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A Guide to an Effective Clinical Trial Protocol in CGMP & CGCP as a Tool for Sustenance of Ethical Principles and Regulatory Requirements in the Pharmaceutical and Research Industry

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Abstract

The Clinical Trial Protocol is the foundation upon which the study design is built. According to the Pharmaceutical Research and Manufacturers of America (PhRMA), the primary goal of a trial is to generate new knowledge about a potential medicine so that regulatory authorities can determine whether the medicine is safe and effective and the primary purpose of clinical trial is to advance the knowledge of researchers and regulators so that new treatments and cures can be developed.

A guide to an effective Clinical Trial Protocol in $_C$GMP & $_C$GCP as a tool for sustenance of Ethical Principles and Regulatory requirements in the Pharmaceutical and Research Industry is a contemporary perspective on how professionals in the medical, pharmaceutical and research industries can utilize available resources in developing their clinical trial protocol based on sound scientific and ethical doctrines or principles with the primary intention of protecting research subjects or participants while adding meaning to the necessity for the continuation of research practices in our society.

Additionally, a well-articulated clinical trial protocol and subsequent amendment(s) in practice, as the case may be, will further enhance professionals' understanding and limitation(s) with greater emphasis on risk management, continuation of the study and importantly when to stop if it is deemed necessary or if the risk/benefit ratio becomes high enough to compromise either the study participants and or compromise ethical principles as enunciated in the Declaration of Helsinki, the Belmont report and the GCP principles contained in the International Conference on Harmonization (ICH).

Keywords: Clinical trial; GCP protocol; Declaration of helsinki; Clinical research

Abbreviations: PK: Pharmacokinetic; PD: Pharmacodynamic; FDA: Food and Drug Administration; GCP: Good Clinical Practices; GMP: Good Manufacturing Practices; ICH: International Conference on Harmonization; IRB: Institutional Review Board; HIPAA: Health Insurance Portability and Accountability Act; C_{MAX}: The Peak Plasma Concentration of a Drug after Administration; T_{MAX}: Peak Time; AUC: Area under the Curve; $t_{1/2}$: Terminal Half-life

Introduction

The Clinical Trial Protocol is the foundation upon which the study design is built. According to the Pharmaceutical Research and Manufacturers of America (PhRMA) [1], the primary goal of a trial is to generate new knowledge about a potential medicine so that regulatory authorities can determine whether the medicine is safe and effective and the primary purpose of clinical trial is to advance the knowledge of researchers and regulators so that new treatments and cures can be developed.

Without clinical research studies, no new medicine would be made available for treatment, consequently the importance of clinical trials in contemporary dispensation cannot be overemphasized.

The protection of human subjects in line with the ethical principles as enumerated in the Belmont Report and in the Declaration of Helsinki, and that integrated into the good clinical practices as contained in the International Conference on harmonization (ICH) [2], and the conduct of clinical trials which must be based on scientifically sound study design can only be achieve by adhering to the approved clinical trial protocol.

Consequently a well articulated study protocol is a recipe for quick review and favorable response in the scientific environment based on its sound study design and protection of the human subjects [3].

This article is a contemporary attempt to highlight essential components of the protocol that clearly manifest the adherence to these principles, help professionals in the clinical trial and pharmaceutical industry navigate the complex regulations that have become second nature in clinical research and provide ways of avoiding the abuse of human subjects involved in the study.

Hopefully, by the end of this discussion, participants will be able to understand the basis for each components and elements of the study protocols that potentially position it to first get quick approval from the scientific community and most importantly be able to define within the scope of science that it is aware of the critical requirements of protecting the human subjects involved in the study.

Additionally, any amendments sequel to the initial protocol will

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strictly maintain the same principles of sound scientific design and the ethical principles in order to continue to protect human subjects in the study.

The protocol is the basic tool of clinical trials and if well written and the study design is sound, the study will have the capacity to generate valid date that are acceptable to the scientific community including especially the Food and Drug Administration (FDA) and other regulated bodies as the case may be.

Contemporary Good Manufacturing Practices, in line with Good Clinical Practices is very critical of the uniqueness and essentiality of the study Protocol and consequently conspicuously monitored the implementations, and outcome, and in addition of amendments that often takes place as the study progresses.

