রেজিস্টার্ড নং ডি এ-১

বাংলাদেশ গেজেট

অতিরিক্ত সংখ্যা

কর্তৃপক্ষ কর্তৃক প্রকাশিত

বুধবার, এপ্রিল ৫, ২০১৭

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার

স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়

জনস্বাস্থ্য-০১ অধিশাখা

প্রজ্ঞাপন

তারিখ : ০৭ চৈত্র, ১৪২৩ ব:/২১ মার্চ, ২০১৭ খ্রি:

নং স্বাপকম/জনস্বাস্থ্য-১/ঔষধ-৩১/২০০২(অংশ-১)-৩৪০, তারিখ : ১১-১১-২০১৫ সংখ্যক স্মারকের মাধ্যমে স্বাস্থ্য ও পরিবার কল্যাণ মন্ত্রণালয়ের সচিব মহোদয় গত ০১-০৯-২০১৫ খ্রি: তারিখে Good Clinical Practice এর খসড়া Guideline এর বিষয়ে অনুষ্ঠিত সভায় সদয় অনুমোদন প্রদান করিলেন :

Guidelines for Good Clinical Practice (GCP) for Trials on Pharmaceutical Products Bangladesh

1. GLOSSARY

1.1 Adverse Drug Reaction (ADR)

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.

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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, diagonosis, 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).

1.2 **Adverse Event (AE)**

Any untoward medical occurrence in a patient or clinical investigation participant 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 (investgational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 **Amendement (to the protocol)**

See Protocol Amendment.

1.4 **Applicable Regulatory Requirement(s)**

Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 **Approval (In relation to Institutional Review Boards)**

The affirmative decision of the (IRB) that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 **Approved Training in Good Clinical Practice**

Training which is approved by the National Committee for Clinical Research (NCCR). The content of the training must incorporate the co-curriculum as stipulated by the committee.

1.7 **Audit**

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activites 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).

1.8 **Audit Certificate**

A declaration of confirmation by the auditor that an audit has taken place.

1.9 **Audit Report**

A written evaluation by the sponsor's auditor of the results of the audit.

1.10 **Audit Trail**

Documentation that allows reconstruction of the course of events.

1.11 **Blinding/Masking**

A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the participant(s) being unaware, and double blinding usually refers to the participant(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.12 **Case Report Form (CRF)**

A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial participant.

1.13 **Clinical Trial Exemption (CTX)**

An approval by the DCA authorizing the applicant to manufacture any local product for the purpose of clinical trial.

1.14 **Clinical Trial Import License (CTIL)**

DGDA, authorizing the licensee to import any product for purposes of clinical trials, not withstanding that the product is not a registered product.

1.15 **Clinical Trial/Study**

Any investigation in human participants 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 invetigational 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.

1.16 **Clinical Trial/Study Report**

A written description of a trial/study of any therapeutic, prophylactic, diagnostic agent conducted in human participants, 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).

1.17 **Clinical Trials**

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.

Phase I

These are the first trials of a new active ingredient or new formulations in man, often carried out in healthy volunteers. Their purpose is to establish a preliminary evaluation of safety, and a first outline of the pharmacokinetic and, where possible, a pharmacodynamics profile of the active ingredient in humans.

Phase II

These trials are performed in a limited number of subjects and are often, at a later stage, of a comparative (e.g. placebo-controlled) design. Their purpose is to demonstrate therapeutic activity and to assess short-term safety of the active ingredient in patients suffering from a disease or condition for which the active ingredient is intended. This phase also aims at the determination of appropriate dose ranges or regimens and (if possible) clarification of dose-response relationship in order to provide an optimal background for the design of extensive therapeutic trials.

Phase III

Trials in larger (and possibly varied) patient groups with the purpose of determining the short-and long-term safety/efficacy balance of formulation(s) of the active ingredient, and of assessing its overall and relative therapeutic value. The pattern and profile of any frequent adverse reactions must be investigated and special features of the product must be explored (e.g. clinically-relevant drug interactions, factors leading to differences in effect such as age). These trials should preferably be of a randomized double-blind design, but other designs may be acceptable, e.g. long-term safety studies. Generally, the conditions under which these trials are carried out should be as close as possible to normal conditions of use.

Phase IV

Studies performed after marketing of the pharmaceutical product. Trials in phase IV are carried out on the basis of the product characteristics on which the marketing authorization was granted ans are normally in the form of postmarketing surveillance, or assessment of therapeutic value of 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.

1.18 **Comparator (Product)**

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

1.19 **Compliance (in relation to trials)**

Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.20 **Confidentiality**

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

1.21 **Contract**

A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribtuion of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.22 **Coordinating Committee**

A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.23 **Coordinating Investigator**

An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.24 **Contract Research Organization (CRO)**

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

1.25 **Direct Access**

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

1.26 **Documentation**

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

1.27 **Drug Control Authority (DCA)**

A regulatory authority established for the purpose of regulating the Control of Drugs.

1.28 **Directorate General of Drug Administration (DGDA)**

This DGDA supervises and implements all prevailing Drug Regulations in the country and regulates all activities related to import, procurement of raw and packing materials, production and improt of finished drugs, export, sales, pricing, etc.

1.29 **Essential documents**

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see Annexure-2).

1.30 **Good Clinical Practice (GCP)**

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial participants are protected.

1.31 **Herbal/Animal Medicinal Products**

Plant/animal-derived materials or products with therapeutic or other human health benefits which contain either raw or processed ingredients from one or more plants/animals.

1.32 **Independent Data-Monitoring Committee (IDMC)/Data and Safety Monitoring Board (DSMB)**

Independent data-monitoring committees that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.33 **Impartial Witness**

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the participant or the participant's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the participant.

1.34. **Independent Ethics Committee (IEC)/Institutional Review Board (IRB)**

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human participants involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favorable opinion on the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial participants and providing continuing review of trial protocol and amendments and of the methods and material to be used. The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should alow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.35 **Informed Consent**

A process by which a participant 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 participant's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.36 **Inspection**

The act by a regulatory authority(ies) of conducting an official review of documents, facilites, 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 (CROs) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.37 **Institution (medical)**

Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.38 **Interim Clinical Trial/Study Report**

A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.39 **Investigational Product**

A pharmaceutical form of an active ingredient including plant/animal-derived medicinal products or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication (off-label use), or when used to gain further information about an approved use.

1.40 **Investigator**

A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also sub investigator.

1.41 **Investigator/Institution**

An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.42 **Investigator's Brochure**

A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human participants.

1.43 **Legally Acceptable Representative**

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

1.44 **Monitoring**

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

1.45 **Monitoring Report**

A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.46 **Multicentre Trial**

A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.47 **Nonclinical Study**

Biomedical studies not performed on human participants.

1.48 **Opinion (in relation to Independent Ethics Committee)**

The judgment and/or the advice provided by an Independent Ethics Committee (IEC).

1.49 **Original Medical Record**

See Source Documents.

1.50 **Well-being (of the trial participants)**

The physical and mental integrity of the participants participating in a clinical trial.

1.51 **Protocol**

A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.52 **Protocol Amendment**

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

1.53 **Quality Assurance (QA)**

All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.54 **Quality Control (QC)**

The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.55 **Randomization**

The process of assigning trial participants to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.56 **Regulatory Authorities**

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.35). These bodies are sometimes referred to as competent authorities.

1.57 **Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)**

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/incapacity, or

- is a congenital anomaly/birth defect (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.58 **Source Data**

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

1.59 **Source Documents**

Original documents, data and records (e.g. hospital records, clinical and office charts, laboratory notes, memoranda, participants' 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, participant files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.60 **Sponsor**

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.61 **Sponsor-Investigator**

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administrated to, dispensed to, or used by a participant. 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.

1.62 **Standard Operating Procedures (SOPs)**

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.63 **Sub Investigator**

Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions, (e.g., associates, residents, research fellows). See also Investigator.

1.64 **Participant/Trial Participant**

An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.65 **Participant Identification Code**

A unique identifier assigned by the investigator to each trial participant to protect the participant's identity and used in lieu of the participant's name when the investigator reports adverse events and/or other trial-related data.

1.66 **Trial Site**

The location(s) where trial-related activities are actually conducted.

1.67 **Unexpected Adverse Drug Reaction**

An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definations and Standards for Expedited Reporting).

1.68 **Vulnerable Participants**

Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with partcipation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable participants include patients with incurable diseases, persons in

nursing homes, unemployed, illiterate or impoverished persons, and patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

Introduction:

As per WHO guideline a functional NRA has 6 functions to perform independently such as Licensing and Marketing Authorization, Post Marketing Surveillance and AEFI, Laboratory Access, Regulatory / GMP Inspection, Lot Release and Regulatory oversight of clinical trials. Except Regultory oversight of clinical trials, DGDA has been performing other five funcations. For this reason DG, DGDA has formed a technical coordinating committee to formulate a proper guideline to conduct clinical research / clinical trial for pharmaceutical drugs in the country.

