



## GUIDANCE ON CLINICAL TRIALS APPLICATIONS

**Document No:** PHSR/GL/CT/006  
**Document History:** 1<sup>st</sup> Edition  
**Effective Date:** 20-05-2022

**Drug Regulatory Authority of Pakistan**  
Islamabad - Pakistan



## 1. HISTORY

This is the first edition of these guidelines.

## 2. APPLICATION

These guidelines are applicable on the sponsors, researchers, investigators, clinical research organization (CRO), who intends to submit a new application for conduct of a clinical trial 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 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.

These guidelines are drawn in conformity with the legal requirements of the Bio- Study Rules 2017, Drug Act 1976 and DRAP Act, 2012. 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 pharmacodynamic 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 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 trial using such registered or unregistered products must receive written approval (i.e. license for Clinical Trial Site & Clinical Studies) from DRAP, under the Bio-Study Rules 2017 for that purpose.

Approval of clinical trial application by the DRAP for conduct of the clinical trial does not absolve the applicant from compliance with another applicable law or regulation of the country. Furthermore, assessment of a clinical trial application and assessment of registration dossier for the same products are two distinct processes. Approval of a clinical trial 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

<b>ADR</b>	Adverse Drug Reaction
<b>AE</b>	Adverse Event
<b>AIDS</b>	Acquired Immune Deficiency Syndrome
<b>CIOMS</b>	Council of International Organization for Medical Science
<b>CoA</b>	Certificate of Analysis
<b>CRO</b>	Contract Research Organization
<b>CTA</b>	Clinical Trial Application
<b>CSC</b>	Clinical Studies Committee
<b>DIBD</b>	Development International Birth Date
<b>DLP</b>	Data Lock Point
<b>DRAP</b>	Drug Regulatory Authority of Pakistan
<b>DSUR</b>	Development Safety Update Report
<b>GCP</b>	Good Clinical Practice
<b>GLP</b>	Good laboratory Practice
<b>GMP</b>	Good Manufacturing Practice
<b>IB</b>	Investigator's Brochure
<b>ICH</b>	International Conference on Harmonization
<b>IRB</b>	Institutional Review Board
<b>IRC</b>	Institutional Review Committee
<b>ISCTN</b>	International Serial Clinical Trial Number
<b>LPLV</b>	Last Patient Last Visit
<b>LSO</b>	Last Subject Out
<b>NBC</b>	National Bio-ethics Committee
<b>PI</b>	Principal Investigators
<b>PBRER</b>	Periodic Benefits-Risk Evaluation Report
<b>SAE</b>	Serious Adverse Events
<b>TRS</b>	Technical Review Series
<b>WHO</b>	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.



<b>Applicable Regulatory Requirement(s)</b>	Drug Regulatory Authority of Pakistan, law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.
<b>Approval (In relation to Institutional Review Boards)</b>	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.
<b>Audit</b>	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).
<b>Audit Certificate</b>	A declaration of confirmation by the auditor that an audit has taken place.
<b>Audit Report</b>	A written evaluation by the sponsor's auditor of the results of the audit.
<b>Audit Trail</b>	Documentation that allows reconstruction of the course of
<b>Blinding/Masking</b>	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).
<b>Case Report Form (CRF)</b>	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.
<b>Certified Copy</b>	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.



<b>Clinical Application</b>	<b>Trial</b>	The clinical trial application (CTA) is the dossier that includes all documentation pertaining to the conduct of clinical trial 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).
<b>Clinical Trial Import License (CTIL)</b>		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.
<b>Clinical Trial/ Study Report</b>		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).
<b>Clinical Trial/Study</b>		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.
<b>Clinical (Phase)</b>	<b>Trials</b>	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:
<b>Comparator Product</b>		An investigational or marketed product (i.e. active control) or placebo, used as a reference in a clinical trial.
<b>Compliance (in relation to trials)</b>		Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.
<b>Confidentiality</b>		Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.



<b>Contract</b>	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.
<b>Contract Research Organization (CRO)</b>	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.
<b>Coordinating Committee</b>	A committee that a sponsor may organize to coordinate the conduct of a multicenter trial.
<b>Coordinating Investigator</b>	An investigator assigned the responsibility for the coordination of investigators at different centers participating in a multicenter trial.
<b>Direct Access</b>	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.
<b>Documentation</b>	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.
<b>Drug Reaction</b>	for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH guidelines (e.g., E2A (clinical safety data management), for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).
<b>Drug Regulatory Authority of Pakistan (DRAP)</b>	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.
<b>Essential Documents</b>	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)
<b>Good Clinical Practice (GCP)</b>	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.



