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Research Clinical Trial – A Review

Dr. Ishita Attri[1], Dr. Rajwinder Dhaliwal[2]

[1,2]Medical College and Research Center

ABSTRACT

Majority of healthcare professionals are struggling with conducting and writing a protocol for a research study. Thus, the purpose of this article is to summarize significant steps and necessary guidelines for producing a standard research protocol, roles and responsibilities of various team members involved in the study, and conduction of actual clinical trial including its initiation, phases (I-III), termination or post-marketing surveillance phase. It is important to note that the quality of a clinical trial largely depends on the protocol to achieve success in the research study.

KEYWORDS: Clinical Trial, Clinical Trial Protocol, Medical Intervention, Research Question, Informed Consent

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INTRODUCTION

A clinical trial, according to WHO is "any research study that prospectively assigns individual or groups of human participants to one or more health-related interventions to evaluate the effects on health outcomes" [1]. In simple words, a clinical trial is any research study that tests medical interventions on the human participants to see the effects of that particular intervention on the humans. The medical intervention includes but is not limited to drugs, biological products (blood, cells, micro-organisms), and new technology or equipment (radiology, devices).

Conduction of a clinical trial requires a well-designed study plan, known as the clinical trial protocol. It must be compliant with the Good Clinical Practice (GCP) guidelines defined as "an international ethical and scientific quality standard for designing, conducting, recording and reporting trial that involves the participation of the human subjects."[4]. the clinical trial protocol is prepared by the sponsor or the principal investigator, and they submit the protocol with a clinical trial application (CTA) to regulatory authorities. The local regulatory authority (where the study is supposed to conduct) evaluates and either approves or rejects the clinical trial protocol before initiating the actual clinical trial. Table 1 shows some examples of regulatory authorities of different countries, whereas Table 2 shows individuals involved in a clinical trial with their specific roles.

CLINICAL TRIAL PROTOCOL

The clinical trial protocol is a written agreement and a communication document among sponsors, investigators, subjects, and the research community. The protocol would be developed at the beginning of the clinical trial and remains unchanged except for minor updates. It includes several components, such as background information, research question, research design, and organization of a clinical trial of a research study [8]. The Standard Protocol Items: Recommendation for Interventional Trials has published a guide for developing a clinical trial protocol as shown in Table 4 [9].

A. Background or Literature Revision

Background information regards to the research questions is based on the existing literature and provides a rationale for the study topic. It has significant information answering questions like why these questions are important. Is there any previous research on this question? How will this new research affect our knowledge and public health? Thus, the background section of the protocol includes details from the publication of the past studies as well as from the present clinical trials. It answers the potential deficiencies or gaps in the past studies, ideas behind the objective of the research, and benefits of the current research, clinical trial to the community. In addition, it has a basis for the research question.

A. Study Objective

The research questionis the main objective of the study; it's the uncertainty that investigator wants to

resolve. It is prepared by the sponsor and the principal investigator after a careful revision of the clinical areas of the investigation and the current exiting literature. A good research question have essential characters: feasible, interesting, novel, ethical and relevant [5]. It can be made strong by using the PICOT format (summarizes the research question) or passing the "so what?" test [6].

The research question is divided into primary and secondary questions. The primary question is the focus of the study and the one that the investigator and sponsor are most interested in answering. However, the study is not limited to one question, and other related questions are known as secondary questions. The primary question is framed into a hypothesis and tested through the clinical trial resulting in its approval or rejection.

The hypothesis is a statement based on the evidence from the previous studies suggesting a correction between two or more variables. It is classified into null and alternative hypotheses. Null Hypothesis (Ho) means there is no actual relationship among the variable and vice versa for the alternative hypothesis (H1) [10].

B. Study Design

The information regards to methods and materials is another significant part of the clinical trial protocol. This section explains where, who and how a research study will be conducted [10]. Firstly, it is important to decide the type of study the investigator wants to do. This decision is based on the need to collect the type of data and yield a piece of meaningful information. There are mainly two types of studies used to test a hypothesis, experimental or observational studies (Table 5) [11]. The experimental studies can be either randomized or non-randomized controlled trials. The observational studies can be divided into analytical (cohort study, Case-Control study, and case-control study) or descriptive studies.