The committee has reviewed ICH GCP guideline (E6), WHO GCP guideline (TRS 850, annex-3), Malaysian GCP guideline, Pan American Health Organization (PAHO) GCP guideline, Indian GCP guideline (Schedule Y) etc. and adopted topics for Bangladesh Guideline.

2. **The principles of Bangladesh GCP**

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial participant and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial participants are the most important consideration and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval/favorable opinion.

2.7 The medical care given to, and medical decisions made on hehalf of, participants should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every participant prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could indentify participants should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)/NATIONAL RESEARCH ETHICS COMMITTEE (NREC)

3.1 Responsibilities

3.1.1 An IRB/IEC NREC should safeguard the rights, safety, and well-being of all trial participants. Special attention should be paid to trials that may include vulnerable participants. An IRB/IEC should follow the rules, regulation and Ethical guideline of Bangladesh Medical Research Council (BMRC).

3.1.2 The IRB/IEC/NREC should obtain the following documents: Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, participants recruitment procedures and written information to be provided to participants. Investigator's Brochure (IB), available safety information, information about payments and compensation available to participants, the investigator’s current curriculum vitae and/or other documentation

evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities. The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed, and the dates for the following:

- Approval/favorable opinion;

- Modifications required prior to its approval/favorable opinion;

- Disapproval/negative opinion; and

- Termination/suspension of any prior approval/favorable opinion.

3.1.3 The IRB/IEC/NREC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC/NREC requests.

3.1.4 The IRB/IEC/NREC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human participants, but at least once a year.

3.1.5 The IRB/IEC/NREC may request more information than is outlined in paragraph 5.8.10 be given to participants when, in the judgment of the IRB/IEC/ NREC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the participants.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the participant's legally acceptable representative (see 5.8.12, 5.8.14), the IRB/IEC/ NREC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial participants or the participant's legally acceptable representative is not possible (see 5.8.15), the IRB/IEC/NREC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8 The IRB/IEC/NREC should review both the amount and method of payment to participants to assure that neither presents problems of coercion or undue influence on the trial participants. Payments to a

participant should be prorated and not wholly contingent on completion of the trial by the participant.

3.1.9 The IRB/IEC/NREC should ensure that information regarding payment to participants, including the methods, amounts, and schedule of payment to trial participants, is set forth in the written informed consent form and any other written information to be provided to participants. The way payment will be prorated should be specified.

3.2 Composition, Functions, and Operations

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institutional/trial site. Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter. A list of IRB/IEC members and their qualifications should be maintained. All of these related matter need to follow current and regular updated rules, regulation of Bangladesh Medical Research Council.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspects of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.2.7 An institution without IRB/IEC may request BMRC, to make decisions on behalf of the said institution.

3.3 Procedures

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favorable opinion of minor change(s) in ongoing trials that have the approval/favorable opinion of the IRB/IEC.

3.3.6 Specifying that no participant should be admitted to a trial before the IRB/IEC issues its written approval/favorable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favorable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the participants or when the change(s) involves only logistical or administrative aspects of the trial (e.g. change of monitor(s), telephone number(s) (see 5.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial participants (see 3.3.7, 5.5.2, 5.5.4).

(b) Changes increasing the risk to participants and/or affecting significantly the conduct of the trial (see 5.10.2).

(c) All adverse drug reactions (ADRs) those are both serious and unexpected.

(d) New information that may affect adversely the safety of the participants or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/ institution concerning:

(a) Its trial-related decisions/opinions.

(b) The reasons for its decisions/opinions.

(c) Procedures for appeal of its decisions/opinions.

3.4 Records

Summary of approved protocols should be submitted to BMRC by the respective IRB/IEC. BMRC has the right to query any matter arising regarding ethical issue of the research at any time. The IRB/IEC should retain all relevant records (e.g. written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the DGDA. The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

3.5 Registration regarding IRB/IEC

All IRB/IEC require to be registered with BMRC. An Application for registration of IRB/IEC shall be made to the BMRC in accordance with the requirements.

3.6 BMRC has to approve all ethical clearance submitted to BMRC within 03 (three) months; if fails, ethical clearance shall be obtained from IRB/IEC of individual institution.

4. ROLE OF THE DRUG REGULATORY AUTHORITY, DGDA

The role of DGDA is to provide the legal framework for clinical trials.

1. Approval of CRO, institution or other clinical trial facilities involved in clinical trial.

2. Approval of study protocol.

3. Clinical trial inspection.

4. Evaluation of study findings in case of marketing authorization.

5. Pharmacovigilance

The aim should be two-fold: (i) to protect the safety and rights of the participants participating in a trial, and (ii) to ensure that trials are adequately designed to meet scientifically sound objectives. These aims may be met by several means, including the specification of the investigator's qualifications and requirement for review and approval of the protocol by relevant scientific and/or ethics committees.

Drug regulatory authorities should have a mandate to review protocols and, where necessary, to protect the safety of participants to require protocol revisions and/or termination of trials.

Regulations should allow for on-site inspections of the quality and reliability of the data obtained, with due concern for confidentiality.

4.1 General Responsibilities

The national drug regulatory authority should ensure that the protocols for clinical trials are submitted in advance for review and are in accordance with existing national regulations. On the basis of its review of clinical trial protocols and/or reports, the regulatory authority may propose revisions or request additional data on a clinical trial or terminate a trial.

The drug regulatory authority should evaluate the adequacy of supervision of the trial by reviewing the monitor's reports to the sponsor. In addition, the authority should be able to conduct on-site inspections of the reliability and quality of reported results.

National regulations should specify the procedures for reporting and handling cases of misconduct discovered in connection with clinical trials.

4.2 On-site inspections

As permitted by national regulations, the drug regulatory authority may carry out on-site inspections of the clinical trial site. Such inspections may be carried out routinely, randomly and/or for specific reasons, and should consist of a comparison of the procedures and practices of the investigator with those set out in the protocol and reports submitted to the drug regulatory authority by the investigator or the sponsor.

The inspection should determine whether the investigator has custody of the required records or, if not, who has assumed this responsibility. The data archives should be tested for ease of retrieval.

Inspections may include data audit. The drug regulatory authority should have easy access to all patient files and raw data used for and generated during the trial.

5. INVESTIGATOR

5.1 Investigator's Qualifications and Agreements

5.1.1 The investigator(s) should be qualified by education, approved training in Good Clinical Practice Certification, and experience to assume responsibility for the proper conduct of the trial, should meet all the qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

5.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information, and in other information sources provided by the sponsor.

5.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

5.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

5.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

5.2 Adequate Resources

5.2.1 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

5.2.2 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

5.2.3 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

5.3 Medical Care of Trial Participants

5.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

5.3.2 During and following a participant's participation in a trial, the investigator/ institution should ensure that adequate medical care is provided to a participant for any adverse events, including clinically significant laboratory values, related to the trial. The investigator/ institution should inform a participant when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

5.3.3 Although a participant is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's rights.

5.4 Communication with IRB/IEC

5.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures and any other written information to be provided to participants.

5.4.2 A part of the investigator's/institutions written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

5.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents participant to review.

5.5 Compliance with Protocol

5.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, by the regulatory authority(ies), and which was given approval/favorable opinion by the IRB/IEC. The investigator/ institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

5.5.2 The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favorable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial participants, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

5.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

5.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial participants without prior IRB/IEC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:

(a) To the IRB/IEC for review and approval/favorable opinion,

(b) To the sponsor for agreement and, if required,

(c) To the regulatory authority (ies).

5.6 Investigational Product(s)

5.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

5.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution’s duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

5.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each participant, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial participants. Investigators should maintain records that document adequately that the participants were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

5.6.4 The investigational product(s) should be stored as specified by the sponsor (see 6.13.2 and 6.14.3) and in accordance with applicable regulatory requirement(s).

5.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

5.6.6 The investigator, or a person designated by the investigator/ institution, should explain the correct use of the investigational product(s) to each participant and should check, at intervals appropriate for the trial, that each participant is following the instructions properly.

5.7 Randomization Procedures and Unblinding

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

5.8 Informed Consent of Trial Participants

5.8.1 In obtaining and documenting informed consent, the investigator should comply with GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/favorable opinion of the written informed consent form and any other written information to be provided to participants.

5.8.2 The written informed consent form in Bangla any other written information to be provided to participants should be revised whenever important new information becomes available that may be relevant to the participant’s consent. Any revised written informed consent form, and written information should receive the IRB/IEC's written approval/ favorable opinion in advance of use. The participant or the participant’s legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the participant’s willingness to continue participation in the trial. The communication of this information should be documented.

5.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a participant to participate or to continue to participate in a trial.

5.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the participant or the participant's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

5.8.5 The investigator, or a person designated by the investigator, should fully inform the participant or, if the participant is unable to provide informed consent, the participant's legally acceptable representative, of all pertinent aspects of the trial including the written information given approval/favorable opinion by the IRB/IEC.