<b>Herbal/ Animal Medicinal Products</b>	Plant/Animal-derived materials or products with therapeutic or other human or animal health benefits which contain either raw or processed ingredients from one or more plants/animals.
<b>Impartial Witness</b>	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.
<b>Independent Data-Monitoring Committee (IDMC) /Data and Safety Monitoring Board (DSMB)</b>	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.
<b>Informed Consent</b>	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-VI).
<b>Inspection</b>	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).
<b>Institution (Medical)</b>	Any public or private entity or agency or medical or dental facility where clinical trials are conducted.
<b>Institutional Review Committee (IRC) or Institutional Review Board (IRB)</b>	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.
<b>Interim Clinical Trial/ Study Report</b>	A report of intermediate results and their evaluation based on analyses performed during the course of a trial.



<b>Investigational Medicinal Products (IMPs)</b>	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.
<b>Investigator</b>	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.
<b>Investigator Institution</b>	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.
<b>Investigator's Brochure</b>	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 Section 11 of these guidelines).
<b>Manufacture</b>	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.
<b>Manufacturer</b>	A company that carries out at least one step of production as well as the final release of the finished product.
<b>Monitoring</b>	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.
<b>Monitoring Plan</b>	A document that describes the strategy, methods, responsibilities, and requirements for monitoring the trial.
<b>Monitoring Report</b>	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.
<b>Multi-center Trial</b>	A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.
<b>Opinion (in relation to Independent Ethics Committee)</b>	The judgment and/or the advice provided by an Independent Ethics Committee (IEC).



<b>Phase I</b>	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
<b>Phase II</b>	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.
<b>Phase III</b>	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.
<b>Phase IV</b>	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.
<b>Product (synonym: medical product)</b>	A drug in a pharmaceutical dosage form, a medical device or a cosmetic, having a singular identity, composition, characteristics and origin.



<b>Protocol</b>	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.
<b>Protocol Amendment</b>	A written description of a change(s) to or formal clarification of a clinical trial protocol.
<b>Quality Assurance (QA)</b>	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 in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).
<b>Quality Control (QC)</b>	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.
<b>Randomization</b>	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.
<b>Registered Product</b>	Any product approved or permitted to be marketed in the country by DRAP
<b>Serious Adverse Event or Serious Adverse Drug Reaction</b>	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.
<b>Side effect</b>	Unintended effect occurring at normal dose related to the pharmacological properties of a drug.
<b>Source Documents</b>	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).



<b>Sponsor</b>	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
<b>Sponsor-Investigator</b>	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.
<b>Sub investigator</b>	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.
<b>Subject Identification Code</b>	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.
<b>Subject/ Trial Subject</b>	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 investigational product(s) or as a control.
<b>Trial Site</b>	The location(s) where trial-related activities are actually conducted.
<b>Unexpected Adverse Reaction</b>	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure
<b>Unregistered Product</b>	Any product that is not registered or permitted to be marketed in the country by the DRAP.
<b>Well-being (of the trial subjects)</b>	The physical and mental integrity of the subjects in a clinical trial.



## **6. REQUIREMENT FOR CONDUCT OF CLINICAL TRIALS OR CLINICAL STUDIES: -**

According to Bio-Study Rules, 2017, a clinical trial or clinical study may only be started or conducted in the Pakistan if:

- the clinical trial site and Contract Research Organization (CRO) is approved by DRAP;
- the Institutional Review Board (IRB) and National Bioethics Committee (NBC) have granted a favorable opinion to the clinical trial / clinical study;
- the clinical trial / clinical study is approved /registered by the Clinical Studies Committee of DRAP.

## **7. KEY RESPONSIBILITIES OF INSTITUTIONS AND STAKEHOLDERS IN THE CLINICAL TRIALS: -**

### **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 trials 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 trial in Pakistan, in respect of any therapeutic good unless he or she is in possession of a certificate / license issued by the DRAP.

### **7.2. National Bio Ethics Committee (NBC):**

NBC-PHRC is responsible for ethical approval of all Clinical Trials to be conducted in Pakistan, prior approval from NBS-PHRC, is mandatory for CTA to DRAP, as per Rule 9(1) of the Bio-Study Rules 2017.

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

As per Rule 9(1) & (3) of the Bio-Study Rules 2017. IRB / IRC of the Public or Private Health Institutions shall be responsible for ethical clearance & periodic review of the clinical trial, being carried out in the institution, and submission of their reports to the CSC.



### **7.3. Sponsors and Investigators:**

The sponsor is the person who takes responsibility for the initiation, management and/or financing of a clinical trial. The sponsor may delegate any or all of his trial-related duties and functions to another person / 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 and the data generated complies with the applicable regulatory requirements.

