Review Article

Development and Writing of Clinical Trial Protocol

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Received: 24-10-2021; **Revised:** 18-12-2021; **Accepted:** 22-12-2021; **Published on:** 15-01-2022.

ABSTRACT

The protocol of clinical trial serves as the study planning, conduct, reporting and appraisal. Writing a research proposal is one of the most challenging and difficult task as research is a new area for the majority of postgraduates and new researchers. In the field of medicines in order to ensure better understanding of human biology and improve their health standards, conducting the clinical trials remain a key approach. In general all randomized clinical trials require a protocol to explain rationale, method adopted, measures to ensure the safety of study subjects, about research funders and organizational details right from the beginning of trial till reporting of the final results. Multiple discrepancies have been observed in clinical trials, and all of them have to be addressed to make clinical research safe for humans. In conclusion, the development of comprehensive protocol not only provides a mechanism to ensure the monitoring of trial but also safeguards the study subjects and increases the reliability of trial results.

Keywords: Clinical trial protocol, Informed consent, Institutional Review Board, Researcher.

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DOI: 10.47583/ijpsrr.2022.v72i01.011

DOI link: http://dx.doi.org/10.47583/ijpsrr.2022.v72i01.011

INTRODUCTION

The protocol is defined as a document that gives sufficient detail to enable understanding of the background, rationale, objectives, study population, interventions, methods, statistical analyses, ethical considerations, dissemination plans, and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigor from ethics approval to dissemination of results. [1]

It is an important document produced by study investigators detailing a priori the rationale, proposed methods and plans for a way a clinical test are going to be conducted. [2,3] This key document is employed by external reviewers (funding agencies, regulatory bodies, research ethics committees, journal editors, peer reviewers, institutional review boards and, increasingly, the broader public) to know and interpret the rationale, ethical considerations and methodological rigour of the test. Additionally, trial protocols provide a shared point of regard to support the research team in conducting a high-quality study.

Despite their importance, the standard and completeness of published trial protocols are variable. [2, 3]The SPIRIT statement was published in 2013 to supply guidance for the minimum reporting content of a clinical trial protocol and has been widely endorsed as a world standard. [4, 5] Minimum guidance applicable for all clinical trial interventions but recognises that certain interventions may require extension or elaboration of these items provided by SPIRIT statement published in 2013.

What Is a Protocol?

Clinical research is conducted consistent with an idea (a protocol) or an action plan. The protocol demonstrates the rules for conducting the trial. It illustrates what is going to be made within the study by explaining each essential a part of it and the way it is administered. It also describes the eligibility of the participants, the length of the study, the medications and therefore the related tests.

A protocol is directed by a chief researcher. The health of the participants are going to be regularly checked by members of the research team to ultimately make sure the study's safety and effectiveness.

Why the Clinical Trial Protocol Is Needed?

In general, all the randomized clinical trials essentially require a protocol to illucidate the rationale, adopted method, measures to make sure the security of study participants, proposed statistical analysis, information about organizational/administrative and research funder details right from the time of trial inception till reporting of the results. Thus, transparent, detailed and clearly written protocols remain an important element to perform a clinical trials because as it enables timely and comprehensive assessment of the trial. [6, 7] In most of the protocol discrepancies (viz. designation of primary outcomes or sample size calculations or role of sponsor and investigator, etc.) are observed which seriously questions the reliability of the clinical trials result. [7, 8]

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The protocol may be a key internal control tool for all aspects of a clinical trials, being necessary for several reasons:

- It ensures the safety and health of all the study participants
- It provides a particular study plan
- It defines and manages the trial, and thus it should be strictly followed by all the study investigators
- It guarantees the integrity of knowledge, allowing the mixture and comparison of knowledge across all investigators and/or study sites
- It informs the study administrators, which regularly are a contract research organization(CRO)
- It is required to get ethical approval from the Research Ethics Committee or Institutional Review Board (IRB) [9]

Purpose of Research Proposal

Aim

- To raise the question to be researched and clarify its importance.
- To gather existing knowledge and discuss the efforts of other researches who have worked on the related questions (Literature review).
- To formulate a hypothesis and objectives.
- To suggest the methodology required for solving the question and achieving the objectives.
- To discuss the need and limitations in achieving the objectives. [10]

Components of a Research Protocol

The topics that ought to be covered during a protocol are given below.