5.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as nontechnical as practical and should be understandable to the participant or the participant's legally acceptable representative and the impartial witness, where applicable.

5.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the participant or the participant's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the participant or the participant's legally acceptable representative.

5.8.8 Prior to a participant's participation in the trial, the written informed consent form should be signed and personally dated by the participant or by the participant's legally acceptable representative, and by the person who conducted the informed consent discussion.

5.8.9 If a participant is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to participants is read and explained to the participant or the participant's legally acceptable representative, and after the participant or the participant's legally acceptable representative has orally consented to the participant's participation in the trial, and, if capable of doing so, has signed and/or thump printed and personally dated the informed consent form, the witness should sign and personally date the consent form.

By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and appropriately understood by, the participant or the participant's legally acceptable representative, and that informed consent was freely given by the participant or the participant's legally acceptable representative.

5.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to participants should include explanations of the following:

(a) That the trial involves research.

(b) The purpose of the trial.

(c) The trial treatment(s) and the probability for random assignment to each treatment.

(d) The trial procedures to be followed, including all invasive procedures.

(e) The participant's responsibilities.

(f) Those aspects of the trial that is experimental.

(g) The reasonably foreseeable risks or inconveniences to the participant and, when applicable, to an embryo, fetus, or nursing infant.

(h) The reasonably expected benefits. When there is no intended clinical benefit to the participant, the participant should be made aware of this.

(i) The alternative procedure(s) or course(s) of treatment that may be available to the participant, and their important potential benefits and risks.

(j) The compensation and/or treatment available to the participant in the event of trial-related injury.

(k) The anticipated prorated compensation, if any, to the participant for participating in the trial.

(l) The anticipated expenses, if any, to the participant for participating in the trial.

(m) That the participant's participation in the trial is voluntary and that the participant may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the participant is otherwise entitled.

(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the participant's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the participant, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the participant or the participant's legally acceptable representative is authorizing such access.

(o) That records identifying the participant will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the participant's identity will remain confidential.

(p) That the participant or the participant's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the participant's willingness to continue participation in the trial.

(q) The person(s) to contact for further information regarding the trial and the rights of trial participants, and whom to contact in the event of trial-related injury.

(r) The foreseeable circumstances and/or reasons under which the participant's participation in the trial may be terminated.

(s) The expected duration of the participant's participation in the trial.

(t) The approximate number of participants involved in the trial.

(u) The source of the investigational product that may be culturally unacceptable.

5.8.11 Prior to participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the participants. During a participant's participation in the trial, the participant or the participant's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to participants.

5.8.12 When a clinical trial (therapeutic or non therapeutic) includes participants who can only be enrolled in the trial with the consent of the participant's legally acceptable representative (e.g., minors, or patients

with severe dementia), the participant should be informed about the trial to the extent compatible with the participant's understanding and, if capable, the participant should assent, sign and personally date the written informed consent.

5.8.13 Except as described in 5.8.14, a non therapeutic trial (i.e., a trial in which there is no anticipated direct clinical benefit to the participant) should be conducted in participants who personally give consent and who sign and date the written informed consent form.

5.8.14 Non therapeutic trials may be conducted in participants with consent of a legally acceptable representative provided the following conditions are fulfilled:

(a) The objectives of the trial cannot be met by means of a trial in participants who can give informed consent personally.

(b) The foreseeable risks to the participants are low.

(c) The negative impact on the participant's well-being is minimized and low.

(d) The trial is not prohibited by law.

(e) The approval/favorable opinion of the IRB/IEC is expressly sought on the inclusion of such participants, and the written approval/favorable opinion covers this aspect. Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Participants in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

5.8.15 In emergency situations, when prior consent of the participant is not possible, the consent of the participant's legally acceptable representative, if present, should be requested. When prior consent of the participant is not possible, and the participant's legally acceptable representative is not available, enrollment of the participant should require measures described in the protocol and/or elsewhere, with documented approval/favorable opinion by the IRB/IEC, to protect the rights, safety, and wellbeing of the participant and to ensure compliance with applicable regulatory requirements. The participant or the participant's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 5.8.10) should be requested.

5.9 Records and Reports

5.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

5.9.2 Data reported on the CRF, That are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

5.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 6.18.4(n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

5.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see Annexure 2.) and as required by the applicable regulatory requirement(s). The investigator/ institution should take measures to prevent accidental or premature destruction of these documents.

5.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application and until there are no pending or contemplated marketing applications or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 6.5.12).

5.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

5.10 Progress Reports

5.10.1 The Investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

5.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/ IEC (see3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to participants.

5.11 Safety Reporting

5.11.1 All serious adverse events (SAEs) detected or being notified should be reported within two working days to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed within seven days by detailed, written reports. The immediate and follow-up reports should identify participants by unique code numbers assigned to the trial participants rather than by the participants' names, personal identification numbers, and/or addresses. The investigator must notify the unexpected serious adverse drug reactions to the regulatory authority (ies) and IRB/IEC within seven (7) working days.

5.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

5.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g. Autopsy reports and terminal medical reports).

5.12 Premature Termination or Suspension of a Trial

If the trial is prematurely terminated or suspended for any reason, the investigator/ institution should promptly inform the trial participants, should ensure appropriate therapy and follow-up for the participants, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority (ies). In addition:

5.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

5.12.2 If the sponsor terminates or suspends a trial (see 6.21), the investigator should promptly inform the institution where applicable and the investigator/

institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

5.12.3 If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

5.13 Find Report(s) by Investigator

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority (ies) with any reports required.

6. SPONSOR

6.1 Quality Assurance and Quality Control

6.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

6.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.24) to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

6.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

6.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

6.2 Contract Research Organization (CRO)

6.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor, The CRO should implement quality assurance and quality control.

6.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

6.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

6.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

6.3 Medical Expertise

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

6.4 Trial Design

6.4.1 The sponsor or CRO should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, physicians, pharmacists and related professionals) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

6.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) the Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct and which are appended as annexures.

6.5 Trial Management, Data Handling, and Record Keeping

6.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

6.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial. The IDMC should have written operating procedures and maintain written records of all its meetings.

6.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

a) Ensure and document that the electronic data processing system(s) conforms to the sponsor’s established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation)

b) Maintains SOPs for using these systems.

c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trial, edit trial).

(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 5.1.5 and 5.9.3).

(f) Maintain adequate backup of the data.

(g) Safeguard the blinding, if any (e.g., maintain the blinding during data entry and processing).

6.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

6.5.5 The sponsor should use an unambiguous participant identification code that allows identification of all the data reported for each participant.

6.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial. (see Annexure 2).

6.5.7 The sponsor should retain all sponsor-related essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

6.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e., for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

6.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

6.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

6.5.11 The sponsor-specific essential documents should be retained until at least 2 years after the last approval of a marketing or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirement(s) or if needed by the sponsor.

6.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial-related records are no longer needed.

6.6 Investigator Selection

6.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training (including approved GCP training) and experience and should have adequate resources properly conduct the trial for which the investigator is selected. If organization of a coordinating

committee and/or selection of coordinating investigator(s) are to be utilized in multicenter trials, their organization and/or selection are the sponsor's responsibilities.

6.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/ institution to review the protocol and the information provided.

6.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 5.1.3), and with the protocol agreed to by the sponsor and given approval/ favorable opinion by the IRB/IEC (see 5.5.1);

(b) To comply with procedures for data recording/reporting;

(c) To permit monitoring, auditing, and inspection (see 5.1.4). and

(d) To retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 5.9.4 and 6.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

6.7 Allocation of Duties and Functions

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

6.8 Compensation to Participants and Investigators

6.8.1 If required by the applicable regulatory requirement(s), the sponsor must provide insurance or must indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial except for claims that arise from malpractice and/or negligence.

6.8.2 The sponsor's policies and procedures should address the costs of treatment of trial participants in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

6.8.3 When trial participants receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

6.9 Financing

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

6.10 Notification/Submission to Regulatory Authority(ies)

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

6.11 Confirmation of Review by IRB/IEC

6.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favorable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to participants, participant recruiting procedures, and documents related to payments and compensation available to the participants, and any other documents that the IRB/IEC may have requested.

6.11.2 If the IRB/IEC conditions its approval/favorable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to participants, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favorable opinion was given by the IRB/IEC.

6.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC re-approvals/re-evaluations with favorable opinion, and of any withdrawals or suspensions of approval/favorable opinion.

6.12 Information on Investigational Product(s)

6.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

6.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available. (See Annexure-2).

6.13 Manufacturing, Packaging, Labeling, and Coding Investigational Product(s)

6.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, (if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GCP, and is coded and labeled in a manner that protects the blinding, if applicable. In addition, the labeling should comply with applicable regulatory requirement(s).

6.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

6.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

6.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

6.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g., stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

6.14 Supplying and Handling Investigational Product(s)

6.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

6.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favorable opinion from IRB/IEC and regulatory authority(ies). All importation of clinical trial drugs should go through customs even though a clinical trial import license has been obtained.