### **7.4. 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.

## **8. APPLICATION FOR CLINICAL TRIAL / CLINICAL STUDY: -**

### **8.1. Who can apply:**

The application for approval of Clinical Trial Site(s) (CTS) should be from Principal Investigator (PI) or Co-Principal Investigator (Co-PI) working at the applied site. Whereas for Clinical Trials Sponsor or the Principal investigator of the study may apply to conduct a clinical trial in Pakistan.

### **8.2. Where to Apply:**

The application for approval of Clinical Trial Sites & to conduct a clinical trial in Pakistan shall be submitted to:

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

**OR**

**Secretary CSC / Additional Director,**  
Division of Pharmacy Services,  
Drug Regulatory Authority of Pakistan  
3<sup>rd</sup> Floor, T.F Complex, 7 – Mauve Area,  
G-9/4, Islamabad.

### **8.3. Application Fee:**

Every application for approval of Clinical Trial Site(s) & conducting a clinical trial shall be accompanied with a non- refundable processing fee, as approved and notified by the Authority. Fee challan can be generated online using following link:( A separate guideline

for online challan generation is also available on DRAP website (<https://fee.dra.gov.pk/login>)

After generating fee challan using above mentioned link need to be paid in the nearest 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. The Application for Clinical Trial Site & Clinical Trials (CTA):**

- i. Application for approval of Clinical Trial Site shall be made on prescribed Form I of the Bio-Study Rules 2017. Form-I along with guidance/explanatory notes attached as Annexure-I
- ii. Application for authorization of the conduct of a Clinical Trial shall be made on prescribed Form II of the Bio-Study Rules 2017. Form-II along with guidance/explanatory notes attached as Annexure-II
- iii. Application for Renewal of License of the Clinical Trial Site, shall be made on prescribed Form III of the Bio-Study Rules 2017. Form-III along with guidance/explanatory notes attached as Annexure-III
- iv. All Application forms are available at the DRAP Head Office or on the DRAP website ([www.dra.gov.pk](http://www.dra.gov.pk)) at the Division of Pharmacy Services section.
- v. Only one copy of completed form shall be submitted for each application.
- vi. 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).
- vii. The detail 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 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 CTA 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 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. Requests for additional publications may delay the application.

### **8.7. Electronic Format:**

The Protocol, Investigators Brochure, and Reference publications should also be supplied on appropriate data storage device. Microsoft Word version 7 or later is an acceptable format, as well as Portable Document Format (PDF) files.

### **8.8. Language:**

Application for Clinical Trial License 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:**

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 (CTA) 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 Clinical Trial Sites & conduct of Clinical Studies shall essentially be complete in the first instance if it includes all documents, study Protocol & Investigator Brochure should be in accordance with Section 6 & Section 7 of the ICH- GCP Guidelines respectively, and appendices and one copy of the complete checklist.

Applications for approval of Clinical Trial Site(s) thoroughly reviewed and evaluated by the Division of Pharmacy Services & if any shortcomings observed then shared with applicant for fulfilment & if the applications found complete then forwarded to Chairman CSC/ CSC for constitution of inspection panel. Inspection panel after inspection submit report which will be placed before CSC for its consideration & decision.



Whereas all applications of Clinical Trials thoroughly reviewed and evaluated by the Division of Pharmacy Services and if any shortcomings observed then shared with applicant for fulfilment & if the applications found complete then all technical documents (Clinical & Non-Clinical Data, Investigator's Brochure & Study Protocol & other related documents) are shared with expert members of CSC for technical evaluation & comments if any. Thereafter, applications shall be placed before the CSC in its upcoming meeting for the consideration. All applications should be accompanied with prescribed fee.

### **9.2. Application Reference Number:**

When an application is received, an acknowledgement of receipt 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 DRAP. If changes such as protocol amendments, consent form updates and additional trial sites are made, DRAP must be immediately informed. The DRAP may request for further supplementary data or documentation when 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. A new CTA 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 Data, Clinical Data, Investigator's Brochure & Study Protocol) of every Clinical Study application shared electronically for technical evaluation, review & comments by the CSC expert members. After receipt of any comments, all comments received from experts will be placed before CSC for decision.

The application if required, maybe reviewed by experts designated / nominated by Clinical Studies Committee (CSC). There will be confidentiality agreement with the reviewers and committee members to ensure that the content of the application remains confidential.

The initial review may result in queries that need to be answered by the applicant. The reviewers will not have direct contact with the applicant and all correspondence should be directed through Pharmacy Services Division, DRAP only.



The reviewers will generate a report that shall be placed before the CSC in its very next meeting for the consideration.

### **9.5. Approval of CTA:**

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 receipt of approval of the protocol by the National Bio-ethics Committee (NBC-PHRC) of Pakistan Health Research Council.

