial Reports:

All applicants informed that, as per Rule 8 of the Bio-Study Rule 2017, progress reports and final results of the clinical trial at the completion of the investigation must be communicated to the CSC. In the case of trials lasting for more than 6 months, an interim report shall be submitted at 6 months' intervals or as may be directed by the CSC or Pharmacy Services Division, DRAP. The interim report shall include the number of patients so far treated, number and type of Serious Adverse Events (SAEs) reported, number of discontinued patients and the reasons for discontinuation.

Progress or safety reports submitted by IRB/ERC, Sponsor, CROs or Principal Investigators shall be presented before CSC and decisions taken by the CSC shall be communicated. All progress or safety reports shall be stored with primary/main application file of the Clinical Trial.

The PI or sponsor shall submit an End of Study Summary Report pertaining to the sites conducting the trial to DRAP, within 3 months from the Last Patient Out (LPO)/ Last Patient Last Visit (LPLV) date.

In case of a multi-center trial within the country, with different end times, a report on each site shall be submitted before the end of the 3rd month from the last subject out. A Final Report on the trial findings shall then be submitted not later than 3 months of completion of the whole trial.

17.3. Sub-Committee of CSC for review of ADR/AE/SAE/SUSAR/DSUR, Progress / Final Report or Clinical Study Reports (CSR):

The CSC will nominate a sub-committee of experts who will be responsible for review of ADR/AE/SAE/SUSAR/DSUR, Progress / Final Report or Clinical Study Reports (CSR) with assistance of concerned assessor/evaluator along with the Secretary and Chairman CSC for deliberation, decision and for issuance of guidance and directions

This Sub-Committee will operate under supervision of the Chairman CSC and will prepare its report regarding submitted ADR/AE/SAE/SUSAR/DSUR, Progress / Final Report or Clinical Study Reports (CSR) and place before the CSC for final deliberation, decision and for issuance of guidance and directions

17.4. Product Accountability and procedure for Destruction/Disposal unused IMPs:

All clinical trials materials and Investigational Medicinal Products (IMP) that have been used, partially used, unused, or destroyed but are no longer required for the study, including expired clinical trials IMP, returned by the subjects, must be collected from all clinical study sites (if any), reconciled and disposed of appropriately, in accordance with current guidelines and legal

requirements. The IMPs not required for the clinical trial/ study must be returned to the Sponsor or destroyed (as the case may be) through suitable drug disposable company after written permission by the Sponsor. In any of aforementioned case, according to Rule 8(13) of the Bio-Study Rules 2017, the destruction of IMPs should be carried out after seeking approval and directions (if any) from the CSC / the Chairman CSC through Pharmacy Services Division. The Sponsor/Principal Investigator will submit an application along with IMPs reconciliation / accountability / Utilization report, within 3 months from the Last Subject Out date and prescribed processing fee in miscellaneous head, to the Chairman CSC for nomination of panel for verification of IMPs reconciliation and observance of IMPs destruction.

17.4.1. Procedure(s) for IMPs Reconciliation & Destruction:

The destruction of IMPs is the responsibility of the Sponsor and the Principal Investigator. All Site Investigators should reconcile the IMPs with the help of their study team under supervision of Study monitor or Clinical Research Associate (CRA), and will return to the country Principal Investigator as per reconciliations sheet. The country Principal Investigator after verification and final reconciliation will make a request to the DRAP along with IMPs reconciliation sheet along with Drug Import License(s) (DIL) and related documents for IMPs destruction/return to the Sponsor as per written instructions of the Sponsor. The Clinical Studies Committee (CSC) / the Chairman CSC will decide the application and allow for return / re-export of IMPs to the Sponsor or will nominate expert panel for physical verification of IMPs reconciliation and observance of destruction of IMPs or may give any other directions as deem fit.

17.4.2. Storage of IMPs for disposal:

All returned IMPs and materials (empty or partially empty containers of IMPs etc.), no longer required for the study, including IMPs not dispensed and/or expired, must be stored in a specifically allocated area of pharmacy (designated for storage of IMPs only) that is access controlled and not accessible to unauthorized persons. Returned IMPs and clinical trial material must also be stored separately from unused IMPs available to be dispensed in the trial. IMPs may need to be destroyed if it is no longer required for the study and/or expired, will be kept as quarantined stock. Damaged containers of clinical trials materials and/or IMPs must be kept in a sharp colored bin or a yellow clinical waste bag on site for destruction. Returned and unused IMPs should be stored in the original containers. Before sending request to Pharmacy Services Division/CSC for return/destruction of IMPs, any discrepancy in quantity, wastage etc., must be investigated, satisfactorily explained and reconciliation accepted (by the Sponsor) for each IMP involved in the clinical trial. All accountability logs related to the IMPs being returned/destroyed must be updated and also informed to CSC/Pharmacy Services Division accordingly.

17.4.3. Re-Export/Returning IMPs to the Sponsor for Destruction:

The Sponsor may arrange to remove all un-used/returned and/or expired IMPs at end of the clinical trial/ study. This is usually done by the Study Team; Study Monitor/Clinical Research Associates may help in supervision of reconciliation of the IMPs record. The IMPs can be returned to Sponsor after permission of the CSC/the Chairman CSC. The manner of shipment of IMPs to be returned must be shared by the Sponsor and will be followed by the PI. The IMPs need to be returned, should be packed according to requirements defined by the Sponsor and should be documented. The shipment must have mechanism of being track and traced.

17.4.4. Destruction of IMPs:

If the Sponsor does not require to return the IMPs, then written instruction/SOP for destruction of the IMPs need to be provided by the Sponsor. The PI/ Sponsor will make arrangements with a suitable drug disposal company for IMPs destruction process or any other recommended process keeping in view the nature of IMPs including investigational vaccines, biohazards materials etc. The IMP items to be sent for destruction must be placed in an appropriate bag/container depending upon the waste type under supervision of designated person by the PI. The bag/container should be tied/sealed and marked for destruction. The patient identity (if any) must be removed from any IMPs prior to destruction to maintain confidentiality. Any dispensing labels removed from the IMPs must be disposed of in confidential waste.

The IMPs receipt for destruction form is authorized by the PI and signed by the PI's authorized persons handing over and collecting the package or drum having IMPs. The destruction process should be witnessed by panel constituted by the CSC/ the Chairman CSC.

Note: - *This guideline does not cater for radioactive substances. For such substances, the international guidelines for radioactive substances will be applied.*

17.4.5. Documents of IMPs destruction:

All IMPs sent for destruction must be recorded. The record of the IMPs destruction should clearly identify:

a. IMPs purchase/ Import record with DIL and shipment clearance certificate(s).
b. IMPs reconciliation sheet with details of number of IMPs received, used, un-used, partially used, returned, expired, wasted and broken/damaged IMPs.
c. Date of IMPs destruction.
d. Name/Code, strength and dosage form of the IMPs.
e. Batch numbers and expiry dates.
f. Patients numbers involved (only if required), and
g. The actual quantities of IMPs sent for destruction.
h. Qualification Certificate of IMPs Disposal Firm.
i. Certificate of Destruction/Incineration issued by the Disposal Firm.

The record must be signed and dated by the designated person sending the IMPs for destruction, and checked by a second designated member of the relevant pharmacy for storage of IMPs / clinical trials team and complete a Certificate of Destruction and any Sponsor supplied documentation for recording destruction. The destruction certificate should be witnessed/signed by panel constituted by CSC/ Chairman CSC.

The PI will submit a complete report along with above mentioned documents and IMPs Destruction Certificate duly signed by the PI and DRAP's nominated officers, and/or written evidence of re-export of the unused drug supplies to country of origin (whichever applicable). This report will be placed before the CSC or Chairman as authorized by CSC, for consideration and decision and directions, if any.

17.5. Archiving:

It is the responsibility of the investigator and the sponsor to archive and ensure the safety of all the documents related to the trial. The license holder/applicant should inform DRAP in writing prior to destroying the documents. Documents shall be retained for a minimum period of 5 years, after Clinical Trial completion.