6.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from participants, and return of unused investigational

product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s).

6.14.4 The sponsor should:

a) Ensure timely delivery of investigational product(s) to the investigator(s).

(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s). (see Annexure-2).

c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).

d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

6.14.5 The sponsor should:

a) Take steps to ensure that the investigational product(s) are stable over the period of use.

(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

6.15 Record Access

6.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

6.15.2 The sponsor should verify that each participant has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

6.16 Safety Information

6.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

6.16.2 The sponsor should promptly notify all concerned investigator(s)/ institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of participants, impact the conduct of the trial, or alter the IRB/IEC's approval/favorable opinion to continue the trial.

6.17 Adverse Drug Reaction Reporting

6.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/ institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

6.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

6.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

6.18 Monitoring

6.18.1 Purpose

The purposes of trial monitoring are to verify that:

a) The rights and well-being of human participants are protected.

b) The reported trial data are accurate, complete, and verifiable from source documents.

c) The conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with GCP, and with the applicable regulatory requirement(s).

6.18.2 **Selection and Qualifications of Monitors**

a) Monitors should be appointed by the sponsor.

b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to participants, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

6.18.3 **Extent and Nature of Monitoring**

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for onsite monitoring, before, during, and after the trial; however, in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

6.18.4 **Monitor's Responsibilities**

The monitor(s), in accordance with the sponsor's requirements, should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

(a) Acting as the main line of communication between the sponsor and the investigator.

(b) Verifying that the investigator has adequate qualifications and resources (see 5.1, 5.2, 6.6) and remain adequate throughout the trial period, that facility, including laboratories equipment, and staff is adequate to safely and properly conduct the trial and these remain adequate throughout the trial period.

(c) Verifying, for the investigational product(s):

(i) The storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.

(ii) That the investigational product(s) are supplied only to participants who are eligible to receive it and at the protocol specified dose(s).

(iii) That participants are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).

(iv) That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.

(v) That the disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.

(d) Verifying that the investigator follows the approved protocol and all approved amendment(s), if any.

(e) Verifying that written informed consent was obtained before each participant's participation in the trial.

(f) Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trial supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).

(g) Ensuring that the investigator and the investigator's trial staff are adequately informed about the trial.

(h) Verifying that the investigator and the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.

(i) Verifying that the investigator is enrolling only eligible participants.

(j) Reporting the participant recruitment rate.

(k) Verifying that source documents and other trial records are accurate, complete, kept up-to-date, and maintained.

(l) Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.

(m) Checking the accuracy and completeness of the CRF entries, source documents, and other trial-related records against each other. The monitor specifically should verify that:

(i) The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.

(ii) Any dose and/or therapy modifications are well documented for each of the trial participants.

(iii) Adverse events, concomitant medications, and intercurrent illnesses are reported in accordance with the protocol on the CRFs.

(iv) Visits that the participants fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.

(v) All withdrawals and dropouts of enrolled participants from the trial are reported and explained on the CRFs.

(n) Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialed by the investigator or by a member of the investigator's trial staff who is authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents. (see Annexure 5).

(q) Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

6.18.5 **Monitoring Procedures**

The monitor(s) should follow the sponsor’s established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

6.18.6 **Monitoring Report**

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken, and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

6.19 Audit

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

6.19.1 **Purpose**

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

6.19.2 **Selection and Qualification of Auditors**

(a) The sponsor should appoint individuals, who are independent of the clinical trials/ systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

6.19.3 **Auditing Procedures**

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of Participants in the trial, the type and complexity of the trial, the level of risks to the trial Participants, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority (ies) should not routinely request the audit reports. Regulatory

authority(ies) may seek access to an audit report on a case-by case basis when evidence of serious GCP noncompliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

6.20 Noncompliance

6.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement (s) by an investigator/institution, or by member (s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

6.20.2 If the monitoring and/or auditing identify serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/ institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority (ies).

6.20.3 The DGDA will enforce the rules and punitive action will be decided by the DGDA.

6.21 Premature Termination of Suspension of a Trial

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority (ies) of the termination or suspension and the reason (s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason (s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement (s).

6.22 Clinical Trial/Study Reports

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency (ies) as required by the applicable regulatory requirements (s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the relevant regulatory authority requirement.

6.23 Multicentre Trials

For multicentre trials, the sponsor should ensure that :

6.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority (ies), and given approval/ favorable opinion by the IRB/IEC.

6.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided those are designed to capture the additional data.

6.23.3 The responsibilities of coordinating investigator (s) and the other participating investigators are documented prior to the start of the trial.

6.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

6.23.5 Communication between investigators is facilitated.

7. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT (S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page (s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

7.1 General Information

7.1.1 Protocol title, protocol identifying number and date. Any amendment (s) should also bear the amendment number (s) and date (s).

7.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

7.1.3 Name and title of the person (s) authorized to sign the protocol and the protocol amendment (s) for the sponsor.

7.14 Name, title, address and telephone number (s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

7.1.5 Name and title of the investigator (s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

7.1.6 Name, title, address and telephone number (s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

7.1.7 Name(s) and address (es) of the clinical laboratory (ies) and other medical and/or technical departments(s) and/or institutions involved in the trial.

7.2 Background Information

7.2.1 Name and description of the investigational product (s).

7.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that is relevant to the trial.

7.2.3 Summary of the known and potential risks and benefits, if any, to human participants.

7.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period (s)

7.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement (s)

7.2.6 Description of the population to be studied.

7.2.7 References to literature and data that are relevant to the trial and that provide background for the trial.

7.3 Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial.

7.4 Trial Design

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial

design. A description of the trial design should include :

7.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

7.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

7.4.3 A description of the measures taken to minimize/avoid bias, including :

(a) Randomization.

(b) Blinding.

7.4.4 A description of the trial treatment (s) and the dosage and dosage regimen of the investigational product (s). Also include a description of the dosage form, packaging, and labeling of the investigational product (s).

7.4.5 The expected duration of participant participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

7.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual participants, parts of trial and entire trial.

7.4.7 Accountability procedures for the investigational product (s), including the placebo(s) and comparator (s), if any.

7.4.8 Maintenance of trial treatment randomization codes and procedures for breaking code.

7.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written of electronic record of data), and to be considered to be source data.

7.5 Selection and withdrawal of Participants

7.51. Participant inclusion criteria.

7.5.2 Participant exclusion criteria.

7.5.3 Participant withdrawal criteria (i.e terminating investigational product treatment/ trial treatment) and procedures specifying :

(a) When and how to withdraw participants from the trial/investigational product treatment.

(b) The type and timing of the data to be collected for withdrawn participants.

(c) Whether and how participants are to be replace.

(d) The follow-up for participants withdrawn from investigational product treatment/trial treatment.

7.6 Treatment of Participants

7.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), and dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for participants for each investigational product treatment/trial treatment group/arm of the trial.

7.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

7.6.3 Procedures for monitoring participant compliance.

7.7 Assessment of Efficacy

7.7.1 Specification of the efficacy parameters.

7.72 Methods and timing for assessing, recording, and analyzing of efficacy parameters.

7.8 Assessment of Safety

7.8.1 Specification of safety parameters.

7.8.2 The methods and timing for assessing, recording, analyzing safety parameters.

7.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

7.8.4 The type and duration of the follow-up of participants after adverse events.

7.9 **Statistics**

7.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

7.9.2 The number of participants planned to be enrolled. In multicentre trials, the numbers of enrolled participants projected for each trial site should be specified. Reson for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

7.9.3 The level of significance to be used.

7.9.4 Criteria for the termination of the trial.

7.9.5 Procedure for accounting for missing, unused, and spurious data.

7.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation (s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

7.9.7 The selection of participants to be included in the analyses (e.g all randomized participants, all dosed participants, all eligible participants, evaluable participants).

7.10 Direct access to source Data/documents

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

7.11 Quality Control and Quality Assurance

7.12 Ethics

Description of ethical considerations relating to the trial. (Section 1.33)

7.13 Data Handing and Record Keeping

7.14 financing and Insurance

Financing and insurance if not addressed in a separate agreement.

7.15 Publication Policy

Publication policy, if not addressed in a separate agreement.

7.16 Supplements

(NOTE : Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

8. INVESTIGATOR'S BROCHURE

8.1 *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 participants. 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 participants 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 of 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.

8.2 General Considerations

The IB should include:

8.2.1 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.

8.2.2 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.

8.3 Contents of the Investigator's Brochure

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

8.3.1 Table of Contents

8.3.2 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.

8.3.3 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 products(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.

8.3.4 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.

8.3.6 Nonclinical Studies

Introduction

The results of all relevant nonclinical pharmacology, toxicology pharmaco-kinetic, 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 unfavourable and unintended effects in humans. The information provided may include the following as appropriate, if known/ available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g milligram/kilogram (mg/kg))
- Dose interval
- Route of administration
- Duration of closing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
- Nature and frequency of pharmacological or toxic effects
- Severity or intensity of pharmacological or toxic effects
- Time to onset of effects
- Reversibility of effects
- Duration of effects
- 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.