The decisions of the Clinical Studies Committee (CSC) will be communicated to the applicants in writing, by the Secretary CSC after approval of minutes of the CSC meeting.

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

### **9.6. Reliance in CT 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 and regional or international bodies like WHO, ICH and others. Any application for approval or registration of clinical trial 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.

Clinical Studies Committee (CSC) approved the following Stringent Regulatory Authorities (SRAs) for reliance & consideration of relevant clinical trial decisions, reports or other information as provided under Rule 13 (8) of the Bio-Study Rules:

- i. The United States Food and Drug Administration (U.S. FDA)
- ii. The Medicines and Healthcare Products Regulatory Agency, UK (MHRA)
- iii. The European Medicines Agency (EMA).
- iv. Health Canada.
- v. The Therapeutic Goods Administration (TGA), Australia.
- vi. Pharmaceutical & Medical Devices Agency-PMDA, Japan.

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 Trial may apply for an import license (for same quantities as mentioned in the Clinical trial application) on Form-4 of the Drugs (Import & Export) Rules 1976 if importation of IMPs is required for the trial. 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 approval of the conduct of clinical studies 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 a trial duration 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 from each study conducted in Pakistan should be submitted to the DRAP. Following review of all submissions, DRAP will then pronounce itself on the conduct of that clinical trial.

## **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 Conduct of Clinical Trials, as per Rule 7(10) of the Bio-Study Rules 2017, CSC may process the application of a clinical trial on fast-track basis if it feels 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 best of public interest, Chairman CSC may call CSC meeting exercising his power conferred in Rule 13(7) of the Bio-Study Rules, for fast track processing of the application without initial scrutiny by the Division of Pharmacy Services & 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 Trial for non-routine/health emergency, so may inform accordingly with CT application for consideration of CSC.

## **11. TIMELINES & PROCESS FLOW FOR ROUTINE & NON-ROUTINE CLINICAL TRIALS APPLICATIONS**

It is for information that, all Clinical trial applications are processed on the basis of FIFO. Upon receipt of an application for Clinical Trial, it is initially scrutinized/evaluated within 30 working days. If there are any deficiencies / shortcoming in the application, so a shortcoming letter shall be communicated to the applicant for fulfilment, within 05-10 working days after getting approval from Chairman CSC.

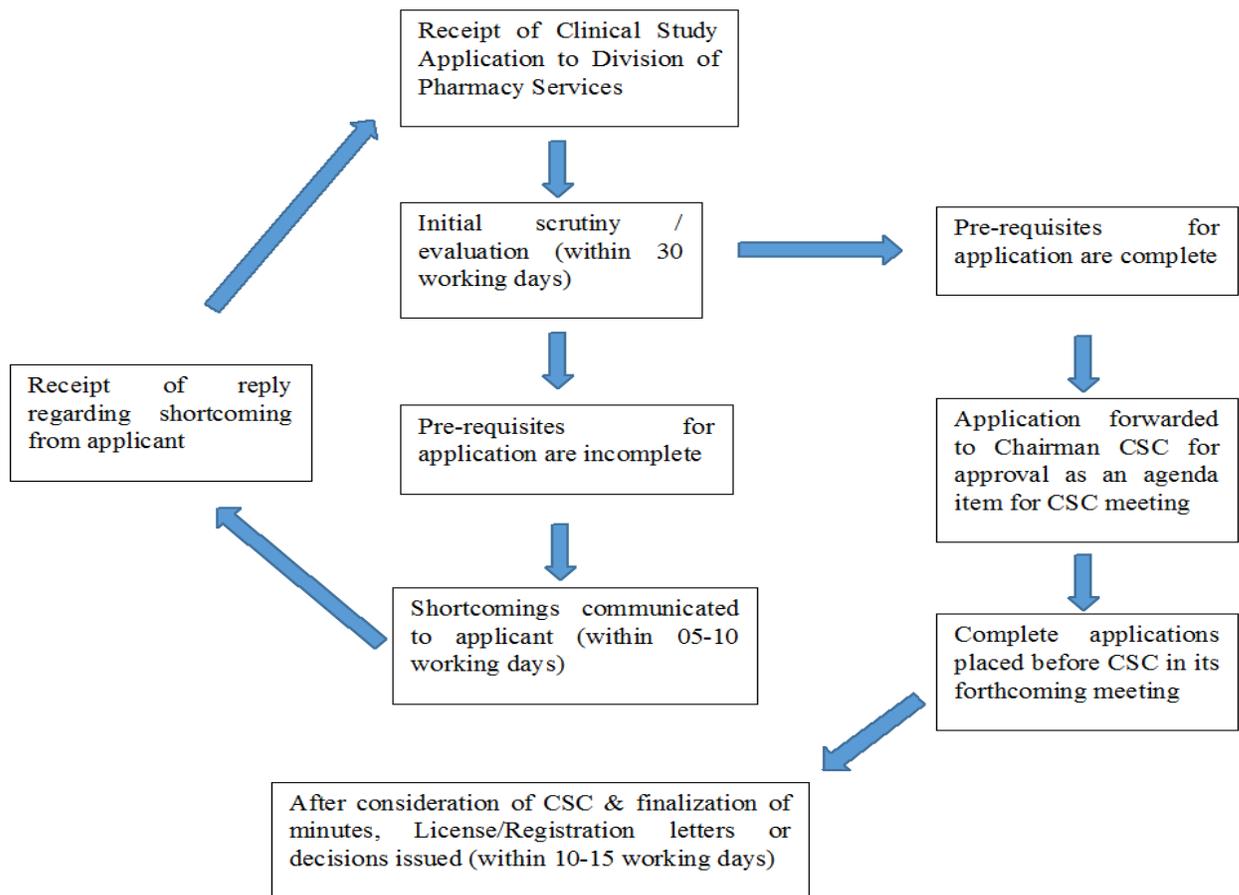
Upon receipt of shortcoming application again evaluated by the Division of Pharmacy Services as per approved SOPs within stipulated timelines (i.e. 30 working days).