18. CLINICAL TRIAL REGISTRY OF PAKISTAN: -

Pharmacy Services Division, DRAP according to Rule 20 of the Bio-Study Rules 2017, shall maintaining its own clinical trial registry for approved clinical trials involving human subjects, and being conducted in Pakistan. (https://ctr.dra.gov.pk/)

As per Rule 20(2) of the Bio-Study Rules 2017, Clinical trial registry means an official catalog, containing publicly accessible record of approved clinical trials. Content, format and information uploaded to the database of National Clinical Trial Registry is as below:

01	**Clinical Studies Name**	
Title:		
Trial Acronym		
Brief Summery		
Trial Design	**Allocation:**	
	Intervention Model:	
	Assignment Masking:	
	Primary Purpose:	
Medical Condition		
Trial Phase		
Investigational Product		
Control No.		
Approval Date		
Duration of Trial		

Status	
Target Enrollment	
Eligibility Criteria	
Sex/Gender	
Age Group	
Approved Study Sites in Pakistan	
Participating Countries	
Sponsor	
Funder	
Global Trial Coordinator	
Global Chief Investigator	
Trial Coordinator / Principal Investigator in Pakistan	
Last Update On	

The Clinical Trial Registry of Pakistan (CTRP) is a primary registry, which may in future, be linked to the registry network of the International clinical trials registry platform of the WHO (WHO-ICTRP). It shall be a not-for-profit registry, with free and open access to researchers, clinicians, and the general public.

The PI will be responsible for uploading of trial data on CTRP or by designated person, within 30 days, after approval of Clinical Research by the CSC.

19. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL/RESEARCH: -

19.1. Introduction:

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated:

1) Before the clinical phase of the trial commences,
2) During the clinical conduct of the trial, and
3) After completion or termination of the trial.

A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority (ies).

The sponsor and investigator/institution should maintain a record of the location(s) of their

respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search, and retrieval.

Essential documents for the trial should be supplemented or may be reduced where justified (in advance of trial initiation) based on the importance and relevance of the specific documents to the trial.
The sponsor should ensure that the investigator has control of and continuous access to the CRF data reported to the sponsor. The sponsor should not have exclusive control of those data.

When a copy is used to replace an original document (e.g., source documents, CRF), the copy should fulfill the requirements for certified copies.

The investigator/institution should have control of all essential documents and records generated by the investigator/institution before, during, and after the trial.

19.2. Before the Clinical Phase of the Trial Commences:

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Title of Document		Purpose	Located in the Files of	
			Investigator/Institution	Sponsor
I.	**INVESTIGATOR'S BROCHURE**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	√	√
II.	**SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	√	√
III.	**INFORMATION GIVEN TO TRIAL SUBJECT**		√	√
	- INFORMED CONSENT FORM (including all applicable translations)	To document the informed consent	√	√
	- ANY OTHER WRITTEN INFORMATION	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	√	√
	- ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	√	–

IV.	**FINANCIAL ASPECTS OF THE TRIAL**	To document the financial agreement between the investigator/institution and the sponsor for the trial	√	√
V.	**INSURANCE STATEMENT** (where required)		√	√
VI.	**SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,** e.g.:	To document agreements	—	—
	- investigator/institution and sponsor		√	√
	- investigator/institution and CRO		√	√ (where required)
	- sponsor and CRO		—	√
	- investigator/institution and authority(ies) (where required)		√	√
VII.	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favorable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favorable opinion. To identify the version number and date of the document(s)	√	√
VIII.	**INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION**	To document that the IRB/IEC is constituted in agreement with GCP	√	√ (where required)
IX.	**REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL** (where required)	To document appropriate authorization/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	√ (where required)	√ (where required)
X.	**CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of Subjects	√	√

XI.	**NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and/or ranges of the tests	√	√
XII.	**MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s), and support reliability of results	√ (where required)	√
XIII.	**SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	—	√
XIV.	**NSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	√	√
XV.	**SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS**	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	√	√
XVI.	**CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED**	To document identity, purity, and strength of investigational product(s) to be used in the trial	—	√
XVII.	**DECODING PROCEDURES FOR BLINDED TRIALS**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	√	√ (third party if applicable)
VIII.	**MASTER RANDOMISATION LIST**	To document method for randomization of trial population	—	√ (third party if applicable)
XIX.	**PRE-TRIAL MONITORING REPORT**	To document that the site is suitable for the trial (may be combined with 9.2.20)	—	√
XX.	**TRIAL INITIATION MONITORING REPORT**	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 9.2.19)	√	√

19.3. During the Conduct of the Clinical Trial:

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes

available.

Title of Document		Purpose	Located in the Files of	
			Investigator/ Institution	Sponsor
I.	**INVESTIGATOR'S BROCHURE UPDATES**	To document that investigator is informed in a timely manner of relevant information as it becomes available	√	√
II.	**ANY REVISION TO:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to Subjects - advertisement for subject Recruitment (if used)	To document revisions of these trial related documents that take effect during trial	√	√
III.	**DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:** - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given approval/favorable opinion - continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify the version number and date of the document(s).	√	√
IV.	**REGULATORY AUTHORITY(IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:** - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	√ (where required)	√
V.	**CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUBINVESTIGATOR(S)**	(see 9.2.10)	√	√
VI.	**UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL**	To document normal values and ranges that are revised during the trial (see 9.2.11)	√ (where required)	√

VII.	**UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS** - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that test, remain adequate throughout the trial period (see 9.2.12)	√ (where required)	√
VIII.	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT**	(See 9.2.15.)	√	√
IX.	**CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS**	(see 9.2.16)	–	√
X.	**MONITORING VISIT REPORTS**	To document site visits by, and findings of, the Monitor	–	√
XI.	**RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS** - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	√	√
XII.	**SIGNED INFORMED CONSENT FORMS**	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also, to document direct access permission (see 9.2.3)	√	–
XIII.	**SOURCE DOCUMENTS**	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	√	–
XIV.	**SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)**	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	√ (copy)	√ (original)
XV.	**DOCUMENTATION OF CRF CORRECTIONS**	To document all changes/additions or corrections made to CRF after initial data were recorded	√ (copy)	√ (original)
XVI.	**NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS**	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with Section 4.11 of the ICH-GCP Guidelines.	√	√

XVII.	**NOTIFICATION BY SPONSOR AND/OR INVESTIGATOR, WHERE APPLICABLE, TO REGULATORY AUTHORITY(IES) AND IRB(S)/IEC(S) OF UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS AND OF OTHER SAFETY INFORMATION**	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with Section 5.17 and 4.11.1 of the ICH-GCP Guidelines and of other safety information in accordance with 5.16.2 and 4.11.2 of the ICH-GCP Guidelines.	√ (where required)	√
VIII.	**NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION**	Notification by sponsor to investigators of safety information in accordance with 5.16.2 of the ICH-GCP Guidelines.	√	√
XIX.	**INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY(IES)**	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority (ies) in accordance with 5.17.3 of the ICH-GCP Guidelines.	√	√ (where required)
XX.	**SUBJECT SCREENING LOG**	To document identification of subjects who entered pre-trial screening	√	√ (where required)
XXI.	**SUBJECT IDENTIFICATION CODE LIST**	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	√	–
XXII.	**SUBJECT ENROLMENT LOG**	To document chronological enrolment of subjects by trial number	√	–
XIII.	**INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE**	To document that investigational product(s) have been used according to the protocol	√	√
XIV.	**SIGNATURE SHEET**	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	√	√
XXV.	**RECORD OF RETAINED BODY FLUIDS/ TISSUE SAMPLES (IF ANY)**	To document location and identification of retained samples if assays need to be repeated	√	√

19.4. After Completion or Termination of the Trial

After completion or termination of the trial, all of the documents identified in preceding two Sections should be in the file together with the following;

Title of Document		Purpose	Located in the Files of	
			Investigator/Institution	Sponsor
I.	**INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE**	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	√	√

II.	**DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION**	To document destruction of unused investigational products by sponsor or at site	√ (if destroyed at site)	√
III.	**COMPLETED SUBJECT IDENTIFICATION CODE LIST**	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	√	–
IV.	**AUDIT CERTIFICATE** (if available)	To document that audit was performed	–	√
V.	**FINAL TRIAL CLOSE-OUT MONITORING REPORT**	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	–	√
VI.	**TREATMENT ALLOCATION AND DECODING DOCUMENTATION**	Returned to sponsor to document any decoding that may have occurred	–	√
VII.	**FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)**	To document completion of the trial	√	–
VIII.	**CLINICAL STUDY REPORT**	To document results and interpretation of trial	√ (if applicable)	√

20. REFERENCES

a) The DRAP Act, 2012.
b) The Drugs Act, 1976
c) The Bio-Study Rules, 2017.
d) Latest ICH-GCP Guidelines.

21. APPENDICES/ANNEXURES

ANNEXURE-I

Form -I

[See rule 3]

Application for license to act as center, clinical trial site, CRO or laboratory

I/we……..……..
NIC number…….…....of M/s ……..…….……
business address and telephone number and fax number……..……..…….
……..……..
hereby apply for grant of license to the site for centers or clinical trial site or CRO or laboratory, situated at …….