(a) Nonclinical 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))

(b) 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.

(c) 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:

- single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g irritancy and sensitization)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

8.3.6 Effects in Humans

Introduction:

A thorough discussion of the known effects of the investigational products (s) in humans should be provide, 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.

(a) 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).

(b) 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).

(c) 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.

8.3.7 **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 investigational product.

ANNEXURES

Annex 1 : Informed Consent Template

1. Cheek list 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 of 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 participte in a clinical trial

Study Title:

Study Number:

Subject's Initials:_____Subject's Name:_____
Date of Birth/Age:_____

Please initial box (Subject)

(i) I confirm that I have read and understood the [ ]

information sheet dated ____ for the above study and

have had the opportunity to ask questions.

(ii) I understand that my participation in the study is [ ]

voluntary and that I am free to withdraw at any

time, without giving any reason, without my

medical care or legal rights being affected.

(iii) I understand that the Sponsor of the clinical trial, [ ]

others working on the Sponsor's behalf, the Ethics

Committee and the regulatory authorities will not

need my permission to look at my health records

both in respect of the current study and any further

research that may be conducted in relation to it,

even if I withdraw from the trial. I agree to this

access. However, I understand that my identity will

not be revealed in any information released to third

parties or published.

(iv) I agree not to restrict the use of any data or results [ ]

that arise from this study provided such a use is

only for scientific purpose(s)

(v) I agree to take part in the above stuby. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable Representative:_____

Date:_____ / _____ /_____

Signatory's Name:_____

Signature of the Investigator:_____Date:___ / ____ /___

Study Investigator's Name:_____

Signature of the Witness _____Date:___ / ____ /___

Name of the Witness:_____

Annex 2: Requirement for conducting Clinical Trial

		Located in files of	
Title of Document	Purpose	Investigator/ Institution	Sponsor
2.1 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			
2.1.1 INVESTIGATOR'S BROCHURE	To document that relevant and current scientific information about the investigational product has been provided to the investigator	x	x
2.1.2 SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND amendment(s) and CRF SAMPLE CASE REPORT FORM (CRF)	to document investigator and sponsor agreement to the protocol	x	x
2.1.3 INFORMATION GIVEN TO TRIAL SUBJECT -INFORMED CONSENT FORM (including all applicable Translation)	To document the informed consent	X	X
-ANY OTHER WRITTEN INFORMATION	To document that participants will be given appropriate written information (content and wording) to support their ability to givefully informed consent	x	X
-ADVERTISEMENT FOR SUBJECT RECRUITMENT (if used)	To document that recruitment measures are appropriate and not coercive	x	

2.1.4 FINANCIAL ASPECTS OF THE TRIAL	To document the financial agreement between the investigator/ institution and the sponsor for the trial	x	x
2.1.5 INSURANCE STATEMENT (where required)	To document that compensation to subject(s) for trail-related injury will be available	x	x
2.1.6 SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.: -investigator/institution and XX sponsor -investigator/institution and x (where CRO required) -sponsor and CRO -investigator/institution and xx authority(ies) (where required)	To document agreements	 x x x	 X X (where required) X x
2.1.7 DATED, DOCUMENTED APPROVAL/FAVORABLE OPINION OF INSTITUTIONAL, REVIEW BOARD (IRB)/INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: -protocol and any amendments -CRF (if applicable) -informed consent form(s) -any other written information to be provided to the subject(s) -advertisement for subject recruitment (if used) -subject compensation (if any) -any other documents given approval/favorable opinion	To document that the trial has been subject to IRB/IEC review and given approval/ favorable opinion. To identify the version number and date of the document(s)	x	x

2.1.8 INSTITUTIONAL REVIEW BOARD/ INDEPENDENT ETHICS COMMITTEE STATUS	To document that the IRB/IEC is constituted in agreement with GCP XX and approved by BMRC or National Ethical Committee	x	x
2.1.9 REGULATORY AUTHORITY (IES) AUTHORIZATION/ APPROVAL/NOTIFICATION OF PROTOCOL (where required)	To document approriate authorization/approval/ notification by XX the regulatory authority (ise) has been obtained prior to initiation (where (where of the trial in compliance with the applicable regulatory required) required) requirement(s)	x	x
2.1.10 CURRICULUM VITAE AND/ OR OTHER RELEVANT DOCUMENTS EVIDENCING QUALIFICATIONS OF INVESTIGATOR(S) AND SUB-INVESTIGATOR(S)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of participants	x	x
2.1.11 NORMAL VALUE(S)/ RANGE(S) FOR MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S) AND/OR TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and/or ranges of the tests	x	x
2.1.12 MEDICAL/ LABORATORY/TECHNICAL PROCEDURES/TESTS -certification or -accredition or -established quality control	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	x

and/or extrnal quality assessment or -other validation (where required)			
2.1.13 SAMPLE OF LABEL (S) ATTACHED TO INVESTIGATIONAL PRODUCT CONTAINER (S)	To document compliance with appilicable labeling regulations and appropriateness of instructions provided to the participants	x	x
2.1.14 INSTRUCTIONS FOR HANDLING OF INVESTIGATIONAL PRODUCT(S) AND TRIAL-RELATED MATERIALS (if not included in protocol or investigator's Brochure)	To document instructions needed to ensure proper storage, XX packaging, dispensing and disposition of investigational products and trial-related materials	x	x
2.1.15 SHIPPING RECORDS FOR INVESTIGATIONAL PRODUCT(S) AND TRIAL RELATED MATERIALS	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and acccountability	x	x
2.1.16 CERTIFICATE(S) OF ANALYSIS OF INVESTIGATIONAL PRODUCT(S) SHIPPED	To document identity, purity, and strength of investigational product(s) to be used in the trial. GMP certificate of the facility.	x	x

2.1.17 DECODING PROCEDURES FOR BLINDED TRIALS	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind (third party if for the remaining subject's treatment applicable)	x	x
2.1.18 TRIAL INITIATION MONITORING REPORT	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with Annexure 2.2.19)	x	x
2.2 During the Clinical Conduct of the Trial In addition to having on file 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			
2.2.1 INVESTIGATOR'S BROCHURE UPDATES	To document that investigator is informed in a timely manner of relevant information as it becomes available	x	x
2.2.2 ANY REVISION TO: -protocol/amendment(s) and CRF -informed consent form -any other written information provided to participants -advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	x	x
2.2.3 DATED, DOCUMENTED APPROVAL/FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB)/ INDEPENDENT ETHICS	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favorable opinion. To identify	x	x

COMMITTEE (IEC) OF THE FOLLOWING: -protocol amendment(s) -revision(s) of: -informed consent form -any other written information to be provided to the subject -advertisement for subject recruitment (if used) -any other documents given approval/favorable opinion -continuing review of trial (where required)	the version number and date of the document(s)		
2.2.4 REGULATORY AUTHORITY(IES) AUTHORIZATIONS/ APPROVALS/ NOTIFICATIONS WHERE REQUIRED FOR: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	x
2.2.5 CURRICULUM VITAE FOR NEW INVESTIGATOR(S) AND/OR SUB-INVESTIGATOR(S)	(see Annexure 2.2.1)	x	x
2.2.6 UPDATES TO NORMAL VALUE(S)/RANGE(S) FOR MEDICAL/LABORATORY/ TECHNICAL PROCEDURE(S)/TEST(S) INCLUDED IN THE PROTOCOL	To document normal values and ranges that are revised during the trial (see Annexure 2.2.11)	x	x
2.2.7 UPDATES OF MEDICAL/ LABORATORY/ TECHNICAL PROCEDURE(S)/ TEST -certification or -accreditation or	To document that tests remain adequate through out the trial period (see Annexure 2.2.12)	X (where required)	x

-established quality control and/or external quality assessment or -other validation (where required)			
2.2.8 DOCUMENTATION OF INVESTIGATIONAL PRODUCT(S) AND TRIAL- RELATED MATERIALS SHIPMENT	(see Annexure 2.2.15)	x	x
2.2.9 CERTIFICATE(S) OF ANALYSIS FOR NEW BATCHES OF INVESTIGATIONAL PRODUCT	(see Annexure 2.2.16)		**X**
2.2.10 MONITORING VISIT REPORTS	To document site visits by, and findings of, the monitor		**X**
2.2.11 RELEVANT COMMUNICATIONS OTHER THAN SITE VISITS -letters -meeting notes -notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	x	x
2.2.12 SIGNED INFORMED CONSENT FORMS	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subjcet in trial. Also to document direct access permission (see Annexure 2.2.3)	x	

2.2.13 SOURCE DOCUMENTS	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
2.2.14 SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	To document that the investigator or authorized member of the investigator's staff confirms the observation recorded	X (copy)	X (original)
2.2.15 DOCUMENTATION OF CRF CORRECTIONS	To document all changes/ additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
2.2.16 NOTIFICATION BY ORIGINATING INVESTIGATOR TO SPONSOR OF SERIOUS ADVERSE EVENTS AND RELATED REPORTS	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 5.11	x	x
2.2.17 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 6.17 and 5.11.1 and of other safety information in accordanc with 6.16.2	X (where required)	x