In order to receive favorable response from the scientific and regulatory communities especially the FDA in terms of clinical research conducted within the USA, every protocol must attempt to satisfy and provide sound, scientific and ethical answers to regulatory requirements by the FDA through the Code of Federal Regulations among others. The most critical regulations pertaining to carrying out clinical research in the United States under the watch dog of the FDA [4-8] are:

(1) 21 CFR Part 50: Protection of Human Subjects

(2) 21 Code of Federal Regulation Part 54 – Financial Disclosure by Clinical Investigators

(3) 21 Code of Federal Regulation Part 56 – Institutional Review Boards

(4) 21 Code of Federal Regulation Part 312 – Investigational New Drug Application and

(5) 21 Code of Federal Regulation Part 314 – Application for FDA Approval to Market a New Drug.

In order words, the key issues that must be addressed for a clinical trial protocol to be effective and meet the minimum standard needed for approval in terms of the principles on conducting such clinical studies are:

a. Protecting Research Participants

b. Conduct of clinical trials in line with applicable laws and regulations (including ICH for global studies).

c. Ensuring Objectivity in Research and,

d. Disclosure of Clinical Trial Results.

My discussion will now focus on the contents of a clinical trial protocol and explain how each of the above regulatory requirements from the FDA among others are met, and therefore in part fulfill the guidelines necessary to adhere to CGMP, CGCP & QA/QC in this highly regulated field.

General Information

The topic of general information in a sound clinical trial protocol is to establish the title, identifying number and date of the protocols, any amendment(s), the amendment(s) number(s) and date(s) and a concrete and effective contacts amongst the Sponsor, Monitors and Investigators, the trial sites and other regulatory bodies involved in the study.

The name and address of the sponsor and monitor (if different from the sponsor), name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor, name, title and address and telephone numbers of the sponsor's medical experts for the trial, and furthermore the 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 sites.

Additionally, the name, title and 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 different from the investigator) and last but not the least the names and addresses of the clinical laboratories and other medical and/or technical department(s) and or institutions involved in the trial.

Background Information (Scientific Rationale)

The name and description of the investigation product(s), a summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that is relevant to the trial, and of the known and potential risks and benefits, if any to human subjects are essential topics under the background information. In addition, the description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s), a statement of commitment that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s), the population to be studied and references to literatures and data that are relevant to the trial and that provide background for the trial must be established.

Trial Objectives and Purpose

A detailed description of the objectives and the purpose of the trial are also very critical to help support the need to gain scientific community approval especially the FDA in the US.

The trial is to;

- Determine the PK profile of CGMP compound when administered as repeated bolus injection?
- To determine the PK profile of CGMP compound when administered as an infusion etc…
- Secondary objectives: to determine the safety and tolerability of bolus and infusion doses of CGMP compound in healthy adults etc.

Trial Design

Without doubt, the scientific integrity of the trial and the credibility of the date from the trial depend substantially on the trial design, and consequently it is very important to have sound ethical principles, pragmatic and quality assurance trial design.

In most cases, the trial design must manifest to the regulatory bodies and the scientific communities what the study is all about, how it is going to be implemented in line with ethical principles as enumerated in the Belmont Reports and in the Declaration of Helsinki and also that of the GCP! [9,10].

Trial design must address the following descriptive functions at the minimum to be able to receive a favorable response:

1. It must include specific statement of the primary endpoints and the secondary endpoints, if any to be measured during the trial. The primary endpoints are mostly focus on the pharmacokinetics effects of the compound, while the secondary

endpoints attempts to evaluate linear relationship, dose proportionality of C_{max} and AUC following the administration of the compound among others.

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 the trial design, procedures and stages.
3. A description of the measures taken to minimize/avoid bias, including (e.g.): Randomization and Blinding
4. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s), in addition to describing the dosage form, packaging and labeling of the IP(s).
5. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
6. A description of the "Stopping rules" or "discontinuation criteria" in other words, "early termination" or "end of study" criteria for individual subjects, parts of trial, and entire trial.
7. Accountability procedures for the IP (s), including the placebo (s) and comparator(s), if any.
8. Maintenance of trial treatment randomization codes and procedures for breaking codes.
9. The identification of any data to be recorded directly on the Case Report Forms- CRFs (i.e., no prior written or electronic record data), and to be considered to be a source data.

Selection and Withdrawal of Subjects

The clinical protocol is also intended to protect human subjects that are involved in clinical research as recommended by the Belmont Report and the Declaration of Helsinki and consequently it is very important to ensure that the ethical principles of Right of the Person, Justice and Beneficence is guarded and protected and this part of the protocol does exactly that.