2. Type of the site meant for (whichever is applicable): -
   - (i) Bio-equivalence and Bio-availability studies
   - (ii) CRO
   - (iii) Laboratory
   - (iv) Clinical trials-
     - (a) Phase I
     - (b) Phase II
     - (c) Phase III
     - (d) Phase IV

3. I enclose: -
   - (a) Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors).
   - (b) Details of premises including layout plan of the site.
   - (c) Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies.
   - (d) Names and qualifications of the above sections along with their staff.
   - (e) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Name of the applicant
Signature
Seal of the firm/Company

Date:…….

EXPLANATORY NOTES ON FORM-I

Application for approval & licensing of Clinical Trial Site, CROs, BA/BE Studies Center and Bio-Analytical Laboratory shall be made on application Form–I of the Bio-Study Rules, 2017, addressed to the Chairman or Secretary, CSC. The fee challan shall be generated from official website of DRAP, using this link (https://fee.dra.gov.pk/login). A separate guideline in this regard is also available on DRAP website.

1. **Type of the site meant for (whichever is applicable)**
   Application Form-I of the Bio-Study Rules is for approval of Clinical Trial Site, CROs, BA/BE Studies Center & Bio-Analytical Laboratory. Applicants needs to specify by encircle/tick for any one of the following (Phase or Phases of Clinical Trial also need to be specified):
   - (i) Bio-equivalence and Bio-availability studies
   - (ii) CRO
   - (iii) Laboratory
   - (iv) Clinical trials-
     - (a) Phase I
     - (b) Phase II
     - (c) Phase III
     - (d) Phase IV
2. **Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors):**
   Applicant needs to provide any legal document (e.g. SECP Certificate, Registration of Firm Certificate, Health Care Commission Registration Certificate, any other law or act etc., which may clarify legal status of the organization)
3. **Details of premises including layout plan of the site:**
   Applicant need to provide complete layout plan of the applied site/premises with detail of each section.
4. **Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies:**
   Applicant need to provide complete list of section wise equipment/machinery available for testing for analytical or bio-analytical and clinical studies.
5. **Names and qualifications of the above sections along with their staff:**
   Applicant need to provide organogram & complete list of officers or staff working at the site/premises applied for approval.
6. **Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.:**
   Applicant need to provide details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc., this requirement is not applicable on CROs & Bio-analytical Laboratories.
7. **Undertaking on stamp paper:**
   Applicant need to provide undertaking on stamp paper (amount of stamp paper is not specified).

ANNEXURE -II

Form – II
[See rule 7]

Application for approval and registration of clinical trial

I/we ……..……..
NIC number ……...of M/s ..... business address and telephone number ..... hereby apply for approval or registration of clinical trial, titled….....as per detail below:

(1) Name of Investigational product, including all available names; trade, generic or INN name etc. ...……..……

(2) Purpose of trial defining the indication along with the anticipated cost of the project and sources of fund……..
(3) Phase of the clinical trial to be conducted and its proposed duration……
(4) Proposed center for trial……..……
(5) List of participating countries……..
(6) Investigator brochure along with summary.....……..……..
(7) Pre-clinical, clinical data, safety studies…….
(8) Final protocol…….…….
(9) Detail of the investigator (Principal investigator and others along with CVs…..….
(10) IRB approval……..……
(11) Ethical committee composition (names and designations) ……..…….
(12) Site approval by the Ethics committee……..…….
(13) Informed consent (English and Urdu) ……..……..
(14) Summary protocol or synopsis (Investigational Product) ……
(15) Adverse Event Reporting Form or CIOMS Form…….……
(16) Name of the monitors or clinical research associate……
Evidence of registration in country of origin (GMP certificate along with CoPP or Free sale certificate) ……..……
(17) Copy of registration letter if registered in Pakistan……..
(18) Proposed label of investigational product……
(19) Quantity of investigational products to be used in the trial along with justification
(Note: All the quantities of the investigational product should be procured from one single source)

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Name of the applicant
Signature
Date: …….
Seal of the firm/Company

CHECKLIST FOR FORM-II / CLINICAL TRIAL/STUDY APPLICATION

S. No.	Required Documents
1.	Application on prescribed form along with Fee
2.	Investigator Brochure
3.	Final Protocol
4.	Informed consent form (English and Urdu)
5.	List of participating countries (If applicable)
6.	Phase of trial
7.	Quantities of Investigational Product to be imported or procured
8.	Site of the trial
9.	C.V of investigator
10.	Ethical committee approval with complete composition of committee i.e. Name and designations of the members
11.	Approval from National Bio-ethics Committee (PHRC)
12.	GMP certificate along with Free Sale Certificate or Certificate of Pharmaceutical Product (For locally manufactured product GMP Cert., COA of the Product and Registration Letter will be required)
13.	Pre-clinical, clinical data and safety studies.
14.	Summary of the protocol
15.	Summary of the Investigator Brochure
16.	Adverse Event Reporting form
17.	No. of Patients to be enrolled in each center
18.	Name of monitors or clinical research associate
19.	Evidence of registration in country of origin
20.	Copy of registration letter (if registered in Pakistan)
21.	Sample of label of Investigational Product
22.	Duration of trial
23.	Undertaking on stamp paper.

EXPLANATORY NOTES FOR FORM-II

1. **Application along with Fee**

   Application for approval or registration of Clinical Trial shall be made on application Form–II of the Bio-Study Rules, 2017, addressed to the Chairman or Secretary, CSC. The fee challan shall be generated from official website of DRAP, using this link (https://fee.dra.gov.pk/login). A separate guideline in this regard is also available on DRAP website.

2. **Investigator Brochure (As per ICH GCP Guidelines)**

   The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. The IB must be prepared in accordance with the format given under ICH GCP Guidelines.

3. **Final Protocol (As per ICH GCP Guidelines)**

   The protocol is a document that describes how a clinical trial shall be conducted. The core components of a protocol include, objective(s), design, methodology, statistical considerations and organization of the clinical trial. The clinical trial protocol must be prepared in accordance with the format given under ICH GCP Guidelines.

4. **Informed consent form (English & Urdu)**

   Informed consent means a process by which a subject voluntarily confirms his willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. It is documented by means of a written, signed and dated information. The informed consent form is required to be prepared in both English and Urdu. A very basic language should be used which can be understood easily.

5. **List of participating countries (If applicable)**

   In case of a multi-country trial, the complete list of participating countries should be provided.

6. **Phase of trial**

   Mention the phase of clinical trial in accordance with the protocol.

7. **Quantity of Drug(s) to be imported/procured/manufactured for the trial**

   Mention justifiable quantities of the trial material which shall be required for the study.

8. **Site(s) of the trial**

   Mention the names and addresses of the clinical trial sites where the trial shall be conducted. All the participating sites must be licensed under the Bio-study Rules, 2017.

9. **C.Vs of investigator(s)**

   Provide the detailed CVs of all participating investigators.

10. **Ethical committee approval with complete composition of committee i.e. Name and designations of the members**

    The approval of Institutional Review Board (IRB) is required to be provided with complete details of the composition of the approving Board/Committee, mentioning name and designations of the members.

11. **Approval from National Bio-ethics Committee**

    The approval of the National Bio-ethics Committee, Govt. of Pakistan, is mandatory requirement for conducting a clinical trial. The applicant is required to seek a prior approval from NBC and submit the copy of the same along with the application for registration of a clinical trial.

12. **GMP certificate along with Free Sale Certificate/Certificate of Pharmaceutical Product**

    The Investigational Medicinal Product (IMP) must be procured from a GMP compliant source and in case if the IMP is approved in the country of origin, an evidence in this regard must be provided, in

the form of a copy of Free Sale Certificate or Certificate of Pharmaceutical Product (CoPP). For locally manufactured product GMP Certificate, Certificate of Analysis and Registration Letter shall be required.

13. Pre-clinical, clinical data and safety studies.

Detailed reports of the previously conducted In-vivo, In-vitro pre-clinical studies, relevant clinical data and safety studies on the Investigational Product should be provided.

14. Summary of the protocol

A short summary of the clinical trial protocol should be provided for quick review.

15. Summary of the Investigator Brochure

A short summary of the Investigator Brochure should be provided for quick review.

16. Adverse Event Reporting form

The applicant should provide a specimen of the Adverse Event Report Form for collection of the data related to the adverse events related to the study.

17. No. of Patients to be enrolled in each center

Number of participants should be provided which are planned to be enrolled for the study. For multicenter trial, separate detail should be provided for each center.

18. Name of monitors/clinical research associate

Provide names of the clinical trial monitors or research associates which shall be engaged in the study at each participating site.

19. Evidence of registration of study drug in country of origin

If the IMP is approved in the country of origin, evidence in this regard must be provided.

20. Copy of registration letter (if drug is registered in Pakistan)

For locally manufactured product, a valid Registration Letter, issued by DRAP, shall be required.