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

In case of any 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, Chairman CSC may call meeting of CSC for urgent disposal of applications related to health emergencies. After consideration & decision of CSC & finalization of minutes of CSC meeting, CSC decisions shall be communicated to applicants within 07 working days.



PROCESS FLOW CHART FOR PROCESSING OF APPLICATIONS FOR CLINICAL STUDIES



**12. ETHICAL APPROVAL OF THE CLINICAL TRIAL: -**

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 Trial/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) or Institutional Review Board (IRB), and National Bio-ethics Committee (NBC), Islamabad.

**12.1. Institutional Review Committee (IRC) or Institutional Review Board (IRB):**

As per rule 9 of the Bio-Study Rules 2017, IRC 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 / 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) or Institutional Review Board (IRB)

## **12.2. 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.



### 13. AMENDMENTS AND URGENT SAFTY MEASURES: -

As per Rule 8 (10), no amendments in the approved protocol of trial or study can be made without seeking prior approval from CSC. If amendment is essential, it is recommended that the application should be withdrawn and the complete amended version re-submitted. If DRAP requires amendments, only the revised section may be replaced.

As per Rule 15 of the Bio-Study Rules 2017, DRAP adopted ICH-GCP Guidelines, so the protocol should be in accordance with Section 6 of the ICH-GCP guidelines.

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 14 days after receipt of the amendment by DRAP, if no notification to the contrary is received by the applicant within that period.

Information to be supplied when submitting a protocol amendment;

- i. An amended CTA form should be completed.
- ii. A **Bold Heading** should note that this is an Amendment and the date.
- iii. Each amendment should be BOLD and in a BOX at the relevant position in the text.
- iv. A table in a covering letter should detail all amended parts of the Application Form.
- v. The reasons for the amendments must be provided.
- vi. The possible consequences for participants already enrolled must be described.
- vii. Where an amended Participant Information Leaflet & Informed Consent form may be required any additional risks or safety issues should be highlighted.
- viii. The amended supporting documents should be appended, including any new



relevant publications.

- ix. Prescribed processing fee in miscellaneous head as applicable.

The Pharmacy Services Division, DRAP will review the application together with supporting approval from the IRB / IRC and NBC-PHRC. It will be referred to Clinical Studies Committee (CSC) in its very next meeting for expert review and consideration for approval of the amendment(s).

#### **14. AUDIT OR INSPECTION FOR GCP COMPLIANCE: -**

An inspection or audit of Clinical Trial Site and or Clinical Trial Studies may be conducted by the Experts nominated by the Clinical Studies Committee (CSC) or DRAP. The aim is to evaluate the acceptability of clinical data submitted to DRAP, and to ensure that legislation, Good Clinical Practice (GCP) principles and practices as elaborated in the latest version of ICH-GCP Guidelines, the Bio-Study Rules, 2017 and in this guideline are adhered. The nominated experts or responsible officer of the regulatory authority may contact the PI or sponsor for the date of inspection when required, an official letter also communicated by the Division of Pharmacy in this regard.

- i. Inspection of Clinical Trial Site may be conducted by panel or team nominated by the Chairman CSC upon direction of CSC or by Chairman 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.