2.2.18 NOTIFICATION BY SPONSOR TO INVESTIGATORS OF SAFETY INFORMATION	Notification by sponsor to investigators of safety information in accordance with 6.16.2	x	x
2.2.19 INTERIM OR ANNUAL REPORTS TO IRB/IEC AND AUTHORITY (IES)	Interim or annual reports provided to IRB/IEC in accordance with 5.10 and to authority (ies) in accordance with 6.17.3	X	X (where required)
2.2.20 SUBJECT SCREENING LOG	To document identification of particpants who entered pre-trial screening	X	X (where required)
2.2.21 SUBJECT IDENTIFICATION CODE LIST	To document that investigator/institution keeps & confidential list of names of all participants allocated to trial numbers on enrolling in the trial. Allows investigator/ institution to reveal identity of any subject	X	
2.2.22 SUBJECT ENROLLMENT LOG	To document chronological enrollment of participants by trial number	X	
2.2.23 INVESTIGATIONAL PRODUCTS ACCOUNTABILITY AT THE SITE	To document that investigational product(s) have been used accordingly to the protocol	X	X

2.2.24 SIGNATURE SHEET	To document signatures and initials of all persons authorized to make entries and/or corrections on CRFs	X	X
2.2.25 RECORD OF RETAINED BODY FLUIDS/TISSUE SAMPLES (IF ANY)	To document location and indentification of retained samples if assays need to be repeated	X	X
2.3 **After Comopletion or Termination of the Trial** After completion or termination of the trial, all of the documents identified in Annexure (2.2 and 2.3) should be in the file together with the following			
2.3.1 INVESTIGATIONAL PRODUCT(S) ACCOUNTABILITY AT SITE	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to participants, returned by the participants, and returned to sponsor	x	x
2.3.2 DOCUMENTATION OF INVESTIGATIONAL PRODUCT DESTRUCTION	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	x
2.3.3 COMPLETED SUBJECT IDENTIFICATION CODE LIST	To permit identification of all participants enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	

2.3.4 AUDIT CERTIFICATE (if available)	To document that audit was performed		x
2.3.5 FINAL TRIAL CLOSE-OUT MONITORING REPORT	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		x
2.3.5 TREATMENT ALLOCATION AND DECODING DOCUMENTATION	Returned to sponsor to document any decoding that may have occurred		x
2.3.7 FINAL REPORT BY INVESTIGATOR TO IRB/IEC WHERE REQUIRED, AND WHERE APPLICABLE, TO THE REGULATORY AUTHORITY (IES)	To document completion of the trial	x	
2.3.8 CLINICAL STUDY REPORT	To document results and interpretation of trial	X (if applicable)	x

Annexure 3:

Regulatory Requirement for Bio-Equivalence study

Generic Product: a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance are considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. The purpose of establishing bioequivalence is to demonstrate equivalence in biopharmaceutics quality between the generic medicinal product and a reference medicinal product in order to allow bridging of preclinical tests and of clinical trials associated with the reference medicinal product.

In bioequivalence studies, the plasma concentration time curve is generally used to assess the rate and extent of absorption. Selected pharmacokinetic parameters and preset acceptance limits allow the final decision on bioequivalence of the

tested products. AUC, the area under the concentration time curve, reflects the extent of exposure. Cmax, the maximum plasma concentration or peak exposure, and the time to maximum plasma concentration, tmax, are parameters that are influenced by absorption rate. The number of studies and study design depend on the physico-chemical characteristics of the substance, its pharmacokinetic properties and proportionality in composition, and should be justified accordingly. In particular it may be necessary to address the linearity of pharmacokinetics, the need for studies both in fed and fasting state, and the possibility of waiver for additional strengths.

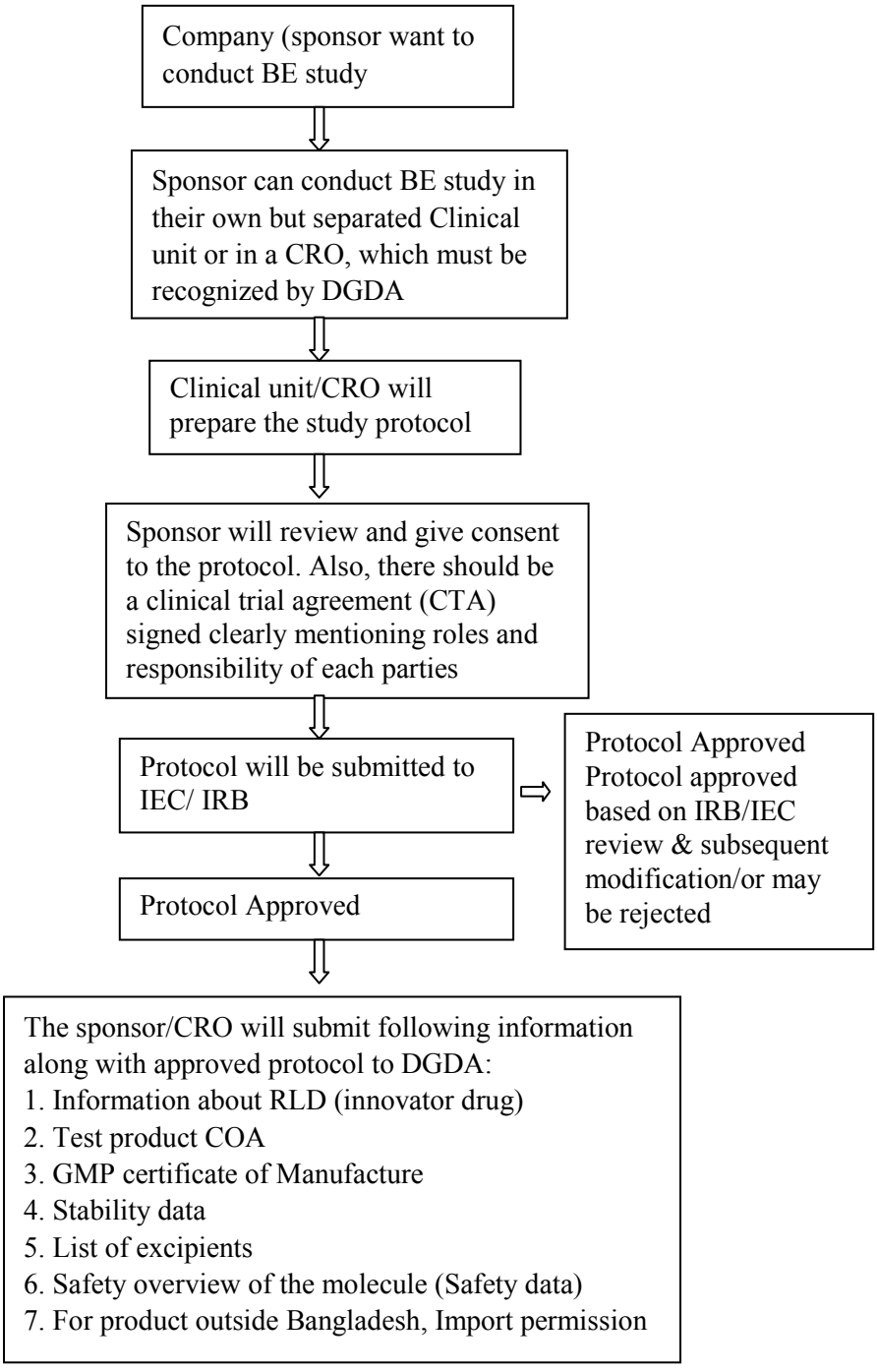
Standard design: If two formulations are compared, a randomised, two-period, two-sequence single dose crossover design is recommended. The treatment periods should be separated by a wash out period sufficient to ensure that drug concentrations are below the lower limit of bioanalytical quantification in all subjects at the beginning of the second period. Normally at least 5 elimination half-lives are necessary to achieve this. In studies to determine bioequivalence after a single dose, the parameters to be analysed are AUC(0-t), and Cmax. For these parameters the 90% confidence interval for the ratio of the test and reference products should be contained within the acceptance interval of 80.00-125.00% For further readings, EMEA GUIDELINE ON "THE INVESTIGATION OF BIOEQUIVALENCE" (CPMP/EWP/QWP/1401/98 Rev. 1/Corr) and US FDA "Guidance for industry: Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA" is recommended.