This section of the protocol provides answers to questions such as:

1. What are the subject inclusion and exclusion criteria?
2. What are the subject withdrawal criteria?
3. How the study does handles the above number 2 situation, and specifies procedures such as; when and how to withdraw subjects from the trial/IP treatment. The type and timing of the data to be collected for withdrawn subjects. Additionally whether and how subjects are to be replaced and the follow-up for subjects withdrawn from the IP treatment/trial treatment.
4. Selection and withdrawal of subjects must be fair and without discrimination on the basis of sex, race, income and otherwise.

Treatment of Subjects

Considering the fact that the treatment(s) administered during clinical trial, as is typical in the research environment, designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge expressed for example, in theories, principles and statements of relationships, it is essential that its handling; the name (s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for each IP treatment/trial treatment group/arm of the trial are in compliance with the protocol.

The protocol must also address the type of medication(s)/ treatment(s) permitted (including rescue medication) and those not permitted before and/or during the trial in addition to enumerating the procedures for monitoring subject compliance.

Assessment of Efficacy and Safety

The specific efficacy and safety variables to be assessed and laboratory tests to be conducted, their schedule (days of study, time of day, relation to meals, and the timing of critical measures in relation to test drug administration, e.g., just prior to next dose, 2 hours after dose), the methods for measuring them, and the persons responsible for the measurements should be described. If there were changes in personnel carrying out critical measurements, these should be reported. (ICH E3 P.11)

It is usually helpful to display graphically in a flow chart the frequency and timing of efficacy and safety measurements; visit numbers and times should be shown, or, alternatively, times alone can be used (visit numbers alone are more difficult to interpret). Any specific instructions (e.g., guidance or use of a diary) to the patients should also be noted. (ICH E3 P.11)

Analysis of efficacy

Treatment groups should be compared for all critical measures of efficacy (primary and secondary endpoints; any pharmacodynamic endpoints studied), as well as benefit/risk assessment(s) in each patient where these are utilized. In general, the results of all analyses contemplated in the protocol and an analysis including all patients with on-study data should be performed in studies intended to establish efficacy. The analysis should show the size (point estimate) of the difference between the treatments, the associated confidence interval, and, where utilized, the results of hypothesis testing. (p19)

Additionally Pharmacokinetic parameters assessments may be based on the PK sample collections, with measurements being determine in a given Bio-analytical laboratory per protocol specification. Sponsors often determine the PK parameters such as $C_{MAX,}$ AUC, $T_{MAX,}$ and $t_{1/2}$, among others.

Analysis of safety (Adverse Events)

On the other hand safety assessments are clinical vital signs and parameters and diagnostic laboratory parameters such as comprehensive metabolic panel assessment among others.

Analysis of safety-related data can be considered at three levels. First, the extent of exposure (dose, duration, number of patients) should be examined to determine the degree to which safety can be assessed from the study. Second, the more common adverse events and laboratory test changes should be identified, classified in some reasonable way, compared for treatment groups, and analyzed, as appropriate, for factors that may affect the frequency of adverse reactions/events, such as time dependence, relation to demographic characteristics, relation to dose or drug concentration. Finally, serious adverse events and other significant adverse events should be identified, usually by close examination of patients who left the study prematurely because of an adverse event, whether or not identified as drug related, or who died.

An Adverse Events (AE) is the development of an undesirable medical condition or deterioration of a pre-existing medical condition following or during exposure to a pharmaceutical product whether or

not considered causally related to the product. An undesirable medical condition can be symptoms (e.g., nausea, chest pain), signs (e.g. tachycardia, enlarged liver), or the abnormal results of an investigation (e.g. laboratory findings, ECG).

There should be a very explicit section covering adverse events and adverse event reporting in the protocol as a way of protecting the human subjects involved in the research in addition to understanding the pharmacodynamics of the IP(s).

Statistics

The statistical analyses planned in the protocol and any changes made before outcome results were available should be described. In this section, emphasis should be on which analyses, comparisons, and statistical tests were planned, not on which ones were actually used. If critical measurements were made more than once, the particular measurements (e.g., average of several measurements over the entire study, values at particular times, values only from study completers, or last on-therapy value) planned as the basis for comparison of test drug/ investigational product and control should be specified. Similarly, if more than one analytical approach is plausible, e.g., changes from baseline response, slope analysis, life-table analysis, and the planned approach should be identified. Also, whether the primary analysis is to include adjustment for covariates should be specified. (ICH E3 P14) .This part of the protocol must therefore;

1. Describe the statistical methods to be employed, including the timing of any planned interim analysis.
2. The number of subjects planned to be enrolled. In multicenter trials, the number of enrolled subjects projected for each trial site should be specified. Reason for the choice of sample size, including reflections on (or calculations of) power of the trial and clinical justification.
3. The level of significance to be used.
4. Criteria for the termination of the trial (e.g. if Cmax is reached at a given dosage)
5. Procedures for accounting for missing, unused, and spurious data.
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 the protocol and /or in the final report, as appropriate).
7. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all doses subjects, all eligible subjects, evaluate-able subjects).