Secondly, the study population is selected based on hypothesis and study design; it is a subset of population with character of interested defined by eligibility criteria like inclusion and exclusion. Main two exclusions characteristics are subjects who have absolute or relative contraindications to investigational product and factors interfering with participant adherence. The inclusion criteria involve subjects who have particular characteristics that must be present in order to be included in the research. The criteria are meant to ensure subject's safety during the study, to minimize withdrawals and ensure that the need of the study is reached. It should also consider how to recruit these subjects, what the study sample size based on the research question is, and constructs a well-designed informed consent.

Informed consent is essential for conducting a clinical trial. It is a process whereby the potential subjects are debriefed about the study and what is requested from/of them. And it's done in a language that they can understand. The participants should be given complete information about the clinical trial, implication of joining, duration of the research and should have enough time to ask questions and discuss with their families or family physician. They should be familiar with the concept of research, and that informed consent is voluntary, and they have the option of dropping out of research at any time if they cannot continue it. If the research study involves minor subjects, then assert form must be obtained from their parents or legal guardian. However, minor study subjects can still say no to participation despite the consent obtained. In addition, Privacy and Confidentially information is discussed with study subjects, especially if any of their information is going to be shared with anyone else and what kind of methods will be used to protect their information [12].

Next, a description of the proposed intervention is included in the protocol. For example, if the intervention is a drug, include brand name, generic name, manufacturer, dates (manufacturing and expiring), dose, route of administration, adverse effects, and so on. Other details about the intervention include the details about the interventional handler (in the majority of the cases, it's the principal investigator), storage (fridge or specific temperature), dissemination at the termination of the clinical trial.

The next part of the study protocol is variables. They are used in the study to calculate the predicted outcomes and make conclusion about cause and outcome. The outcome variable should be observed using randomization to minimize the influences of confounding variables.

Afterward, the study protocol should discuss information (data) collected during the clinical trial. In many cases, the baseline data is collected at the beginning of the study immediately after recruitment and followed by data collected during the trials as well as at the termination of the study. The information is recorded on case report form (CRF), which can be printed or electronic by investigators or CRCs and reported to sponsors [13]. This results in a large amount of data collected, stored in computer software such as excel, and managed through defined data tables, developing the data entry system, and enquiring the data for monitoring and analysis by different methods by clinical data managers.

At last, but not the least, study protocol includes information about statistical analysis of the data. Inferential statistics are commonly used when providing evidence that systematic variation is present among two study groups (control vs. test) and within a group. Systematic variation refers to a pattern in data due to influences of investigational products. The statistical analysis notes if the variation is clinically significant or due to chance because all humans are different

from each other. The analysis of data may face difficulties due to the missing data in cases when subjects drop out of the study. There are various statically analyzing tests such as two-sample Z-test, analysis of variance (ANOVA), chi-square test [14]. Lastly, the clinical trial protocol should include information about the termination of the study.

CONDUCTION OF A CLINICAL TRIAL

A clinical trial begins by recruitment of study subjects by the principal investigator based on the inclusion and exclusion criteria of the clinical trial protocols after obtaining informed consent. It is followed by placing the recruited subjects into one of the groups (test or control) by computer. The principal investigator may hire a clinical research coordinator (CRC) for each clinical trial site and assign them duties such as coordinating, managing, and conducting research at that specific site [15]. Next, the clinical trial, phases I to III is executed as demonstrated.

Phase I involves about 20 – 100 healthy volunteers to monitor the intervention's safety and maximum tolerated dose. It takes about one to two years and conducts at specialized centers like research universities. Phase II tests the drug on 100-300 subjects from the target population to assess the efficacy and adverse side effects. It is done in community settings and takes more than two years. Phase III also tests the drug on the target population but with larger sample size and longer duration. It assesses efficacy, effectiveness, and safety. The successful completion of the first three phases leads to approval for the investigational product to be marketed. The study is terminated and enters phase IV for ongoing monitoring for safety and efficacy. This information is summarized in Table 6.