21. Sample of label of drug

Provide sample specimen of the label of Investigational Medicinal Product.

22. Duration of trial

Provide tentative duration of the study in accordance with the submitted protocol.

ANNEXURE -III

Form – IIA
[See rule 7]

Application for approval and registration of bioequivalence or bioavailability study

I/we ……..

CNIC number ……..... of M/s ……..……..… business address and telephone number and fax number…… hereby apply for approval and registration of BA or BE study, titled ……..…… as per detail below:

(1) Name of Investigational Product (including all available names; trade, generic or INN name, chemical code etc.,)…….……

(2) Dosage Form of Investigational Product ……

(3) Formulation of Investigational Product …….

(4) Pharmacodynamics and Pharmacokinetics of Investigational Product …….

(5) Purpose of study defining the indication along with the anticipated cost of the project and sources of fund……..

(6) Proposed center for study……..……

(7) Investigational design and study plan.....……..…….

(8) Pre-clinical or clinical data or safety studies…….

(9) Final protocol…….…….

(10) Detail of the investigator (Principal investigator, analysts and others along with CV) ……...

(11) IRB approval……..……

(12) Ethical committee composition (names and designations) ……..……..…….

(13) BA/BE Study Site approval by DRAP …….…….

(14) Informed consent (English and Urdu) …….……..

(15) Summary of the protocol or synopsis (Investigational Product) …….

(16) Adverse Event Reporting Form…….……..……

(17) Name of the monitor or clinical research associate……..……

(18) Certificate of Analysis of Test Product and GMP Certificate or Drug Manufacturing License of the Manufacturer ……..……

(19) Details regarding reference product (Country of origin, mode of purchase, shipment procedure) along with any other relevant documents if available……..

(20) Proposed label of investigational product……..

(21) Quantity of investigational product to be used in the study along with justification…….

(Note: All the quantities of the each of investigational product should be procured from one single source)

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Name of the applicant
Signature
Seal of the firm/Company

Date: …….

Note: In case of approval of the applied BA/BE Studies, the applicant will apply for Import license on Form-III of the Drugs (Import and Export) Rules, 1976."

EXPLANATORY NOTES FOR FORM-IIA (Amended)

1. **Application along with Fee**

   Application for approval or registration of BA/BE study shall be made on application Form–IIA (Amended) of the Bio-Study Rules, 2017, addressed to the Chairman or Secretary, CSC. The fee challan shall be generated from official website of DRAP, using this link (https://fee.dra.gov.pk/login). A separate guideline in this regard is also available on DRAP website.

2. **Details regarding IMPs**
   - Name of Investigational Product (including all available names; trade, generic or INN name, chemical code etc.)
   - Dosage Form of Investigational Product.
   - Formulation of Investigational Product
   - Pharmacodynamics and Pharmacokinetics of Investigational Product.

3. **Details regarding purpose of BA/BE Study and Funding**
   - Purpose of BA/BE Study defining the indication.
   - Anticipated cost of the project
   - Sources of funding for the project/BA/BE Study.

4. **Proposed center for study/ BA/BE Study Site approval by DRAP**

   Mention name with address and DRAP licence granted to the Center for BA/BE Studies.

5. **Investigational design and study plan**

   Describe BA/BE Study plan along with its design.

6. **Investigator Brochure (As per ICH GCP Guidelines)**

   The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. The IB must be prepared in accordance with the format given under ICH GCP Guidelines.

7. **Pre-clinical or clinical data or safety studies**

   Attach all IMPs related published Pre-Clinical, Clinical and Safety data.

8. **Final Protocol (As per ICH GCP Guidelines)**

   The protocol is a document that describes how a clinical trial shall be conducted. The core components of a protocol include, objective(s), design, methodology, statistical considerations and organization of the clinical trial. The clinical trial protocol must be prepared in accordance with the format given under ICH GCP Guidelines.

9. **Detail of the Investigator(s)**

   Attach details regarding Principal investigator, analysts and others study team along with CVs.

10. **Ethical approvals from IRB/ERC and NBC**

    IRB/ERC approval along with complete composition of the Committee (names and designations)

11. **Approval from National Bio-ethics Committee**

    The approval of the National Bio-ethics Committee, is mandatory requirement for conducting a Clinical Research/Study. The applicant is required to seek a prior approval from NBC and submit the copy of the same along with the application for registration of BA/BE Study.

12. **Informed consent form (English & Urdu)**

    Informed consent means a process by which a subject voluntarily confirms his willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. It is documented by means of a written, signed and dated

information. The informed consent form is required to be prepared in both English and Urdu. A very basic language should be used which can be understood easily.

13. **Summary of the protocol**
A short summary of the study protocol should be provided for quick review.

14. **Adverse Event Reporting form**
The applicant should provide a specimen of the Adverse Event Report Form for collection of the data related to the adverse events related to the study.

15. **Name of the monitor or clinical research associate:**
Attach details regarding Study Monitors and other Clinical Research Associates (If any).

16. **C.Vs of investigator(s)**
Provide the detailed CVs of all participating investigators.

17. **Certificate of Analysis of Test Product and GMP Certificate or Drug Manufacturing License of the Manufacturer**
The Investigational Medicinal Product (IMP) must be procured from a GMP compliant source. Certificate of analysis & GMP Certificate of the **Test Product** along with Drug Manufacturing licence of the manufacturer need to be provided. Whereas, for **Reference Product** details regarding Country of origin, mode of purchase, shipment procedure along with any other relevant documents if available, need to be provided.

18. **Name of monitors/clinical research associate**
Provide names of the clinical trial monitors or research associates which shall be engaged in the study at each participating site.

19. **Sample of label of Study Drugs**
Provide sample specimen of the label of Investigational Medicinal Product (Test & Reference products).

20. **Duration of the Study**
Provide tentative duration of the study in accordance with the submitted protocol.

21. **No. of Patients to be enrolled in the Study**
Number of participants should be provided which are planned to be enrolled for the study.

22. **Quantity of Drug(s) to be imported/procured for the Study**
Mention justifiable quantities of the study material which shall be imported/procured for the study.

ANNEXURE -IV

Form -III
[See rule 6]
Application for renewal of license to act as center, clinical trial site, CRO or laboratory

I/we ……
NIC number..... of
M/s ……..……..... ……
Business address and telephone number and fax number …… ……
…..... hereby apply for renewal of license for center or clinical trial site or CRO or laboratory.

2. Type of the studies meant for: -

(i) Bio-equivalence and Bio-availability studies

(ii) CRO

(iii) Laboratory

(iv) Clinical trials-

(a) Phase I

(b) Phase II

(c) Phase III

(d) Phase IV

3. I enclose: -

(a) Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their address, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors.

(b) Details of premises including lay out plan of the site.

(c) Details of the section wise equipment and machinery for required for the analytical or bio-analytical and clinical studies.

(d) Name and qualifications of the management, and

(e) Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.

UNDERTAKING

I/we hereby undertake / certify that the contents stated above are correct to the best of my/our knowledge and belief.

Name of the applicant
Signature
Seal of the firm/Company

Date: …….

EXPLANATORY NOTES FOR FORM-III

Application for renewal of Clinical Trial Site, CROs, BA/BE Studies Center and Bio-Analytical Laboratory license shall be made on application Form–III of the Bio-Study Rules, 2017, addressed to the Chairman or Secretary, CSC. The fee challan shall be generated from official website of DRAP, using this link (https://fee.dra.gov.pk/login). A separate guideline in this regard is also available on DRAP website.

1. **Type of the site meant for (whichever is applicable)**

   Application Form-III of the Bio-Study Rules is for renewal of Clinical Trial Site, CROs, BA/BE Studies Center & Bio-Analytical Laboratory licenses. Applicants needs to specify by encircle/tick for the same for which previous license was issued. (Phase or Phases of Clinical Trial also need to be specified):

   (i) Bio-equivalence and Bio-availability studies
   (ii) CRO
   (iii) Laboratory
   (iv) Clinical trials-
      (e) Phase I
      (f) Phase II
      (g) Phase III
      (h) Phase IV

2. **Particulars regarding the legal status of the applicant i.e. in case of proprietorship the names of proprietors and their addresses, in the case of firm the name and names and addresses of its partners and in the case of company the name and address of the company and its directors):**

   Applicant needs to provide any legal document (e.g. SECP Certificate, Registration of Firm Certificate, Health Care Commission Registration Certificate, any other law or act etc., which may clarify legal status of the organization)

3. **Details of premises including layout plan of the site:**

   Applicant need to provide complete layout plan of the applied site/premises with detail of each section.

4. **Details of the section wise equipment and machinery required for the analytical or bio-analytical and clinical studies:**

   Applicant need to provide complete list of section wise equipment/machinery available for testing for analytical or bio-analytical and clinical studies.