Direct Access to Source Data/documents (Confidentiality)

As a result of the complex confidentiality regulations in the United States (HIPAA, Informed Consent, etc), 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, Institutional Review Board (IRB)/ Independent Ethics Committee (IEC) review, and regulatory inspection(s) by providing direct access to source data/documents.

Quality Control (qc) and Quality Assurance (qa)

The protocol in line with ICH E6 (1.46) [11] define QC as 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 and in (1.45), define QA as 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 GCP and the applicable regulatory requirement(s).

The quality assurance and quality control systems implemented to assure the quality of the data should be described in brief. If none were used, this should be stated. Documentation of inter-laboratory standardization methods and quality assurance procedures, if used, should be provided under Appendix 16.1.10. Any steps taken at the investigation site or centrally to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data, such as training sessions, monitoring of investigators by sponsor personnel, instruction manuals, data verification, cross-checking, use of a central laboratory for certain tests, centralized ECG reading, or data audits, should be described. It should be noted whether investigator meetings or other steps were taken to prepare investigators and standardize performance.

Summarily, the protocol must ensure a verifiable mechanism where actions taken in relations to a given study subsequently enhance the credibility of the data generated and that human subjects who are enrolled in such a study are protected from harm and confidentiality considerations are within the scope of the protocol (E.g. monitoring of instrumentations, data generated during laboratory testing among others).

Ethics Consideration

Contemporary clinical research protocol is guided by the Declaration of Helsinki and the Belmont Report, two documents that are very important for the protection and well-being of human subjects in clinical trials sequel to past abuses in clinical research such as;

1. The Tuskegee Syphilis Experiment in the US
2. Japanese Biological Warfare (1932-45)
3. Human Radiation Experiments
4. The Human Experiments at Holmesburg Prison, just to name but few.

Compliance with GCP and ethical considerations

The protocol must state that the study under consideration must be conducted in compliance with the Independent ethics committees/ institutional review boards (IECs/IRBs), informed consent regulations, the Declaration of Helsinki and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines.

Additionally for Electronic Data Capture (EDC) studies, FDA 21 CFR Part 11: Electronic Records, Electronic Signatures; and FDA, Guidance for Industry: Computerized Systems Used in Clinical Trials must be adhered to.

Furthermore, the study will adhere to all local regulatory requirements.

No study is to be initiated without the favorable response from IEC/ IRB for the study protocol/amendment(s), written informed consent form, any consent form updates, subject recruitment procedures (e.g. advertisements) among others. The IEC/IRB approval must identify the protocol version as well as the documents reviewed.

The FDA especially under the Code of Federal Regulations part 50 (21CFR50- Protection of Human subject in research study [12-15]) and 21CFR56- Institutional Review Board) provide applicable regulations that clearly help define the fundamental basis and necessity for the protection of human subjects in addition to other ethical principles that help to burden researchers with the need to minimize the exposure to risk and increase the opportunity for benefit in a given study.

Informed consent and HIPAA authorization (risks and benefits)

Informed consent is defined by the International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice as *"A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after been informed of all aspects of the trial that are relevant to the subjects decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form."(ICH, GCP Federal Register May 9, 1997. Part I. Glossary)*

In addition, here in the US, each subject must also sign a HIPAA (Health Insurance Portability and Accountability Act) authorization form before his/her participation in the study, and a signed copy must be provided to the subject and a signed copy shall be maintained in the subject's clinical file.

The investigator should, with the consent of the subject, inform the subject's primary physician about their participation in the clinical study.

Data Handling and Recordkeeping

Part of a sound and scientific trial is the ability to produce data that is credible, scientific and readily acceptable to the scientific community (ies) especially the FDA. Consequently it is important for the protocol to enumerate how data generated from the study is going to be recorded, its quality assurance is maintained and finally how such data is going to be kept and for how long.