Table 1: Components of Research Protocol.[11, 12]

Sr.no	Components
1	Title of the study
2	Administrative details
3	Project summary
4	Introduction to the research topic, background (Literature review)
5	Preliminary studies
6	Study objectives and/or questions. statement of the matter
7	Methodology: study design, study population and methods of recruitment variables list, sample size, methods of information collection, data collection tools, plan of analytical study
8	Project management: Work plan (Timeline proposed schedule)
9	Strengths and limitations of the study
10	Issues for ethical review and approvals

Title of the Study

Title of proposal should be accurate, short, concise, and identify. [13, 14]

What is the study about, **Who** are the targets, **Where** is that the setting of the study and **when** its get launched, if applicable-

It should make the most objective clear, convey the important purpose of the research and mention the target population. Carry maximum information about the subject during a few words; it is an honest practice to stay the title to within 12-15 words. It should convey the thought about the world of research and what methods are getting to be utilized in a compact, relevant, accurate, attractive, easy to know, and informative way.

Administrative Details

The subsequent administrative details and a protocol content summary should follow the title page:

- Contents page list of relevant sections and sub-sections with corresponding pagination.
- Signature page is signed by senior members of the research team and dated to verify that the version concerned has been approved by them.
- Contact details for the research team members listing postal and telephone numbers and e-mail addresses for members of the research team.

Project Summary

The summary should be distinctive, concise and will sum up all the essentials of the protocol.

Introduction (Background)

The background to the project should be concise and ask the topic straight forwardly. In writing the review, attention should be drawn to the positives, negatives and limitations of the studies quoted. [15, 16] Introduction is concluded by explaining how this study will benefit the community. The literature review should logically cause the statement of the aims of the proposed project and end with the aims and objectives of the study. The review should include the foremost recent publications within the field and therefore the topic of the research is chosen only after completing the literature review and finding some gaps in it.

Introduction should briefly answer the importance of the subject, the gaps/lacunae within the literature, the aim of the study and benefits for the society, from the study.

The research question should be described concisely and precisely. Its getting to be the idea of designing the project. The definition of the matter should be clear in order that a reader can straight forwardly recognize the important meaning of it.

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Study Objectives

The aims should be explicitly stated. These should be limited to the intention of the project and they should arise from the literature review. State the goal you would like to realize.

The study goal emerge from the study questions or hypothesis. These are answers to what are the possible results to the research question or hypothesis under analysis and measure. Aims should be logical and coherent, feasible, concise, realistic, considering local conditions, phrased to obviously meet the aim of the study and associated with what the precise research is meant to accomplish. For instance, to gauge knowledge level regarding cavity in grade school children in KSA (this isn't detailed). The subsequent should be added: Causes, treatment, preventive measures, etc. [17]

Selection and Withdrawal of Participants

- Criteria for inclusion and exclusion of participants.
- Procedures for withdrawal of participants (participant or investigator-initiated):
- When and the way to withdraw participants from the study/investigational product treatment.
- Type and timing of information to be collected for participants who withdraw from the study.
- Whether and the way participants are to get replaced.
- Follow–up for participants withdrawn from trial treatment.

Treatment of Participants

- Pharmacological treatment:
- Names of all products to be administered.
- Doses.
- Dosing schedules.
- Method(s) of administration (i.e. oral, intramuscular).
- Other medications or treatments permitted (including rescue medication)

  And not permitted before and/or during the study.
- Other interventions (i.e., chiropractic, physiotherapy, social therapy,

  Behavioural therapy, counselling):
- Name of intervention (i.e., Motivational Interviewing, Cognitive Behavioral Therapy).
- Frequency of sessions.
- Duration of every session.
- Method of every intervention (i.e. individual, group).
- Treatment adherence.
- All interventions:
- Period(s) of intervention, including follow–up periods for participants in each group.
- Procedures for monitoring participant compliance.
- Identification of who will administer an intervention.

Assessment of Efficacy

This section describes the methods which will be used to determine the success of the

Treatment including:

Criteria for determining the treatment's effectiveness.

Methods and timing for recording, assessing and analyzing the effectiveness criteria.

Assessment of Safety

This section describes how the study is going to be monitored and the way adverse events are going to be addressed.

Methods and timing for recording, assessing and analyzing the security criteria. Procedures to obtain reports of adverse events and illnesses experienced by subjects during the study period and for recording and reporting these events, including expedited reporting procedures.

Methods and Materials

It should describe intimately the 'Where', 'Who', 'How' the research is going to be conducted. It explains the study design, procedures and the techniques which are used to achieve the proposed objectives. It defines the variables and demonstrates intimately how the variables are going to be measured. It gives the proposed methodology for data collection and processing. Methodology composes a crucial part of the protocol. It assures that the hypothesis are going to be confirmed or rejected. It also refers to a radical strategy to achieve the objectives. [18]

The materials and methods are grouped into various subheadings:

Study design (cross-sectional, case-control, intervention study, RCT, etc.)

Proper explanation should tend on why a specific design was chosen (on the idea of proposed objectives and availability of resources).

