

Protocol of a Clinical Trial: Elements, Concerns and Potential Solutions

Saurabh Ram Bihari Lal Shrivastava*, Prateek Saurabh Shrivastava and Jegadeesh Ramasamy

Department of Community Medicine, Shri Sathya Sai Medical College and Research Institute, Kancheepuram, India

*Corresponding author: Dr. Saurabh Ram Bihari Lal Shrivastava, 3rd floor, Department of Community Medicine, ShriSathyaSai Medical College and Research Institute, Ammapettai village, Thiruporur-Guduvancherry Main Road, Sembakkam Post, Kancheepuram-603108, Tamil Nadu, India, Tel: +919884227224; E-mail: drshrishri2008@gmail.com

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Abstract

In the field of medicine in order to ensure better understanding of human biology and improve the health standards of the masses, conducting clinical trials remain a key approach. In general, all the randomized clinical trials essentially require a protocol to explain the rationale, adopted method, measures to ensure the safety of study participants, proposed statistical analysis, information about research funders, and organizational details right from the time of trial inception till reporting of the results. Multiple discrepancies have been identified in the clinical trials, and all of them have to be addressed to make research safe for humans. In conclusion, the development of a comprehensive protocol not only provides a mechanism to ensure the monitoring of the trial throughout its duration, but also safeguards the interests of the study subjects and enhances the reliability of the clinical trial results.

Keywords: Clinical trial; Protocol; Ethics

Introduction

In the field of medicine in order to ensure better understanding of human biology and improve the health standards of the masses, conducting clinical trials remain a key approach [1]. In-fact, prior to the administration of any medicinal product among humans, the efficacy and safety of the product should be proved by the clinical trials which are performed in accordance with the good clinical practice and the ethical guidelines [1,2]. The clinical trials not only test efficacy of an intervention, but also could be used to test the effectiveness of the interested intervention under different circumstances [1,2].

Establishing the Need for a Clinical Trial

This is the preliminary and the most important step to reach to the decision of performing a clinical trial depending upon the scientific question for which answers are desired. However, the decision to perform a clinical trial should be made after considering the magnitude of the problem for which clinical trial is needed; potential evidence available to suggest that newer alternative will definitely add to the existing knowledge; extent of anticipated benefits in terms of well-being/survival rate/cure rate/side effects; availability of a simple approach to perform the same; and ethically justifiable [1-3].

Why A Protocol is Needed?

In general, all the randomized clinical trials essentially require a protocol to explain the rationale, adopted method, measures to ensure the safety of study participants, proposed statistical analysis, information about research funders, and organizational/administrative details right from the time of trial inception till reporting of the results [3,4]. Thus, transparent, detailed and clearly written protocols remain an indispensable element to perform a clinical trial as it enables timely and comprehensive assessment of the trial [3,4]. However, in most of the protocol discrepancies (viz. designation of primary outcomes or

sample size calculations or role of sponsor and investigator, etc.) have been observed which seriously questions the reliability of the clinical trial results [4-6]. Thus, this article attempts to cover all the elements of a protocol which should be taken into consideration before starting the trial.

Protocol and Its Elements

Protocol refers to a document which not only explains the background and the rationale for the trial, but even describes the objective(s), methodology (viz. study design, duration, number of subjects, inclusion and exclusion criteria, study variables, operational definitions, ethical considerations, statistical analysis, etc.) and organization of a trial [7]. In short, protocol is the written mechanism that describes the design and implementation of a clinical trial [8]. Thus, there are two macro-elements of a protocol-clinical trial development-knowledge and science, and clinical trial conduct-execution and project management [7,8].

Protocol Contents

Introduction: This section comprises of the background information pertaining to the disease/treatment in consideration, rationale for the trial, and the proposed hypothesis [9].

Objectives: Objectives refer to the precise statement about the major (primary objective) and minor (secondary objectives) questions that the project is designed to answer. The objectives should be clear, complete and concise; and be feasible in terms of time/money/manpower/other resources. These designed objectives should not be amended after the initiation of the study [9,10].

Study duration: Exact duration of the trial should be specified without being over ambitious or slow. The duration of study should be decided after discussing timelines with study personnel, considering all the major and minor events, with reasonable flexibility [11].