The termination of the study is a complex process involving careful planning. It needs its own written protocol concerning termination activities, dissemination of results, data clean-up, and storage. If the researcher plans to disseminate the results, he should inform the study subjects or their local guardian. The study participants are followed after completion of the study to see when, if any treatment-induced changes occur, and taper off the treatment instead of just stopping use, any events occurring after no more use of the investigational product.

The safety and efficacy of the investigational product require monitoring throughout its entire lifecycle. It is done through the last phase (IV) of the clinical trials or post-marketing surveillance [17]. Post-marketing surveillance requires reporting all relevant information from all sources (physicians, pharmacists, nurses, and patients), conducting formal epidemiological studies, and disseminating this information to health professionals. A known fact is that rare adverse events appear in this phase. Thus, this phase is crucial to public safety and public health.

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TABLES

Table 1. Regulatory Authorities for Clinical Trials

1	The US Food and Drug administration (FDA)
2	The Drugs Controller General of India (DCGI)
3	Health Canada
4	Therapeutic Goods Administration (TGA) of Australia
5	European Union Drug Regulating Authorities (EUDRA)
6	South African Health Products Regulatory Authority (SAHPRA)

Table 2. Clinical Trial Team Members

Role	Responsibilities
Sponsor	An organization who is responsible for initiation, management and financing of a clinical trial[2]
Principle Investigator	Conducts research at the clinical site and is a team leader when there are more than one individual at a trial site.[3]
Sub Investigator	Perform trail related produces and make decisions, supervised by the principle investigator.[3]
Clinical Research Coordinate (CRC)	Hired by the principal investigator to coordinate, manage and conduct research at a specific site.[15]
Clinical Data Manager	Safely store data into computer software such as excel, and manage via defined data tables, develop the data entry system, and enquires the data for monitoring and analysis by different methods.
Static Analyst	Analyses the collected data via various methods and determine the variation among variables (clinical significance)
Subjects	Participants in the clinical trial.
Regulatory Authority	Evaluates and approves the clinical study protocol.
Ethics Review Board	Protects the safety of human research subjects. Ensures study meets ethical standards and regulations.

Table 3. Clinical Trial Protocol Standard Items

1	Background or Literature Revision
2	Objectives / Research Question (Hypothesis) a) Primary Question b) Secondary Question
3	Design of the Study a) Study Population b) Intervention c) Variables d) Data Collection and Variables e) Termination Policy
4	Organization- Investigators and Administration

Table 4. PICOT Format [7]

P - Population	Study sample (Subjects)
I - Intervention	Treatment provided to the study subjects
C - Comparison	Reference group to compare with intervention treatment group
O - Outcome	Result to evaluate the effectiveness of the intervention
T - Time	Duration of the data collection

Table 5. Study Designs

Randomized Controlled Trial (RCT)	• Subjects are randomly assigned to either a control or test groups (received intervention) • Randomization is usually done by computers • Bias is reduces via: 1. Single blinded – subjects are not aware whether they are part of the control or test group. 2. Double blinded - subjects and investigators are not aware of assigned group of participants. 3. Tripled blinded – subjects, investigators or analyst are not aware of assigned group of participants.
Cross- Sectional Study	• Subject's individual data on exposure and outcome is gathered at the same time.
Case- Control Study	• Similar sample subjects of two groups are compared. 1. Case – subjects with a particular outcome 2. Control – subjects without that particular outcome
Cohort- Control Study	• Subjects are samples and classified into groups based on one or more cohorts (group of people with common characteristics like age, sex or address) \

Table 6. Clinical Trial Phases [16]

Phase	Purpose	Subjects	Duration	Site
I	To monitor the intervention safety and maximum tolerated dose	20-100 healthy volunteers	1-2 years	Specialized centers like research university
II	To assess the efficacy and side effects of intervention	100-300 subjects from the target populations	>2 years	Community
III	Same as phase II	Large	1-4 years, longer duration	