A study design is actually the researcher's general decision to acquire the solution(s) to the hypothesis being tested. Here, strategies are going to be applied to develop balanced, correct, objective and meaningful information. It explains the methods which will be used to collect and analyze data. Proper selection of the study design is vital to achieve reliable and valid scientific results. Ethics, logistic concerns, economic features and scientific thorough-ness will determine the planning of the study. Here, the capital concern is given to the legalization of the

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results including potential bias mystifying issues. Randomized controlled clinical test is that the best to document a causal relationship between an exposure and its outcome. [19]

Study population (Study subjects)

Where are you getting to do the research and who is that the study population (why doing research within this place and why selecting this population?).

It describes intimately about the study subjects, all aspects of the choice procedure and sample size calculation. Proper definition of inclusion, exclusion, eligibility and discontinuation criteria of the study subjects should be stated. Allocation of subjects to review arms should be explained and described in details bearing in mind the concealment and randomization process. [20, 21]

Sample size

Sample size calculation is suggested for economical and ethical reasons. The calculation of the sample size must be explained including the facility of the sample. The sampling technique should be mentioned, e.g., randomization which will be utilized in order to get a stratified sample for your target population. Each step involved within the recruitment of the study subjects should be described consistant with the choice criteria (inclusion and exclusion criteria). [21, 22]

Proposed intervention

Detailed description of proposed intervention should be given. Here, all the activities and actions should be recorded and thoroughly explained in their order of occurrence.

- When using drugs, both the brand name and scientific name should be mentioned followed by the name of the manufacturing company, city, and country. Route of drug, frequency of dosage administration and total duration of treatment with the drug should be mentioned.
- When using apparatus its name should tend followed by the name of the manufacturer, city and country. Involved personnel should precisely define:
- Who will be responsible for the interventions?

Data collection methods, instruments used

Data collection tools are:

• Retrospective data (medical records)

• Questionnaires

• Interviews (Structured, Semi-Structured)

• Laboratory test

• Clinical examinations.

• Description of instruments, tools used for data collection, also the methods wont to test the validity and reliability of the instrument should be provided.[23,24,25]

Table 2: Suitable Research design depends on the aim of the study. [19]

Purpose	Study design
To determine frequency and burden of a disease	*cross-sectional survey (prevalence) *cohort study (incidence)
To identify the danger factors	*cohort study *case-control study
To determine prognosis of disease	*cohort study
To determine efficacy/effectiveness of latest treatment	*clinical trials *Community Intervention
To evaluate community programs	*evaluation

Data Managements and Analysis Plan

This section should be written following statistical advice from a statistician. The analysis plan and which statistical tests are going to be wont to check the importance to the research question/hypothesis with appropriate references should be described. Names of variables which will be utilized in the analyses and therefore the name of statistical analysis which will be performed to assess the result should be listed.[26, 27] If computer programs are to be applied, it is important to say the software used and its version.

Project Management

Work plan-A work plan is an overview of the activities of all the phases of the research to be administered consistent with an anticipated time schedule. Proper schedule for accomplishing each major step of the study should be defined. Assigning time frame to every step within the trial are going to be helpful in organizing the structure of the research trial. The personnel (investigators, assistants, laboratory technicians etc.) involved within the study or data collection should be properly trained.

Strengths and Limitations

It's important to say the strengths or limitations of the study, i.e., what study are able to do or cannot achieve is vital, so on prevent wasteful allocation of resources.

Ethical Considerations (Issues for Ethical Review and Approvals)

It should indicate whether the procedures to be followed are in unison with the Declaration of Helsinki. In any case, study shouldn't start unless approval from ethics panel is received.

The following points should be explained:

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- The advantages and risks for the participants involved. The social, physical and psychological effects of the research.
- Details of the knowledge tend to the study patients including alternative treatments/approaches.
- Information should be provided on the free consent of the participants. Information form should contain: Justification for research, outline of study, risks, confidentiality, and voluntary participation should be told patients about the liberty to withdraw from the study whenever they want to. Confidentiality indicates how the private information obtained from the patient are going to be kept secret. (Data safety)

Operational Budgeting and Planning (Budget Summary)
Outline the budget requirement showing head wise expenditure for the instruments, transportation, laboratory tests and price of drug. Within the annexure budget estimate is to be attached. All costs including supplies, communication, equipment, personnel, consumables and funds for patients and data processing are all included within the budget. Each item should be justified.

Annexure

At the ending of the protocol the following annexures are to be attached:

- Informed consent form.
- Case Record Forms (CRFs).
- Budget details.
- (CV) Curriculum Vitae of the chief investigator and co-investigator and their work in the study. CV ensures that the role of every investigator is well defined.
- Copies of any questionnaires or draft questionnaires.
- Letters from ethics committees.