5. **Names and qualifications of the above sections along with their staff:**

   Applicant need to provide organogram & complete list of officers or staff working at the site/premises applied for approval.

6. **Details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc.:**

   Applicant need to provide details of the allied facilities associated with the trial center including ambulatory services, emergency handling etc., this requirement is not applicable on CROs & Bio-analytical Laboratories.

7. **Undertaking on stamp paper:**

   Applicant need to provide undertaking on stamp paper (amount of stamp paper is not specified).

ANNEXURE-V

INVESTIGATOR'S BROCHURE

TITLE PAGE ***(Example)***

SPONSOR'S NAME

Product:

Research Number:

Name(s): Chemical, Generic (if approved)

Trade Name(s) (if legally permissible and desired by the sponsor)

Edition Number:

Release Date:

Replaces Previous Edition Number:

Date:

SAMPLE TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE

NB: References on 1. Publications 2. Reports

These references should be found at the end of each chapter

Appendices (if any)

ANNEXURE-VI

SAMPLE TABLE OF CONTENTS OF STUDY PROTOCOL

- The submitted protocol should have following contents with details as per the latest ICH-GCP Guidelines:

ANNEXURE-VII

INFORMED CONSENT TEMPLATE

1. **Checklist for study Subject's informed consent documents**

1.1 ***Essential Elements:***

1. Statement that the study involves research and explanation of the purpose of the research
2. Expected duration of the Subject's participation
3. Description of the procedures to be followed, including all invasive procedures and
4. Description of any reasonably foreseeable risks or discomforts to the Subject
5. Description of any benefits to the Subject or others reasonably expected from research. If no benefit is expected Subject should be made aware of this.
6. Disclosure of specific appropriate alternative procedures or therapies available to the Subject.
7. Statement describing the extent to which confidentiality of records identifying the Subject will be maintained and who will have access to Subject's medical records
8. Trial treatment schedule(s) and the probability for random assignment to each treatment (for randomized trials)
9. Compensation and/or treatment(s) available to the Subject in the event of a trial-related injury
10. An explanation about whom to contact for trial related queries, rights of Subjects and in the event of any injury
11. The anticipated prorated payment, if any, to the Subject for participating in the trial
12. Subject's responsibilities on participation in the trial
13. Statement that participation is voluntary, that the subject can withdraw from the study at any time and that refusal to participate will not involve any penalty or loss of benefits to which the Subject is otherwise entitled
14. Any other pertinent information

1.2 ***Additional elements, which may be required***

(a) Statement of foreseeable circumstances under which the Subject's participation may be terminated by the Investigator without the Subject's consent.
(b) Additional costs to the Subject that may result from participation in the study.
(c) The consequences of a Subject's decision to withdraw from the research and procedures for orderly termination of participation by Subject.
(d) Statement that the Subject or Subject's representative will be notified in a timely manner if significant new findings develop during the course of the research which may affect the Subject's willingness to continue participation will be provided.
(e). A statement that the particular treatment or procedure may involve risks to the Subject (or to the embryo or fetus), if the Subject is or may become pregnant), which are currently unforeseeable
(f) Approximate number of Subjects enrolled in the study.

2. **Format of informed consent form for Subjects participating in a clinical trial**

Informed Consent form to participate in a clinical trial
Study Title:
Study Number:
Subject's Initials:_____Subject's Name: _____
Date of Birth / Age:

_____
Please initial box (Subject)

ANNEXURE-VIII

Summary Evaluation Report

< File Reference Number> **<Pharmacy Services Division>**

Subject: **<Type of application along with complete title of the Trial/Study>.**

Application for subject cited above is from Dr. <Applicant Name>, <Designation and Institute/Organization Name with its address>, dated XX-ABC-XXXX. Wherein request has been made for approval of subject Clinical Trial. Application is on prescribed Form-II, along with prescribed processing fee of Rs. XXX, XXX/- deposited vide challan no. XXXXXXXXX, dated XX-ABC-XXXX. <Trial/Study enlistment status on other international trial registries and/or approval status in other participating countries>.

2. <Details regarding nature of trial like Multi-Regional Clinical Trial (MRCT)/Multi-Countries Clinical Trial (MCCT)>. <Brief on applied CTS(s) of the country participating in the applied trial/study>

3. The details regarding trial, sponsor & responsible party is as under:

i. **Sponsor:** <Name with address of the trial/study Sponsor(s)>.
ii. **Collaborators**: <Name with address(s) of the trial/study collaborators>.
iii. **Purpose of trial:** <Brief on purpose of trial as mentioned in the attached protocol>
iv. **Quantity of IMPs required along with justification:** <Extract data from application put in the following table along with justification submitted by the applicant/Sponsor>:

IMPs	Molecule	Strength	Pack Size	Manufacturer	No. of Patients	Patient Does	equency	TAL
Packaging site with address: <If any/other than Sponsor/Manufacturer>								

v. **Source(s) of IMPs & Comparator/Ancillary products:**
- <Name & complete address of IMPs manufacturer(s)>
- <Name & complete address of Placebo/Comparator(s) manufacturer(s) (if any)>.
- <Name & complete address of Ancillary products manufacturer(s) (if any)>.

vi. **Wastage and Damage % (along with its justification):**
- Active: XXX * XX% = XXX; Total Import Quantity: XXX + XXX = XXX
- Placebo/Comparator: XXX * XX% = XXX; Total Import Quantity: XXX + XXX = XXX
- Other/Ancillary items to be imported for the trial:
  - <Details & quantity not mentioned>
  - <Details & quantity not mentioned>

vii. **Number of subjects to be recruited:** XXXX Subjects (Globally) & XX Subjects in Pakistan.
viii. **Anticipated cost of the project:** <USD or any other currency mentioned in application) XXX, XXX/->

ix. Study design & details: <Extract data from application and put in the following table>

Study type	
Estimated Enrollment:	
Allocation:	
Intervention Model:	
Masking:	
Primary Purpose:	
Official Title:	
Estimated Study Start Date:	
Estimated Primary Completion Date:	
Estimated Study Completion Date:	

4. <Details regarding applied Clinical Trial Sites comprising of primary & secondary objective(s) of the trial/study>

S.No.	Name & Licence No. of Site(s)	Approval/Renewal Status as per DRAP's Record	Remarks
i.			
ii.			
iii.			
iv.			
v.			

- Primary Outcome Measures/objective(s):
  i. ABC
  ii. XYZ

- Secondary Outcome Measures(s):
  i. abc
  ii. xyz

- Any other outcomes of special interest (if any):
  i. abc
  ii. xyz

5. <The details of the submitted documents are as under>

S. No.	Document	Remarks
1	Application on prescribed Form-II	<Remarks about attachment and shortcoming (if any)>
2	Prescribed Fee	<Remarks about attachment along with challan/fee voucher number with submission date and shortcoming(s) (if any)>
3	Investigator Brochure (s)	<Remarks about attachment along with IB Edition/Version No. and Date and shortcoming(s) (if any)>
4	Final protocol	<Remarks about attachment along with Protocol Edition/Version No. and Date and shortcoming(s) (if any)> <Remarks and details regarding subject's insurance>
5	Informed consent and participant	<Remarks about attachment along with ICF