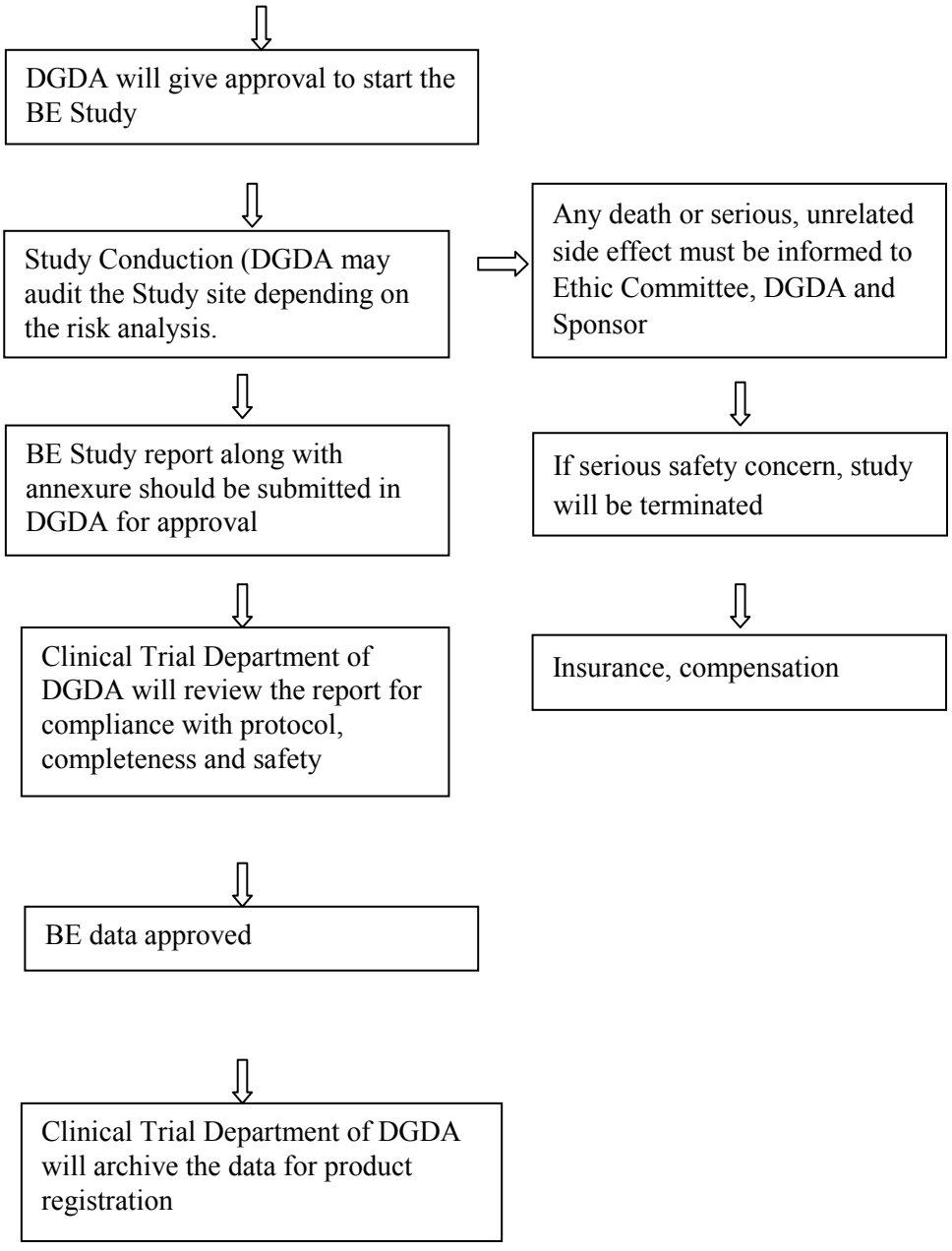
Regulatory procedure: When a company/sponsor want to conduct BE study, it can be conducted in their own but separated clinical unit or in CRO (Contract Research Organization), which must be Pre-approved by DGDA. At first, clinical unit/CRO will prepare the study protocol. Then the sponsor will review and give consent of the protocol for submission to IRB/IEC. Then the Protocol will be reviewed and approved/rejected by IRB/IEC. If required the protocol can be modified maintaining version number. After approval the sponsor/CRO will submit few information (see flow chart 01) along with approved protocol to DGDA.

DGDA will give the approval to start BE study based on protocol review, registration status of study center and GMP compliance of test product. During the study DGDA may audit the study site depending on the risk analysis. Any death or serious unwanted side effect must be informed to IRB, DGDA, and sponsor. If there is any safety concern, the study will be terminated followed by proper compensation, if needed.

After successful completion all study reports with annexure should be submitted in DGDA for final approval Clinical Trial Department of DGDA will review the report for final approval.

Flow Chart 01




DGDA will give approval to start the BE Study
Study Conduction (DGDA may audit the Study site depending on the risk analysis.
Any death or serious, unrelated side effect must be informed to Ethic Committee, DGDA and Sponsor
BE Study report along with annexure should be submitted in DGDA for approval
If serious safety concern, study will be terminated
Clinical Trial Department of DGDA will review the report for compliance with protocol, completeness and safety
Insurance, compensation
BE data approved
Clinical Trial Department of DGDA will archive the data for product registration

Annexure-4: Regulatory requirement for Clinical Trial of Biosimilars and vaccines

Data Requirements for Preclinical Studies

4.1 Prerequisite before Conducting Preclinical Studies

The applicant has to comply with the DGDA requirements like demonstration of consistency of the process and product, product characterization and product specifications. The applicant should submit the data generated along with the following basic clincal information and preclinical study protocols to DGDA for obtaining permission. The toxicology studies should be initiated after the approval of DGDA. The basic information about the reference biologic and similar biologic may include the following:

Basic information about the reference biologic

- information about the drg, route of administration, absorption and elimination rate, therapeutic index, dose, vehicle, mode of administration, dose response etc.
- Available toxicity data on reference biologic.
- Mode of action.

Basic information about the similar biologic

- Known / proposed clinical use
- Target population (Age, sex, pregnancy, lactating, children etc.)
- Dosage (frequency and intervals)-units
- Route / alternate routes of administration
- Final formulation + adjuvants, additives etc.—Toxicology data of adjuvants
- Diluents
- Presentation e.g. pre filled syringe if needed.

The application to DGDA should be accompanied by approval by the Institutional Biosafety Committee (IBSC) of the applicant and approval of Institutional Animal Ethics Committee (IAEC), if available. The applicant should also provide details of the proposed site for conduct of toxicity testing and personal to be involved e.g. study director, principal investigator, pathologist, other Investigators and quality assurance officer at the site.

4.1.1 Preclinical Studies (Pharmacodynamic and Toxicology Studies)

The preclinical studys should be conducted prior to the initiation of any clincial studies. These preclinical studies should be comparative in nature and designed to detect differences if any, between the similar biologic and reference biologic.

The preclinical study design may vary depending upon the clinical parameters such as therapeutic index, the type and number of indications applied.

The approach adopted should be fully justified in the preclinical overview.

Preclinical studies should be conducted with the final formulation of the similar biologic intended for clinical use and for the reference biologic unless otherwise justified. The dosage form, strength and route of administration of the similar biologic should be the same as that of the reference biologic and in case of any differences in these parameters, it should be justified.

The following studies are required for preclinical evaluation:

4.1.2 Toxicological studies

In case of *in vivo* toxicity studies, at least one repeat dose toxicity study in a relevant species is required to be conducted. The duration of the study would be generally not less than 28 days with 14 days recovery period. However the duration may vary depending on the dosage and other parameters on case by case basis. Regarding the animal models to be used, the applicant should provide the scientifc justification for the choice of animal model(s) based on the data available in scientifc literature. However if the relevant animal species is not available and has been appropriately justified, the toxicity studies need to be undertaken in two species i.e. one rodent and other non rodent species, as per the requirements of DGDA. For a 28 days repeated dose toxicity study rodent group may consist of 6-10/sex/group and non-rodent group may consist of 2-3/sex/group. Regarding the route of administration, in cases when the relevant animal model is used, the route of administration would include only the intended route.

The dose should be calculated based on the therapeutic dose of the reference biologic. If required a pilot dose response study should be conducted prior to initiating the toxicity studies. Generally there would be three levels of doses (*viz.* low, medium and high) used in the animal toxicology studies corresponding to 1X, 2X and 5X of human equivalent dose or hihger test dose for repeat dose toxicity studies. Any difference in the levels of doses should be justified and approved prior to the studies. Regarding the schedule of administration, the therapeutic schedules may be used as the basis.

Depending on the route of administration, local tolerance should be evaluated.

If feasible, this evaluation may be performed as a part of above mentined repeat dose toxicity study.

Accordingly the study groups of animals in repeat dose toxicity testing will consist of:

i. Historical Control (Optional)

ii. Vehicle Control

iii. Vehicle Control for recovery group

iv. Formulation without protein (for vaccines) if multiple adjuvants-each to be checked independently

v. 1X similar biologic for study duration (lowest dose)

vi. 1X Reference biologic for study duration

vii 2X Medium dose similar biologic

viii. 5X High dose similar biologic

ix. Similar biologic with a recovery group going beyond the end of study period for 7 to 14 days

The protocols and the study reports should provide complete details of various steps in the toxicity testing as indicated below:

- Procedures prior to euthanasia e.g. blood drawing, body wight, etc.
- Events immediately after euthanasia, necropsy, gross-description, organ weights and organs sampled for histopathology.
- Hematology procedures and parameters-method to be used (automated or manual).
- Statistical methods used.
- Bone marrow either examined as an aspirate/smear or on histopathology section.