Data handling covers recording instructions, which should indicate how data will be collected and there must be study manual, appendix and other forms of instructions that will help study personnel to become acquainted with such procedures prior to and during the study.

Additionally, this section must discuss the use and management of source documents and the procedure for correcting errors without compromising audit trail.

Data Quality Assurance (DQA), which is part of the data handling essentially describe procedures for assessing subjects compliance, any special training or other measure for site personnel to ensure valid data, discuss source document review and provide Good Clinical Practice (GCP) references.

DQA has at least three components: Inspection and Auditing Procedures, Recording of Study Data and Source Data Verification

Authorized personnel from the Sponsor-authorized Quality Assurance personnel may carry out inspections and audits.

Recording

In compliance with GCP, the medical records/medical notes, etc, should be clearly marked and permit easy identification of a subject's participation in the specified study (without compromising confidentiality)

The Investigator must record all data relating to protocol procedures, study drug administration, laboratory data, safety data, and efficacy ratings on the CRFs (eCRFs) provided for the study.

The investigator must, as a minimum, provide an electronic signature (e-signature) on the 'sign off' form of the CRF to attest to the accuracy and completeness of all the data.

Any changes after the CRF has been locked and electronically signed must require the investigator to perform additional e-signature authorizing agreement with the new information of changes to the CRF.

All corrections on the CRF will be automatically tracked and a reason for change is always required.

In the CRF, the audit trail function will allow the changes made to be viewed on each item entered.

Recordkeeping

During the pre-study and initiation visits, the monitor must ensure the archiving facilities are adequate and archiving/retention responsibilities of the Investigator have been discussed. Study documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or planned marketing applications in an ICH region (that is at least 15 years) or at least 2 years have elapsed since the formal discontinuation of the clinical development of the product. This recommendation is however subject to local, national and regional applicable regulatory requirements or by an agreement with the Sponsor.

A change of Principal Investigator either due to relocation or retirements should necessitate contacting the Sponsor so that adequate provision can be made for future maintenance and retention of the records.

Source data verification

The Food and Drug Administration (FDA) 21 Code of Federal Regulation (CFR) Part 11 is a regulation which provides criteria for acceptance by the FDA [16], under certain circumstances, of electronic records, e-signatures and hand written signatures executed to electronic records as equivalent to paper records and hand-written signatures on paper.

As required by GCP, the sponsor assigned monitor must verify, by direct reference to the source documents, that the data required by the protocol are accurately reported on the CRF.

Content of the Source Documents at a minimum must include a statement that the subject is included in a clinical study, the data that informed consent was obtained prior to participation in the study, the identity of the study, diagnosis and eligibility criteria, visit dates (with subject status), study drug administration, and any AEs and associated concomitant medication.

Finally the Investigator and Sponsor must agree based on ICH GCP section 6.4.9, on the validity to use some items as Source Data which may have been recorded directly on the CRF to be use a document.

Financing and Insurance

In line with FDA 21 CFR Part 54, Financial Disclosure by Clinical Investigator is required to help guard against conflict of interest and bias that might have the potential of questioning the credibility of the study.

One potential source of bias in clinical studies is the financial interest of the clinical investigator in the outcome of the study because of the way payment is arranged (e.g., royalty) or because the investigator has a proprietary interest in the product (e.g., a patent) or because the investigator has an equity interest in the sponsor of the covered study.

The protocol will address the overall Sponsor and Investigator responsibilities in relation to the study finances. The Investigator (or appropriate designee) and the Sponsor will sign a clinical study agreement prior to the start of the study. Pertinent consideration shall be how to cover the cost per included subject, which will be based on the calculated costs of performing the study assessments in accordance with the protocol and the specified terms of payments will be described in the contract.

Additionally the contract should describe whether the costs for pharmacy, laboratory and other protocol- required services are being paid directly or indirectly.

In the US, the Sponsor will provide Product Liability insurance for all subjects included in the clinical trial. Where required a hospital specific indemnity agreement will be used. *(An indemnity is a contractual promise by one party to protect the other party from and against certain specified actions, claims or losses).*

Publication Policy

The protocol should clearly state the status of the Sponsor's agreement in terms of, publication and acknowledgment.

In most cases, Sponsors encourages acknowledgement of all individuals/organizations involved in the funding or conduct of the study, including medical writers or statisticians subject to the consent of each individual and entity concerned, including acknowledgment of the Sponsor.

The results of the study may be published or communicated to scientific meetings by the Investigator involved in the study.