Sample size: The sample size should be ascertained based on the primary objective(s) or previous available studies. As a clinician, one

should endeavor to understand the reason for choosing a method for sample size calculations, document and justify the adopted method to reach the desired sample size. In addition, issues like stratification of the sample size into different groups, defining what a completed case/observation is, whether incomplete cases/observations will be included or not, etc., should also be addressed [7,8,10,12].

Compliance with good clinical practice and ethical considerations: From the study subjects' perspective, this element of protocol deserves lots of attention. Each and every clinical trial protocol should be designed in conformity with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines or the Declaration of Helsinki. In addition, adequate measures should be taken to enhance the compliance of clinical trial with the local/central regulations (viz. Schedule Y-India, etc.). Furthermore, the process of obtaining informed consent should be explained in detail and due attention should be taken to incorporate all the mandatory clauses in a participant-friendly language [1,2,13,14].

Criteria for subject selection: The inclusion/exclusion criteria aid in defining study population characteristics and should be designed after considering possible risks and benefits to subjects. In general, these criteria should be non-contradictory, precise, clear, and allow meaningful interpretation of the results. Overall, four categories of criteria are taken into account, namely

Characteristics of study subjects: Gender, age, race, socioeconomic status, weight, pregnancy/lactation, diet/nutritional status, use of caffeine/tobacco/alcohol/drugs, physiological, anatomical/psychological considerations, etc.

Characteristics of the Disease and Its Treatment-Current Clinical Status (Disease/No Disease/Stage of Disease) or Medical History (Allergies, Diseases, Medications, etc.)

Environmental and other factors: Clauses about subject recruitment and cooperation throughout the duration of study, whether subjects can simultaneously participate in another trial, etc.

Results of screening tests: Physical, laboratory investigation and other parameters [15,16].

Methodology: This section of the protocol is the most important section based on which presence of obvious bias/confounding factors in the study can be ruled out. Simultaneously, it has a significant impact on the genuineness of the obtained results and generalizability of the study findings. The methodology section in a clinical trial comprises of

Study design: Type of clinical study, trial design with treatment sequences, information pertaining to controls, level of the blinding and adopted method of randomization method, treatment structure (length of treatment, dose and regimen), and other bias-reducing factors.

Study schedule and visits: This should include timing and description of all procedure(s), observation(s) and assessment(s) for efficacy and safety at the time of screening visit(s)/baseline visit/follow-up visit(s)/final visit. This indirectly ensures uniformity in methodology and collection of data for all procedure(s), observation(s) and assessment(s).

Efficacy variables (endpoints): The endpoint of the clinical trial is dependent upon the formulated objectives; specificity/sensitivity of the intervention; duration of study; budget; clinical relevance; etc.

Efficacy analysis: Under this information about subjects to be included/not included in the analysis should be mentioned (viz. received the drug/intervention for at least specific period, the minimum period of follow-up, the issue about intention-to-treat subjects, etc.).

Study treatment: This should include in detail description of the proposed treatment, such as identity, formulation details and prescribing info; packaging, labeling, storage, expiry; dosage, timing of dose, frequency, duration; guidelines for titration (if applicable); dispensation, returns and accountability; treatment compliance; method of documentation in case research form; and proof of receipt and dispatch.

Termination of study: This section should contain information pertaining to the rules for discontinuation of study subjects; rules for termination of the study (if preliminary results suggest harmful effects among subjects); and mention the name of the body (viz. institutional review board/ethics committee/regulators/investigators/sponsor) who is authorized to terminate/suspend study [7,8,10,17-20].

Safety reporting: Specific definitions for adverse events or serious adverse events; methods and measurements (clinical examination/laboratory investigation) to assess safety and tolerability should be stated prior to the start of the study. In addition, clear definition of "abnormality" and clause for the discontinuation of subjects after observing adverse effects should also be defined [7,11].

Concomitant therapy: Any treatment other than the study treatment(s) should be recorded in the case research form in detail. Also, all prescription and non-prescription therapies permitted/disallowed (before, during and after the trial) should be specified. Furthermore, information about supplemental/rescue/escape medications should also be stated in the protocol [8,16].

Study Management and Materials: Details About

Study materials: Supplier for case research forms, questionnaires, patient diaries, other forms; what is accountable and returnable; what, who and where used/unused supplies can be destroyed.