	information sheet (Urdu to English)	Edition/Version No. and Date and shortcoming(s) (if any)>
6	List of participating countries	<Mention names of participating countries as described in application & countercheck it from other international trial registry (if any) and mention any contradiction if found>
7	Phase of trial.	<Mention **Phase** of the trial/study>
8	Quantity of drug / trial material to be imported on Form 4 under the Drugs (Import & Export) Rules, 1976 and application for import of trial material.	**<Mention following details>** **Wastage and Damage % will be XX%:** Active: XXX * XX% = XXX; Total Import Quantity: XXX + XXX = XXX **Dosage Form** Placebo/Comparator: XXX * XX% = XXX; Total Import Quantity: XXX + XXX = XXX **Dosage Form**
9	Site of the trial	<Provide name and licence number of all applied CTS and shortcoming(s) (if any)> i. a ii. a iii. a
10	Institutional Review Board (IRB) approval of sites with complete composition of committee i.e. names and designation of members.	<Provide details regarding attached IRB/ERC approvals as per applied Clinical Trial Site(s) and shortcomings (if any)> i. a ii. a iii. a
11	Approval of National Bio-ethics Committee (NBC)	<Provide NBC approval reference letter No._____, dated XXth-ABC-XXXX & period of attached NBC approval.>
12	CV's of the Investigators	<Details regarding attached CVs of PI & Co-PI's i. Dr. A (PI) ii. Dr. B (Co-PI) iii. Dr. C (Analyst/Bio-Statistician)
13	GMP certificate along with COPP & free sale certificate of the investigational product.	<Remarks regarding attachment of GMP Certificate(s) and CoPP along with following details:> • <Name(s) & Complete Address(s) of Manufacturer(s) of IMPs> • <Name(s) & Complete Address(s) of Manufacturer(s) of Placebo/Comparator> <Mention also brief regarding shortcomings (if any)>
14	Pre-clinical/clinical safety studies	<Remarks regarding attachment of Pre-clinical/clinical safety studies (as required by applied Phase of the trial)> <Mention also brief regarding shortcomings (if any)>
15	Summary of Protocol	<Remarks regarding attachment of Protocol Summary and brief regarding shortcomings (if any)>
16	Summary of Investigator Brochure	<Remarks regarding attachment of IB Summary and brief regarding shortcomings (if any)>
17	Adverse Event Reporting Form	<Remarks regarding attachment of ADR/AE/SAE Reporting Form and brief regarding shortcomings (if any)>.
18	No of patients to be enrolled in each center.	<Remarks regarding attachment and provided details regarding bifurcation of subject's enrolment at each CTS and brief regarding shortcomings (if any)> i. XXX Subjects will be enrolled at ABC Site. ii. XXX Subjects will be enrolled at BCD Site. iii. XXX Subjects will be enrolled at CDE Site. Total 84 subjects to be enrolled in Pakistan. Total 1490 Subjects to be enrolled globally.
19	Name of Monitors & Clinical Research Associate	<Brief regarding Sponsor's nominated monitoring firm/CRO and name(s) of nominated monitors:> • XXX • ABC

		• XYZ
20	Evidence of registration in country of origin.	<Remarks regarding attachment and brief regarding shortcomings (if any)>
21	Copy of registration letter (if registered in Pakistan)	<Remarks regarding attachment and brief regarding shortcomings (if any)>
22	Sample of label of the investigational product / drug.	<Remarks regarding attachment and brief regarding shortcomings (if any)>
22	Duration of trial	<Mention duration of trial as provided in application/protocol>
23	Undertaking on Stamp paper	<Remarks regarding attachment and brief regarding shortcomings (if any)>

6. <Remarks and details regarding any other documents provided along with application which are not mentioned in Form-II Checklist>

For example:

i. <Investigator Instructions Manual>
ii. <Laboratory Manual>
iii. <Material Transfer Agreement>
iv. <Details of ancillary products/lab kits>
v. <Any other documents etc.>

7. <Evaluator/Assessor remarks about application completeness and brief regarding shortcomings, which has been shared with applicant and applicant reply (if any)>

(NAME OF ASSESOR/EVALUATOR)
Designation (Pharmacy Services Division-DRAP)

ANNEXURE-IX

CONTRACT RESEARCH ORGANIZATION) INSPECTION CHECKLIST

Name of facility: _____
Address: _____
Organization Type: - Public ☐ Not for Profit ☐ Private ☐ Other- _____
Name of Owner / Proprietor: _____
Date of inspection: _____
(dd/mm/yyyy)

i. Organization and personnel	Yes	No	NA	Observations/Recommendations
Organizational chart exists and accurately represents the organization? The following departments are needed: • Clinical Operations • Regulatory • IT Support Departments • HR • Finance • QC				
Are Job Descriptions Available for all personnel?				
Are training records Available?				
Are there personnel curricula (training, matrix/plan) established and documented for each individual?				
Does the training program include new hire training and re-qualification training for personnel?				
Has personnel been appropriately trained to perform functions required by job descriptions?				
Is there a procedure to assess and document personnel competency on an annual basis?				
Have personnel received regulatory training? GCP ☐ Others: _____				
Is there a system in place for personnel to report any safety concerns or incidents?				
Are external contractors/vendors utilized? Are they qualified/ approved for use? Is there an SOP that outlines this process?				
Is there a Quality Assurance Unit?				

If yes, what are the roles of the Quality Control and the Quality Assurance group?				
Does the Quality Assurance Unit perform audits, trend metrics and report the results to the Senior Management?				
Is the Quality Assurance Unit independent from the personnel engaged in the direction or conduct of a clinical trial?				
ii. Standard Operating Procedures / Methods	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a governing SOP that outlines the creation, revision, approval, distribution, document control and retirement of SOPs?				
Is there a current index listing of the SOPs available?				
Is there a schedule for review of the SOPs?				
Are the SOPs in locations where they are used?				
Is there a system for documenting and handling SOP/method deviations and CAPAs?				
Is there a change control system for SOP/Methods?				
Does the Organization have SOPs to cover all the aspects of Clinical Operations e.g., Study start up, Study Conduct and Study Closeout/Completion?				
iii. Facility	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is security and confidentiality adequate so as to prevent unauthorized access to records?				
Is there sufficient space to store materials, archive records and for equipment to function properly?				
Is the facility reasonably maintained and clean?				
Is safety equipment (e.g. fire extinguishers etc.) available?				
If yes, is the equipment maintained?				
Does the Organization have a disaster recovery plan that covers all areas of the facility including computer systems and equipment?				
Are generators utilized at the facility?				
iv. Data handling Procedures and Computer Validation	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is access to computers limited by an individual username and password system (Organization members cannot share a username)?				

How is the computed network and computer systems maintained, if applicable?				
Are there a computer validation master plan and/or SOPs?				
List computers systems and software utilized. Validated?				
Are changes to computer systems controlled and documented?				
Are records of computer system errors maintained and investigated?				
Are records of hardware maintenance and repairs maintained?				
Are computers backed up routinely to prevent loss of data? Is there a backup log?				
Is there a preventative maintenance program for computer systems?				
vii. Records and Reports	**Yes**	**No**	**NA**	**Observations/Recommendations**
Does a documentation control system exists and is functional?				
Is there a SOP or a system for the retention, storage, and destruction of records?				
How does the site ensure the sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?				
viii. Record Retention and Archival	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a dedicated facility/area for the archival of records?				
Is there controlled access to the archival facility?				
Is the environment of the facility monitored and controlled?				
Is the procedure for archiving records outlined in an SOP?				
Is the retention time for records stated in the SOP?				
Is there a method of electronic data archival?				
ix. Clinical Study Site	**Yes**	**No**	**NA**	**Observations/Recommendations**
(IRB/IEC approval is necessary for conducting the clinical trial at a site. If local IRB/IEC is not available NBEC approval shall cover the site)				
Does the facility have an IRB/IEC available?				

Remarks of inspection team:

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Concluding status of inspection / application :(Circle One)

Recommended for approval ☐

Deferred for improvements ☐
Recommended for rejection ☐

	Name	**Signature**
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____

ANNEXURE-X

CLINICAL TRIAL SITE (CTS) INSPECTION CHECKLIST

Name of facility: _____

Address: _____

Organization Type: - Public ☐ Not for Profit ☐ Private ☐ Other- _____

Name of Owner / Proprietor: _____

Date of inspection: _____

(dd/mm/yyyy)

i. General Information	Yes	No	NA	Observations/Recommendations
Is this CTS a primary care, secondary care or tertiary care facility? (Record one in observations section)				
Is this the Composite CTS (Where Principal investigator is located)?				
Is the facility registered with the Healthcare Commission?				
If yes, is the certificate, available for review and is valid?				
Is there enough space available for proper functioning 'for clinical trials?				
Is there an outpatient facility?				
If yes, On an average how many patients visit per day?				
Is there an inpatient facility?				
If yes, how many beds?				
Have any clinical trials been conducted at this CTS in the past?				
If yes, how many clinical trials were conducted? Give details of the Pl as well as nature and duration of the clinical trials.				
How many other studies currently ongoing at the site? If yes, how many clinical trials were conducted? Give details of the Pl as well as nature and duration of the clinical trials.				
Is there a pharmacy / dedicated investigational Medicine dispensing area?				
If yes, does the CTS have required storage facility for routine operations?				
If yes, does the CTS have required trial related Investigational Product storing facility? (Investigational Product Provided by the sponsor as per requirements of the protocol).				
Does the CTS have Laboratory services?				
If yes, is in house or central?				
General Information	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there an X-Ray facility?				
If yes, is it on-house or central?				