However, the Sponsor must be notified and given adequate time to review all relevant literatures concerning the study before it can assent to publication or presentation of the study by the Investigator.

The protocol must also take into consideration patentability and the adverse effect on anticipated publication, in which case it should be delayed. Under such scenario (1) a patent application is filed for the content of publication in accordance with applicable provisions of the clinical study agreement, (2) the Sponsor consent to publication, or (3) the contractual arrangement and agreement governing the relationship between the Sponsor and authors.

Protocol Amendments

Owing to the dynamism in clinical research, especially in context of inevitable changing circumstances aimed at protecting the human subjects involved in the trial while at the same time maintaining both scientific and ethical justification for the study, protocol amendments has become the tool to effectively address these concerns.

The protocol amendments are usually classified into 3 categories based on the degree of substantiality of the amendment, the risk/benefit ratio and the urgency in relation to safety.

Non-substantial amendments

Non-Substantial Amendments are those that are not considered 'substantial'; for instance clerical changes and as such only need to be notified to the IECs/IRBs for information purposes.

Substantial amendments

In the case of Substantial Amendment(s), such a change will have a significant or 'substantial' impact to the conduct of the clinical trial in terms of:

a. The safety or physical or mental integrity of the participating subjects

b. The scientific values of the study;

c. The conduct or management of the study; or

d. The quality or safety of the IP used in the study

Under this scenario, the IECs/IRBs and other regulated bodies that are entitled to the protection of human subjects and the study MUST be notified, if applicable.

It is important to understand that substantial protocol amendments cannot become effective or implementable without the prior approval of the IECs/IRBs and CA (in the case of EU- CA; Competent Authority)

Urgent amendments

This type of amendments are those that require urgent safety measure to protect the study subjects from immediate hazard and as such may be implemented by the Sponsor with subsequent IECs/IRBs and FDA notification immediately. This is in line with the maxim of "do no harm…." stated in the Declaration of Helsinki.

References

References are important because they provide resources to support and better understand the clinical trial or study by providing scientific and regulatory literatures, which are needed for ongoing consultations.

A list of articles from the literature pertinent to the evaluation of the study should be provided.

Copies of important publications should be attached in an Appendix. References should be given in accordance with the internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts."

Appendices

This section should be prefaced by a full list of all Appendices available for the study report. Where permitted by the regulatory authority, some of the following Appendices need not be submitted with the report but need to be provided only on request.

The applicant should therefore clearly indicate those Appendices that are submitted with the report.

N.B.: In order to have Appendices available on request, they should be finalized by the time of filing of the submission.

Study information

- Protocol and protocol amendments.
- Sample case report form (unique pages only).
- List of IEC's or IRB's (plus the name of the committee chair if required by the regulatory authority) and representative written information for patient and sample consent forms.

- List and description of investigators and other important participants in the study, including brief (one page) CV's or equivalent summaries of training and experience relevant to the performance of the clinical study.
- Signatures of principal or coordinating investigator(s) or sponsor's responsible medical officer, depending on the regulatory authority's requirement.
- Listing of patients receiving test drug(s)/investigational product(s) from specific batches, where more than one batch was used.
- Randomization scheme and codes (patient identification and treatment assigned).
- Audit certificates (if available).

This part of the protocol should at the minimum contain the synopsis of the study in addition to the scientific information about the IP(s):

1. Schedule of Observations and Procedures

a. Informed Consent process

b. Eligibility Assessment: demographics, medical history, physical exam, laboratory testing, vital signs etc.

c. Collections of Vital Signs and PK samples, meals and dosing among others during the study and follow up procedures including ET and or EOS.

2. Prescribing Information of the IP(s) used in the study from previous non-clinical and clinical study as the case may be.

a. Clinical Pharmacology: Mechanism of Action, pharmacokinetics, distribution, metabolism and Elimination, Special Populations, hepatic and or renal impairment, Drug-Drug Interaction, among others.

Conclusion

An effective study protocol is critical in the current Good Manufacturing Practice guidelines for the application for clinical study or trial for regulated pharmaceuticals compounds and or even devices for several reasons which cut across scientific, ethical and potential conflict of interest from financial and royalty issues.

In order therefore for a protocol to meet the minimum requirements from the FDA and to receive a favorable response, which may subsequently lead to the marketing of a New Drug or as the case may be a modified version for a different use, it must be able to provide sound scientific design; the purpose of the study, objectives, PKS, PDS, and also protect the human subjects involved in the study by minimizing the risk – benefit index or ratio.

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