In case of histopathological observations, the applicants should consider the following points:

- Every observation considered as deviation from described normal histology needs to be documented and the incidence of each of these in the different groups should be denoted.

- Whether such a feature is significant or not can be decided on review of statistical significance or dose response or if it is within or outside the normal range of values in case of biochemical and hematological observations.

- If all organs from all animals were not examined e.g. in 5 animals only 4 livers were examined, the reason for the 1 liver not being examined should be documented.

- In case of premature death or morbidity the proposed course of action is to be included in the protocol. Other toxicity studies, including safety pharmacology, reproductive toxicity, mutagenicity and carcinogenicity studies are not generally required for evaluation of a similar biologic unless warranted by the results from the repeat dose toxicological studies.

The final report of the study should reflect all the aspects approved in the propocol and the following additional sections/documents:

- DGDA approval of protocol and test center

- Institutional Bio-Safety Committee (IBSC)/Institutional Animal Ethics Committee (IAEC) approval of report

- QA statement

- Signatures of study director and all investigators who were involved in the study

- All quality analytical reports on the test material and vehicle

- Animal feed and animal health certifications

- Protocol deviations if any

- Discussion on the results

- Summary data and any other data, etc

- Conclusion

4.2. Data Requirements for Clinical Trial Application

The quality data submitted should eastablish comparability of similar biologic manufactured at clinical scale against reference biologic.

4.2.1 Pharmacokinetic Studies

Comparative pharmacokinetic (PK) studies should be performed in health volunteers or patients to demonstrate the similarities in pharmacokinetic characteristics between similar biologic and reference biologic on case to case basis.

The design of comparative pharmacokinetic studies should take the following factors into consideraion.

- Half life
- Linearity of PK parameters
- Endogenous levels and diurnal variations of similar biologic under study (where applicable)
- Conditions and diseases to be treated
- Route(s) of administration, and
- Indications

4.2.2. Single Dose Comparative PK Studies

Dosage in the PK study should be within the therapeutic dose range of reference biologic. Appropriate rationale for dose selection should be provided. The route of administration should be the one where the sensitivity to detect differences is the largest. Sample size should have statistical rationale (i.e. statistically justified) and comparability limits should be defined and justified prior to conducting the study.

The analytical method should be validated to have satisfactory specificity, sensitivity and a range of qualification with adequate accuracy and precision. It should have capability to detect and follow the time course of the similar biologic (the parent molecule and/or degradation products) in a complex biological matrix that contains many other proteins.

Differences in elimination kinetics between similar biologic and reference biologic e.g. clearance and elimination half life should be explored. Similarity in terms of absorption/bioavailability should not be the only parameters of interest.

A parallel arm design is more approprite for biologics with a long half life or for proteins for which formation of antibodies is likely or if study is being done in patients. In case of short half life, cross over design may be considered with a scientific justification.

4.2.3 Pharmacodynamic Studies

As for the PK studies in the similar biologic clinical development progrom, the Pharmacodynamic (PD) studies should also be comparative in nature. Comparative, parallel arm or cross-over, PD study in most relevant population (patients or healthy volunteers) is required for detecting differences between reference biologic and similar biologic. If PD marker is avaiable in heathy volunteers, PD in healthy volunteers can be done.

Comparative PD studies are recommended when the PD properties of the reference biologic are well characterized with at least one PD marker being linked to the efficacy of the molecule. The relationship between dose/exposure, the relevant PD marker(s) and response/efficacy of the reference biologic should be well established and used to justify the design. The acceptance ranges for the demonstration of similarity in PD parameters should be predefined and appropriately justified.

The parameters investigated in PD studies should be clinically relevant and surrogate markers should be clinically validated. PD studies may be combined with PK studies, in which case the PK/PD relationship should be characterized. A PK/PD study with 20 subjects may be considered for well known bio-similars or vaccines.

PD study can also be a part of Phase III clinical trials wherever applicable.

4.2.4 Confirmatory Safety and Efficacy Study

Information to establish comparative safety and efficacy in relevant patient population is mandatory for all similar biologics.

Comparative clinical trials are critical to demonstrate the similarity in safety and efficacy profiles between the similar biologic and reference biologic. The design of the studies and the clinical comparability margins of the primary efficacy endpoints are important and should be given careful consideration and should be justified on clinical grounds. In line with the principle of similarity, equivalence trials with equivalence designs (requiring lower and upper comparability margins) are preferred. Sample sizes should have statistical rationale and comparability limits should be defined and justified prior to conducting the study. A comparative safety and efficacy study with 50-100 patients may be considered as adequate for well known bio-similars or vaccines.

The nature, severity and frequency of adverse events should be compared between the similar biologic and reference biologic and should be based on safety data from a sufficient number of patients treated for an acceptable period of time. Efforts should be made to ensure that comparative clinical studies have a sufficient number of patients treated for acceptable period of time in order to allow detection of significant differences in safety between similar biologic and reference biologic.

One or more adequately powered, randomized, parallel group, blinded confirmatory clinical safety and efficacy trials are desirable based on the comparability established during preclinical and PK/PD studies. More than one safety and efficacy study may be required and the similar biologic will be treated as a “stand-alone product” if the similar biologic is not comparable to reference biologic in all preclinical evaluations conducted and/or the PK/PD studies have not demonstrated comparability.

The confirmatory clinical safety and efficacy study can be waived if all the below mentioned conditions are met:

i. Structural and functional comparability of similar biologic and reference biologic can be characterized to a high degree of confidence by physicochemical and *in vitro* techniques.

ii. The similar biologic is comparable to reference biologic in all preclinical evaluations conducted.

iii. PK/PD study has demonstrated comparability and has preferentially been done in an in-patient setting with safety measurement (including immunogenicity) for adequate period justified by the applicant and efficacy measurements.

iv. A comprehensive post-marketing risk measurement plan has been presented that will gather additional safety data with a specific emphasis on gathering immunogenicity data.

The confirmatory clinical safety and efficacy study cannot be waived if there is no reliable and validated PD marker.

4.2.5 Safety and immunogenicity Data

Both pre-approval and post-approval assessment of safety is desired to be conducted for similar biologic.

Regarding pre-approval safety assessment, comparitve pre-approval safety data including the immunogenicity data is required for all similar biologics including those for which confirmatory clinical trials have been waived. This pre-approval safety data is primarily intended to provide assurance of the absence of any unexpected safety concerns.

Comparative safety data based on adequate patient exposure (both numbers and time) must, in conjunction with the published data on the reference biologic provide assurance of absence of any unexpected safety concerns and in conjunction with the proposed non-comparative post-marketing study provide comprehensive approach to the evaluation of safety of the similar biologic.

4.2.6 Extrapolation of Efficacy and Safety Data to Other Indications

Extrapolation of the safety and efficacy data to a particular clinical indication (for which clinical studies has been done) of a similar biologic to other clinical indications may be possible if following conditions are met:

- Similarity with respect to quality has been proven to reference biologic
- Similarity with respect to preclinical assessment has been proven to reference biologic

- Clinical safety and efficacy is proven in one indication
- Mechanism of action is same for other clinical indications
- Involved receptor(s) are same for other clinical indications

New indication not mentioned by innovator will be covered by a separate application.

4.3 Post-Market Data for Similar Biologics

Though similar biologics are not new drug products and their risk will be similar to reference biologic; however as similar biologics are authorized based on a reduced preclinical and clinical data package, it is important to submit the Risk Management Plan to monitor and detect both known inherent safety concerns and potential unknown safety signals that may arise from the similar biologics. The reference biologic shall be maintained throughout the life cycle of the product. The risk management plan should consist of the following:

4.3.1 Pharmacovigilance Plan

The clinical studies done on similar biologics prior to market authorization are limited in nature so the rare adverse events are unlikely to be encountered. Hence a comprehensive pharmacovigilance plan should be prepared by manufacturer to further evaluate the clinical safety in all the approved indications in the post marketing phase. The pharmacovigilance plan should include the submission of periodic safety update reports (PSURs). The PSURs shall be submitted annually to DGDA.

4.3.2 Adverse Drug Reaction (ADR) Reporting

All cases involving serious unexpected adverse reactions must be reported to the licensing authority within 7 days of initial receipt of the information by the applicant.

4.3.3 Post Marketing Studies (PMS)

The clinical studies done on similar biologics prior to market authorization are limited in nature so post marketing studies should be conducted and the reports be submitted to DGDA. The plan of post market studies should be captured in pharmacovigilance plan and update on the studies should be submitted to the DGDA.

By the order of President

(Parveen Akter)
Joint Secretary (Public Health).

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