## **15. REPORTS AND FINAL REVIEW: -**

### **15.1. 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.

Sponsor shall bound the investigator to report all serious adverse events immediately to him except for those that the protocol or investigator's brochure 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 investigator shall supply the sponsor and the Ethics Committee with any additional information requested.

The sponsor shall keep detailed records of all adverse events which are reported to him by the investigator or investigators. These records shall be submitted to the PNPC in connection to the clinical trials report.

Sponsor shall report domestic adverse drug reactions and adverse events occurring during the clinical trials to the PNPC 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 calendar days after knowledge by the sponsor of such a case, and the relevant follow-up information is subsequently communicated within additional eight 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.



Sponsor shall submit DSUR as per International Council on Harmonization (ICH) format for as long as the sponsor conducts clinical trials 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 that

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

- (a) Clinical Trials conducted using an investigational drug whether with or without a registration, 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 DIBD.

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.

## **15.2. 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.

### **15.3. Product Accountability and procedure for Destruction/Disposal unused IMPs:**

All applicants informed that, according to Rule 8(13) of the Bio-Study Rules 2017, the destruction of unused investigational products should be carried out after seeking approval from the CSC which shall nominate officers to accompany during the process of destruction of investigational products.

Principal Investigator will submit an application to Chairman CSC for nomination of panel for observance of IMPs destruction along with Investigational Medicinal Products (IMPs) Accountability / Utilization report to Division of Pharmacy Services, DRAP, within 3 months from the Last Subject Out date.

Chairman CSC will nominate a panel for observance of safe destruction of unused/leftover, expired/spoiled Investigational Medicinal Products (IMPs). After destruction nominated panel issue a Drug Destruction Certificate to Principal Investigator.

Principal Investigator will then submit a complete report to Division of Pharmacy Services, DRAP & the report will be placed before CSC, in very next meeting of the CSC,

The report should include:



- i. Date the trial started and ended and the License/certificate number.
- ii. Clinical Studies License and Clinical Trial Site License for the relevant site.
- iii. Date(s) and quantity received for each trial product
- iv. Balance of the study medical product.
- v. Drugs Destruction Certificate issued by DRAP, and/or written evidence of re-export of the unused drug supplies to country of origin (whichever applicable).

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

#### **15.4. 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.



## 16. CLINICAL TRIAL REGISTRY: -

Pharmacy Services Division, DRAP according to Rule 20 of the Bio-Study Rules 2017, shall maintain 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 Trial Registry is as below:

<b>01</b>	<b>Clinical Studies Name</b>	
<b>Title:</b>		
<b>Trial Acronym</b>		
<b>Brief Summery</b>		
<b>Trial Design</b>	<b>Allocation:</b>	
	<b>Intervention Model:</b>	
	<b>Assignment Masking:</b>	
	<b>Primary Purpose:</b>	
<b>Medical Condition</b>		
<b>Trial Phase</b>		
<b>Investigational Product</b>		
<b>Control No.</b>		
<b>Approval Date</b>		
<b>Duration of Trial</b>		
<b>Status</b>		
<b>Target Enrollment</b>		
<b>Eligibility Criteria</b>		



<b>Sex/Gender</b>	
<b>Age Group</b>	
<b>Approved Study Sites in Pakistan</b>	
<b>Participating Countries</b>	
<b>Sponsor</b>	
<b>Funder</b>	
<b>Global Trial Coordinator</b>	
<b>Global Chief Investigator</b>	
<b>Trial Coordinator / Principal Investigator in Pakistan</b>	
<b>Last Update On</b>	

The clinical trial registry of Pakistan shall be 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.

#### **16.1. U.S. National Trial Registry:**

Drug Regulatory Authority of Pakistan has recently adapted U.S. National Trial Registry as an international registry for all clinical trial approved by the DRAP. Link of the U.S. National Trial Registry is as follows:

<https://clinicaltrials.gov/>

Principal Investigators / Responsible parties (Sponsors) from Pakistan may nominate a focal person from their organizations, to open & maintain PRS (Protocol Registration & Results System) account.

All Principal Investigators / Responsible parties (Sponsors) will enlist their approved Clinical Trials on U.S. National Trial Registry and after getting “NCT” identifier number will inform to Division of Pharmacy Services-DRAP.

NCT Number: The National Clinical Trial number is an identification that ClinicalTrials.gov assigns a study when it is registered. The NCT number is in the format “NCTXXXXXXXX”.



Until an NCT number is assigned, the study is not registered on the U.S. National Trial registry.

**16.2. Trial subject registry: -**

A verifiable record of the clinical trial participants or subjects be maintained to stop duplicate enrolment and also to improve both patient safety and preserve data integrity of clinical trials. The subject identification shall be a closed information from the investigator, directly submitted to the DRAP.