Does the facility have an incinerator? If yes, document the average weight of Hospital waste disposed of per month.				
If No, does the facility', have a contract with a Hospital waste management Company?				
ii. Study Related Staff	**Yes**	**No**	**NA**	**Observations/Recommendations**
Does the CTS have, any of the study related personnel on staff? -Principal Investigator (PI) -Sub-Investigator (Sub-PI) -Coordinator -Nurses -Pharmacists. *Give details in remarks Section				
Are CVs available for Key staff members (Pl, Sub-PI, Coordinator)				
iii Education and Training	**Yes**	**No**	**NA**	**Observations/Recommendations**
Have CTS personnel received or are scheduled to receive any of following trainings? o GCP o Trial related o Safety reporting o Pharmacovigilance Training o Other				
Are training records available for study related staff?				
Security and confidentiality is adequate to prevent unauthorized access to records?				
Is there sufficient space to store materials, archive records, equipment to function properly?				
Are generators and/or UPS available utilized at the facility?				
iv. Safety	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a system in place for personnel to report any safety concern or incidents?				
v. Data Handling procedures and Computer Validation	**Yes**	**No**	**NA**	**Observations/Recommendations**
Does the CTS have adequate IT facilities e.g. Computers, internet available?				
Is access to computers limited by an individual username and password system (Clinical Research team members cannot share a user name)?				
vi. Records and Reports	**Yes**	**No**	**NA**	**Observations/Recommendations**

Is there space available for document storage?				
If yes, do access control systems to the area exist and are functional?				
Is there a SOP or a system for the retention, storage, and destruction of records?				
How does the site ensure the sponsor's proprietary information is not disclosed to unauthorized personnel or external organizations?				
vii. Records Retention and Archival	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a dedicated facility/area for the archival of records?				
Is there control access to the archival facility?				
Is the environment of the facility monitored and controlled?				
Is the retention time for records agreed with the sponsors?				
Is there a method of electronic data archive (if required)?				

Remarks of inspection team:

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Concluding status of inspection / application :(Circle One)

Recommended for approval ☐
Deferred for improvements ☐
Recommended for rejection ☐

	Name	**Signature**
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____

ANNEXURE-XI

LABORATORIES FOR CLINICAL RESEARCH (LAB) INSPECTION CHECKLIST

Name of facility: _____
Address: _____
Organization Type: - Public ☐ Not for Profit ☐ Private ☐ Other: - _____
Name of Owner / Proprietor: _____
Date of inspection: _____
(dd/mm/yyyy)

i. General organization of the site Activity	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is the scope of lab functions well defined?				
Is the site already well equipped and has adequate facilities?				
Are the algorithms for analysis well defined in any manual or SOP?				
Is the facility registered with the Healthcare Commission?				
If yes, is the certificate available for review and is valid?				
ii. Personnel	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are Organization charts, valid at the time of the inspection and at the time when the inspected study was conducted?				
Is there documentation of the number and qualifications of people employed?				
Is the training and experience of the personnel, individual work load of people involved, documented?				
Are CVs available for key staff members (Lab Director, Lab Manager Pathologists etc.)				
iii. Education and Training	**Yes**	**No**	**NA**	**Observations/Recommendations**
Have Lab personnel received or are scheduled to receive any of following trainings? • GLP • Trial related • Safety reporting • Other				
iv. Quality assurance system	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a quality assurance system in place at the laboratory?				
Do they have SOPs that are available, accessible and valid for laboratory operation?				
Are people in charge aware of the SOPs?				
Is there a change control system for SOP/Methods?				

v. Installations and equipment	Yes	No	NA	Observations/Recommendations
Is the facility suitable, equipment available and appropriate for the activity of the laboratory? (This includes energy sources, environment, lighting, test equipment and its calibration)				
vi. Archiving of documentation	**Yes**	**No**	**NA**	**Observations/Recommendations**
What is the nature of the documents kept?				
Is there dedicated place of archiving documents?				
Is there access control to that archiving place?				
Is there adequate? Protection of the documents?				
Is there person responsible for the archives identified and documented?				
Is there documentation of file movements?				
Is there an SOP as to how long the records will be maintained? State in remarks the average retention time.				
vii. Sample tracking Receipt	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a responsible person identified and documented for receipt and handling of biological samples?				
Is there an organized receipt system, and tracking of samples?				
Is there a sample registration system?				
Are dates and times of receipt of the samples, and acknowledgement of receipt documented?				
Is there a list of samples received for each dispatch?				
Is there any protocol of maintaining and monitoring shipment conditions?				
Are there any anomalies noted?				
Is the condition of the samples on receipt documented?				
viii. Storage	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are storage conditions of the study samples satisfactory?				
Do the storage conditions of the samples comply with the protocol?				
Is there assessment of the risk of confusion between samples?				
Is there Identification of the freezer(s) used including model #?				
Are there temperature records of the freezer?				
Is there calibration of the thermometer and its traceability to national/international Standards?				
Are there alarms and other surveillance measures?				
Are the samples labeled, if they are still available?				

Is there documentation of freeze / thaw cycles undergone by the samples?				
ix. Equipment	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there Identification of the equipment (make, model)?				
Is equipment for the study available at the site at the time of inspection?				
Are instructions for equipment use available?				
Does the equipment comply with specific conditions necessary for the clinical studies?				
Is there documentation relating to the qualification, checks, and maintenance of the equipment available?				
x. Calibration of Equipment	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is the equipment compared and calibrated by a 3rd party?				

Remarks of inspection team:

Concluding status of inspection / application :(Tick/Circle only one box)

Recommended for approval ☐
Deferred for improvements
Recommended for rejection ☐
☐

	Name	**Signature**
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____

ANNEXURE-XII

BIO-AVAILABILITY OR BIO-EQUIVALENCE STUDIES CENTER (CENTER) INSPECTION CHECKLIST

Name of facility: _____
Address: _____
Organization Type: - Public ☐ Not for Profit ☐ Private ☐ Other-_____
Name of Owner / Proprietor: _____
Date of inspection: _____
(dd/mm/yyyy)

A. CONDUCT OF INSPECTION OF CLINICAL PART OF BIO-EQUIVALENCE STUDIES

i. Organizational Aspects: Implementation of the BE studies at the clinical site	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are organization charts (facility management and scientific organization charts) available?				
Is there documentation of delegation of responsibilities by the principal investigator?				
Are there systems for QA and QC in place?				
Are disaster plans (e.g. handling of defective equipment and consequences} including first aid in place?				
Is staff qualification, responsibilities, experience, availability, training programs, training records, CV available for review?				
Have any BE studies already been performed here? If yes, what are their number, nature and records if any?				
What proportion of time is allocated to BE study work? (Enter in remarks section)				
Are there contracts between the sponsor or sponsor's representative and the investigator?				
Does the investigator/s tenant have qualifications and experience in the considered clinical area?				
Organizational Aspects: Implementation of the BE studies	**Yes**	**No**	**NA**	**Observations/Recommendations**

at the clinical site				
Is there documentation describing the distribution of duties and functions for the conduct of the BABE study?				
Is there compatibility of the workload of the investigator and the staff with the requirements of the study?				
Is the site organized for the study (organization chart, specific training, specific equipment, specific Procedures)?				
Does the site comply with planned time schedule for the study?				
Are correct versions of the protocol and its amendments implemented Correctly?				
ii. Facilities and equipment	**Yes**	**No**	**NA**	**Observations/Recommendations**
What equipment is being used? List in detail in remarks section or provide list.				
Are investigation up-to-date?				
Are the facilities suitable for the protocol requirements and the characteristics of the study being inspected?				
iii. Management of biological samples	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there documentation available for person in charge of collecting biological samples with dates and handling procedures?				
Is there devised protocol and documentation for storage of the samples before analysis or shipping?				
Are the shipping conditions for biological samples maintained and monitored to prevent degradation?				
iv. Organization of the Documentation	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are the medical reports (Patient's charts, X-ray, etc.)? Available, complete and archived?				
Are there informed consent				

documents available?				
Are there Case Report Forms (CRF) in records?				
v. Monitoring and auditing	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there monitoring and follow up by the sponsor?				
Is SOP and method of study monitoring available by the sponsor?				
Are there QA certificates from research organization available?				
vi. Use of computerized systems	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is a computerized system being used for the BE study? If yes, what is its validation status, version and mode				
vii. Informed consent of subjects	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are the signed and self-dated (by the subject and by the person who conducted the informed consent discussion) consent form actually used and approved by the IEC/IRB?				
Is the patient information sheet actually used and approved by the IEC/IRB?				
Does the center give copy of the informed consent to the patient/attendant?				
viii. Characteristics of the subjects included in the BA/BE study	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are the subjects nominated for the study actually on board and participating in study?				
Is the subjects participation recorded in their medical records				
Do the subjects included fulfill the inclusion criteria and none of the exclusion criteria stated in protocol?				
ix. Subject's Visits Calendar	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there subjects visits calendar available for review and is compiled				
x. Efficacy and safety assessment data	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is the efficacy and safety data recorded in the CRF in agreement with the source medical data obtained during the BE study				
Are adequate data management procedures in place?				