Comprehensive documentation of the study findings: How supplied materials should be used; what forms to be used, how and when to be filled; verification of source documents and archival method; what documents will be given to sponsor; how confidentiality will be maintained; who, how and when monitoring/audits will be conducted.

Mechanism For Systematic Monitoring and Quality Assurance [4,17,18]

Confidentiality: This section of protocol ensures that the identity of the study subjects and the obtained responses will be kept confidential [1,2].

Data analysis: Outline the analysis plan in terms of who does data entry and analysis; method of analysis for safety and efficacy; how to account for missing/unused/spurious data; interim analysis (if planned); data processing and statistical methods [15,19,21].

Communication and publication of results: Specify who has the ownership of the documents/data/results/publication (authorship).

However, sponsors should be consulted before independent publications are planned by the investigator and no attempt should be made to limit the investigator's right to publish. Finally, it should be ensured that appropriate study participants receive a fair, accurate and reasonable representation [19,22].

Observed Discrepancies in Clinical Trials

Table 1 lists out the wide range of discrepancies which have been observed in the protocols of clinical trials [1,9-17]. However, the major discrepancy is with regard to the communication and publication of

results. In contrast to the previous decades where doctors used to treat patients based on their clinical acumen, the modern day physicians extensively rely on the findings of a clinical trial. However, owing to the publication of the results in a biased and selective manner, the published results cannot be trusted blindly. Furthermore, often only those results are being published which reflect that the newer drug has been associated with favorable results (higher cure rate or lesser adverse effects), than the existing drugs (publication bias or outcome reporting bias) [23-25]. In addition, influence of the sponsor in the final reporting of the results has also been noted in various instances [4,24,26].

Element of protocol	Observed discrepancies in clinical trials
Objective	Development of ambiguous objectives; Absence of a strategy to accomplish the objective; Alterations in the objectives after the initiation of the trial
Study duration and Sample size	Development of a protocol without giving adequate attention to the duration of study; No usage of Gantt chart; No rationale for selection of sample size; Use of unscientific criteria to reach to a favorable sample size
Ethical considerations	Significant disparity between the statements made in the protocol and when the study is actually conducted; Variable extent of compliance with the good clinical/laboratory practice guidelines
Criteria for subject selection	In order to meet the sample size, most of the subjects are enrolled in the study without neutralizing the confounding factors which influence the study results to a significant extent
Methodology	Discrepancies have been observed in various facets of the methodology ranging from the study design, data collection tool and technique, endpoint variables, mode of treatment, conditions under which study can be terminated, etc.
Safety reporting	Although, criteria pertaining to safety reporting in a protocol is must, nevertheless, most of them are not reported, as any negative result can seriously question the safety of the proposed newer modality
Concomitant therapy	Most of the details about any concomitant therapy/rescue therapy are either not recorded or even if recorded, does not appear in the final report
Data analysis	No assistance from the statisticians; Use of statisticians to their (sponsor/researcher) advantage; use of irrelevant statistical tests; alterations in the collected data to obtain favorable results

Table 1: Discrepancies in clinical trials.

Recommended Solutions

The government initiative in some of the nations, to ensure mandatory registration of the clinical trials before their initiation is a major step to streamline clinical trials. This step not only enables supervision of the trial in the entire study period, but even assists in publication of these results in the journals. In-fact, the authenticity of the results displayed in a systematic review or a meta-analysis is judged by plotting a funnel plot to assess the presence of publication bias. In addition, it is high time that ethics committee/institutional review boards should not restrict themselves with only providing approval before the start of the study. In contrast, these committees should ensure that all the documented results should be informed to the respective committee, so that the clinical trial can be either revised or terminated based on the preliminary/mid-term results [1,2,13,14].

However, the actual onus lies with the researchers/investigators who should ensure that both their protocols and even the conduction of clinical trials are in accordance with the recommended guidelines, and interests/well-being of people are taken care of. Even the sponsors should understand that by publicizing results (which are incomplete), they are not only misguiding the medical fraternity, but even playing with the lives of people. Finally, by enhancing international collaboration on pharmacovigilance and directing the regulatory bodies to exercise their role with sustained commitment can also play a crucial role [2,19,20].

Conclusion

In conclusion, the development of a comprehensive protocol not only provides a mechanism to ensure the monitoring of the trial throughout its duration, but also safeguards the interests of the study subjects and enhances the reliability of the clinical trial results.

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