## 17. INVESTIGATOR'S BROCHURE

### 17.1. Introduction

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. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and no promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data. This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labeling may be an appropriate alternative, provided that it includes current, comprehensive and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e. a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB. Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor -investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In



cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

## **17.2. General Considerations**

The IB should include:

### **17.2.1. Title Page**

This should provide the sponsor's name, the identity of each investigational product (i.e. research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Annexure-IV.

### **17.2.2. Confidentiality Statement**

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

### **17.2.3. Contents of the Investigator's Brochure**

The IB should contain the following sections, each with literature references where appropriate:

#### **17.2.3.1. Table of Contents**

An example of the Table of Contents is given in **Annexure-V**.

#### **17.2.3.2. Summary**

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

#### **17.2.3.3. Introduction**

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product(s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with



the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

#### **17.2.3.4. Physical, Chemical, and Pharmaceutical Properties and Formulation**

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula (e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties. To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given. Any structural similarities to other known compounds should be mentioned.

#### **17.2.3.5. Non-Clinical Studies**

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavorable and unintended effects in humans. The information provided may include the following, as appropriate, if known/available:

- i. Species tested.
- ii. Number and sex of animals in each group.
- iii. Unit dose (e.g. milligram/kilogram (mg/kg))
- iv. Dose interval.
- v. Route of administration.
- vi. Duration of dosing.
- vii. Information on systemic distribution.
- viii. Duration of post-exposure follow-up.
- ix. Results, including the following aspects:
  - a) Nature and frequency of pharmacological or toxic effects.
  - b) Severity or intensity of pharmacological or toxic effects.



- c) Time to onset of effects.
- d) Reversibility of effects.
- e) Duration of effects.
- f) Dose response.

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation. The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e. the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

#### **17.2.3.6. Non-Clinical Pharmacology:**

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g. Special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

#### **17.2.3.7. Pharmacokinetics and Product Metabolism in Animals:**

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systematic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

#### **17.2.3.8. Toxicology:**

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- i. Single dose.
- ii. Repeated dose.
- iii. Carcinogenicity.



- iv. Special studies (e.g. irritancy and sensitization).
- v. Reproductive toxicity.
- vi. Genotoxicity (mutagenicity)

### **17.2.3.9. Effects in Humans:**

#### **17.2.3.9.1. Introduction:**

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

#### **17.2.3.9.2. Pharmacokinetics and Product Metabolism in Humans**

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:

-Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution and elimination).

-Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.

-Population subgroups (e.g. gender, age and impaired organ function).

-Interactions (e.g. product-product interactions and effects of food).

-Other pharmacokinetic data (e.g. results of population studies performed within clinical trial(s)).

#### **17.2.3.9.3. Safety and Efficacy**

A summary of information should be provided about the investigational product's/product's (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by



indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

#### **17.2.3.9.4. Marketing Experience**

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarized (e.g. formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

#### **17.2.3.9.5. Summary of Data and Guidance for the Investigator**

This section should provide an overall discussion of the nonclinical and clinical data, and should summarize the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

**The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s).**

**Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug a reaction that is based on previous human experience and on the pharmacology of the investigation al product.**



## **18. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL:-**

### **18.1. 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.

**18.2. 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.	<b>FINANCIAL ASPECTS OF THE TRIAL</b>	To document the financial agreement between the investigator/institution and the sponsor for the trial	√	√
V.	<b>INSURANCE STATEMENT</b> (where required)		√	√
VI.	<b>SIGNED AGREEMENT BETWEEN INVOLVED PARTIES,</b> 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.	<b>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b> - 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.	<b>INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE COMPOSITION</b>	To document that the IRB/IEC is constituted in agreement with GCP	√	√ (where required)
IX.	<b>REGULATORY AUTHORITY(IES) AUTHORISATION/APPROVAL/ NOTIFICATION OF PROTOCOL</b> (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.	<b>CURRICULUM VITAE AND/OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)</b>	To document qualifications and eligibility to conduct trial and/or provide medical supervision of Subjects	√	√



XI.	<b>NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and/or ranges of the tests	√	√
XII.	<b>MEDICAL/LABORATORY/TECHNICAL PROCEDURES /TESTS</b> - 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.	<b>SAMPLE OF LABEL(S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER(S)</b>	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects	—	√
XIV.	<b>INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b> (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.	<b>SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS</b>	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.	<b>CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED</b>	To document identity, purity, and strength of investigational product(s) to be used in the trial	—	√
XVII.	<b>DECODING PROCEDURES FOR BLINDED TRIALS</b>	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)
XVIII.	<b>MASTER RANDOMISATION LIST</b>	To document method for randomization of trial population	—	√ (third party if applicable)
XIX.	<b>PRE-TRIAL MONITORING REPORT</b>	To document that the site is suitable for the trial (may be combined with 9.2.20)	—	√
XX.	<b>TRIAL INITIATION MONITORING REPORT</b>	To document that trial procedures were reviewed with the investigator and the investigator's trial staff ( may be combined with 9.2.19)	√	√