Is the protocol established for reporting the adverse and side reactions? Mention reporting channel in remarks				
xi. Concomitant therapy and intercurrent illness	**Yes**	**No**	**NA**	**Observations/Recommendations**
Were concomitant therapy and intercurrent illnesses managed in compliance with the protocol and recorded in the CRF and source medical documents				
xii. Management Of The investigational products	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are there instructions for handling of investigational product(s) and study related materials (if not included in protocol or investigators brochure)?				
Are shipping records for investigational product(s) and study related material available? (Receipt, date(s) of product delivery and quantity, batch (or lot) numbers {check correspondence with the information kept at the sponsor site}, expiration dates and codes assigned to the product and the subject)				
Is there documentation regarding allocation of treatment, randomization and code braking available?				
Is there investigational product(s) accountability at site (pharmacy or investigator)?				
Management of the investigational products	**Yes**	**No**	**NA**	**Observations/Recommendations**
is the date and quantity of investigational Product dispensed or returned, identification of recipients (patient's code or authorized Persons) documented? (Should also contain batch (or lot) numbers, expiration dates and codes assigned to the product and the subject)				
Is there documentation about relabeling, if Applicable?				

Is there documentation on date and quantity of investigational product returned to the sponsor? (Return receipt, batch (or lot) numbers, Expiration dates and codes assigned to the product and the subject)				
Is there documentation of dates, batch (or lot) numbers and quantity of investigational product (s) destruction? (if destroyed at the site)				
Is there documentation of treatment compliance?				
Is there a check on suitability of storage conditions and their records (fridge, freezer and controlled substances, etc.)				
If yes to above, are there specific SOP's for this activity from the pharmacy or institution?				
Is there documentation whether there was controlled access to the investigational product(s) from reception to dispensing?				
Is there documentation of certification of the labeling for compliance with applicable regulations?				

B. **CONDUCT OF INSPECTION OF BIOANALYTICAL PART OF BIO-EQUIVALENCE STUDIES**

i. General organization of the site Activity	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is the scope of laboratory and functions well defined?				
Is the site already well-equipped and has adequate facilities?				
Are the algorithms for analysis well defined in any manual or SOP?				
ii. Personnel	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are organization charts, valid at the time of the inspection and at the time when the inspected study was conducted?				

Is there documentation of the number and qualifications of people employed?				
Is the training and experience of the personnel, individual work load of people involved documented?				
iii. Quality assurance system	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a quality assurance system in place at the laboratory?				
Does the center have SOP's that are available, accessible and valid for study?				
Are people in charge aware of the SOPs is there a change control system for SOP/Methods?				
iv. Installations and equipment				
Is the facility suitable, equipment available and appropriate for the activity of the laboratory and for the Bio-equivalence study to be inspected during the inspection? (This includes energy sources, environment and its calibration)				
v. Archiving of documentation	**Yes**	**No**	**NA**	**Observations/Recommendations**
What is the nature of the documents kept				
Is there dedicated place of archiving documents?				
Is there access control to that archiving documents				
Is there adequate protection of the documents				
Is there person responsible for the archives identified and documents?				
Is there documentation of file movements?				
Is there an SOP as to how long the records will be maintained State in remarks the average retention time?				
vi. Sample tracking receipt	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a responsible person identified and documented for receipt and handling of biological samples?				
Is there an organized receipt system, and tracking of samples?				

Is there a sample registration system?				
Are controls performed on receipt?				
Are dates and times of receipt of the samples, and acknowledgement of receipt documented?				
Is there a list of samples received for each dispatch?				
Is there any protocol of maintaining and monitoring shipment conditions?				
Are there any anomalies noted?				
Is the condition of the samples on receipt documented?				
vii. Storage	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are storage conditions of the BE study samples satisfactory?				
Do the storage conditions of the samples comply with the protocol and the conditions used during BE study inspected?				
Storage	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there assessment of the risk of confusion between samples?				
Is there identification of the freezer(s) used including model#				
Are there temperature records of the freezer?				
Is there calibration of the thermometer and its trace ability to national international standards?				
Are there alarms and other surveillance measures?				
Are the samples labeled, if they are still available?				
Is there documentation of freeze/thaw cycles undergone by the samples				
viii. Destruction	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there documentation of date of destruction or return of the samples				
ix. Sample analysis Bio analytical method used	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is the BE study report consistent with the SOP describing the bio analytical methods and other documents?				
If yes to above are documents available?				
x. Equipment	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there identification of the equipment (make, model)?				

Is equipment for the study available at the site at the time of inspection?				
Are instructions for equipment use available				
Does the equipment comply with specific conditions necessary for the BE study?				
Is there documentation relating to the qualification checks and maintenance of the equipment available?				
xi. Reagents	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are the reagents labeled properly including the expiry date?				
Is there traceability of the reagents use?				
Is there compliance with specific conditions? if any				
xii. Reference standard	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are contents of the certificates of analysis and expiry dates documented and available				
Are the storage conditions optimal?				
Are the conditions for access to reference standard optimal?				
xiii. Calibration ,control samples	**Yes**	**No**	**NA**	**Observations/Recommendations**
Are there dates and conditions of preparation of the stock and working solutions and of the calibration and control samples and the number of aliquots prepared for each sample documented?				
Are the Conditions and duration of storage of the stock solutions, working solutions optimal?				
Are calibration and control samples, compared to their stability, as described in the validation report?				
Is there any matrix used? Mention details if applicable				
Is the number of calibration samples documented? Mention number for each run.				

Is the response function used, including weighting used for each run, if any?				
Is there an acceptance criteria for the calibration curve?				
Is there a criterion for exclusion of calibration samples?				
xiv. Development of the method	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a quick overview of the origin and of the development of the Bio analytical method can be helpful to identify critical steps in the procedure?				
xv. method validation	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there method validation protocol?				
Are there dates of the validation documented?				
Is there adequate documentation of all operations?				
Is there completeness of the validation report, when compared to the various experiments performed?				
Is there consistency of the validation report with the source documents?				
Is there Chromatogram integrations?				
Is there exclusion of calibration samples, if any?				
Is there stability of: 1. The stock solutions? 2. The samples (bench- top, freeze/thaw cycles, long term)? 3. Extracted samples before their injection, if applicable?				
Is there Specificity / selectivity?				
Is there accuracy?				
Is there Limit of quantification?				
Is there Response function Carry-over?				
In case of mass spectrometric methods: matrix?				
Is there Effect of a dilution, if applicable?				
Is there effect of the anticoagulant, if the anticoagulant used for the preparation of the calibration and/or QC samples is different from the anticoagulant used to collect samples during the study?				
xvi. Assays	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is nature and completeness of the documentation available?				

Is there adequacy of the documentation of all operations?				
Is there completeness of the analytical report?				
Is there number, date and composition of the analytical runs?				
Is there Identification of samples and tubes?				
Is there any method for the Assessment of the risk of sample mix-ups?				
Is there any method for assessment of the risk of sample cross contamination?				
Are there Chromatogram integrations?				
Is there Calculation of the concentrations?				
Is there Compliance with pre-defined criteria for the exclusion of calibration samples?				
Are there Criteria of acceptance of the runs, and compliance with pre-established criteria?				
Is there audit trail settings and information recorded in the audit trails?				
Is there Maintenance of blinding, if required by the protocol?				
Are there practicalities of data transfer?				
Is there consistency of the analytical report with the source documents?				
C. CONDUCT OF INSPECTION OF PHARMACOKINETIC AND STATISTICAL ANALYSES PART OF BIO-EQUIVALANCE STUDIES				
i. Pharmacokinetics	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a quality system in place?				
Are personnel involved identified, their qualifications documented and responsibilities clearly stated?				
Is software used?				

Is there software validation system documented?				
Is the software practical and has enough controls of data entry?				
Are sampling times used?				
Is data selected for the calculation of the terminal half-life, if applicable?				
Is the raw data consistent with study report?				
ii. Statistics	**Yes**	**No**	**NA**	**Observations/Recommendations**
Is there a quality system in place?				
Are personnel involved identified, their qualifications documented and responsibilities clearly stated?				
Is software used?				
Is the software practical and has enough controls of data entry?				
Are sampling times used?				
Are there Data line listings and tables of results?				
Is there consistency of the raw data with the calculated pharmacokinetic parameters and with the study report?				

Remarks of inspection team:

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Concluding status of inspection / application :(Tick/Circle only one box)

Recommended for approval ☐

Deferred for improvements ☐

Recommended for rejection ☐

	Name	**Signature**
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____
Inspector:	_____	_____

DRUG REGULATORY AUTHORITY OF PAKISTAN

Pharmacy Services Division, DRAP-NCLB Building, Prime Minister's Health Complex, Park Road, Chak Shahzad, Islamabad, Pakistan.

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