### 18.3. During the Clinical Conduct of the 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.	<b>INVESTIGATOR'S BROCHURE UPDATES</b>	To document that investigator is informed in atimely manner of relevant information as it becomes available	√	√
II.	<b>ANY REVISION TO:</b> - 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 relateddocuments that take effect during trial	√	√
III.	<b>DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) /INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING:</b> - 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 reviewand were given approval/favorable opinion. To identify the version number and date of the document(s).	√	√
IV.	<b>REGULATORY AUTHORITY (IES) AUTHORISATIONS/APPROVALS/NOTIFICATIONS WHERE REQUIRED FOR:</b> - protocol amendment(s) and other documents	To document compliance with applicableregulatory requirements	√ (where required)	√
V.	<b>CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUBINVESTIGATOR(S)</b>	(see 9.2.10)	√	√
VI.	<b>UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL</b>	To document normal values and ranges that are revised during the trial (see 9.2.11)	√ (where required)	√



VII.	<b>UPDATES OF MEDICAL/LABORATORY/ TECHNICAL PROCEDURES/TESTS</b> - 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.	<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS SHIPMENT</b>	(See 9.2.15.)	√	√
IX.	<b>CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCTS</b>	(see 9.2.16)	—	√
X.	<b>MONITORING VISIT REPORTS</b>	To document site visits by, and findings of, the Monitor	—	√
XI.	<b>RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS</b> - 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.	<b>SIGNED INFORMED CONSENT FORMS</b>	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.	<b>SOURCE DOCUMENTS</b>	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.	<b>SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)</b>	To document that the investigator or authorized member of the investigator's staff confirms the observations recorded	√ (copy)	√ (original)
XV.	<b>DOCUMENTATION OF CRF CORRECTIONS</b>	To document all changes/additions or corrections made to CRF after initial data were recorded	√ (copy)	√ (original)
XVI.	<b>NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS</b>	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	√	√

#### 18.4. 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 document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	√	√



II.	<b>DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION</b>	To document destruction of unused investigational products by sponsor or at site	√ (if destroyed at site)	√
III.	<b>COMPLETED SUBJECT IDENTIFICATION CODE LIST</b>	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.	<b>AUDIT CERTIFICATE</b> (if available)	To document that audit was performed	—	√
V.	<b>FINAL TRIAL CLOSE-OUT MONITORING REPORT</b>	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files	—	√
VI.	<b>TREATMENT ALLOCATION AND DECODING DOCUMENTATION</b>	Returned to sponsor to document any decoding that may have occurred	—	√
VII.	<b>FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY(IES)</b>	To document completion of the trial	√	—
VIII.	<b>CLINICAL STUDY REPORT</b>	To document results and interpretation of trial	√ (if applicable)	√



## 19. REFERENCES

- a) The DRAP Act, 2012.
- b) The Drugs Act, 1976
- c) The Bio-Study Rules, 2017.
- d) ICH-Guidelines (E6) for Good Clinical Practices (GCP).



**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.

Date:.....

Name of the applicant  
Signature  
Seal of the firm/Company

## **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).



**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 and fax 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.

Date: .....

Name of the applicant  
Signature  
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 and BA or BE study shall be made on application Form-II and Form-IIA respectively 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 . 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.



**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.

Date: .....

Name of the applicant  
Signature  
Seal of the firm/Company

### **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).



## 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:



**ANNEXURE-V**

**SAMPLE TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE**

- Confidentiality Statement (optional).....
- Signature Page (optional).....
- 1 Table of Contents.....
- 2 Summary.....
- 3 Introduction.....
- 4 Physical, Chemical, and Pharmaceutical Properties and Formulation.....
- 5 Nonclinical Studies.....
  - 5.1 Nonclinical Pharmacology.....
  - 5.2 Pharmacokinetics and Product Metabolism in Animals.....
  - 5.3 Toxicology.....
- 6 Effects in Humans.....
  - 6.1 Pharmacokinetics and Product Metabolism in Humans.....
  - 6.2 Safety and Efficacy.....
  - 6.3 Marketing Experience.....
- 7 Summary of Data and Guidance for the Investigator.....

NB: References on 1. Publications 2. Reports

These references should be found at the end of each chapter

Appendices (if any)



## 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)



**DRUG REGULATORY AUTHORITY OF PAKISTAN**

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Phone: 92-51-9262160

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