Tips for Clinical Trial Protocol Writing

Some relevant tips for clinical trial protocol writing includes:

- Always follow protocol content guidelines and address all items included within the guideline.
- All relevant preclinical and clinical data including published and unpublished data should be mentioned in the background of the protocol.
- All research-related activities should be detailed within the protocol and therefore the consent form. It is important to make sure the consistency of both documents. Moreover, research-related activities must be linked to a research goal.
- Describe intimately all study activities that participants will undergo.
- Getting an independent review of the protocol from colleagues that aren't directly involved within the research plan are often very useful. It can help to spot potentially 'unclear' aspects, where regulatory agencies and therefore the IRB may have difficulties also.
- Consider the perspectives of the regulatory agencies (mainly focused on the 'public good') and therefore the IRB (concerned with the rights and welfare of the individual subjects). Both perspectives are complementary but distinct. Invasive procedures or treatments should be minimized. The minimization of risks is especially important in children and other vulnerable populations. In some cases, you will got to seek advice from an IRB regulatory consultant. [9]

Protocol Amendment

A protocol amendment may be a written description of a change to some aspect(s) of the study as described within the research protocol. Protocol amendments must be submitted in writing to the designated Institutional Review Board (IRB) and must be approved by the IRB before they will be implemented, except when necessary to eliminate instant hazards to the participants or when the change(s) involves only arithmetic or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)). If the study involves a product that's regulated by the U.S. Food and Drug Administration (FDA), the amendment must be submitted to FDA also on the IRB, before enacting the amendment.

Protocol Amendments and Informed Consent

Study participants must be told of protocol amendments. Counting on the character and extent of the amendment, the Informed Consent form could also be revised, and participants will got to complete and sign a replacement Consent Form. A protocol amendment isn't to be confused with a "protocol clarification." A protocol clarification aids within the implementation or conduct of the study and provides internal guidance. It doesn't change the protocol or alter the risk-benefit ratio of the study. A protocol clarification generally doesn't got to be submitted to the IRB. A clarification should be provided in writing to all investigators.

One of the Template Informed Consent Form is given below.

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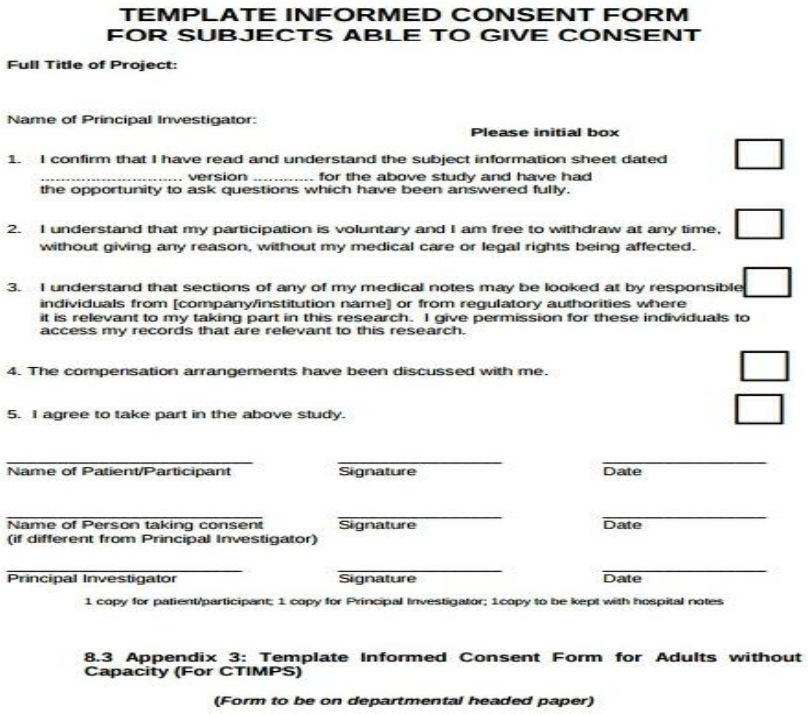

TEMPLATE INFORMED CONSENT FORM
FOR SUBJECTS ABLE TO GIVE CONSENT

Full Title of Project:

Name of Principal Investigator:

Please initial box

1. I confirm that I have read and understand the subject information sheet dated ..... version ..... for the above study and have had the opportunity to ask questions which have been answered fully. ☐
2. I understand that my participation is voluntary and I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [company/institution name] or from regulatory authorities where it is relevant to my taking part in this research. I give permission for these individuals to access my records that are relevant to this research. ☐
4. The compensation arrangements have been discussed with me. ☐
5. I agree to take part in the above study. ☐

Name of Patient/Participant	Signature	Date
Name of Person taking consent (if different from Principal Investigator)	Signature	Date
Principal Investigator	Signature	Date

1 copy for patient/participant; 1 copy for Principal Investigator; 1copy to be kept with hospital notes

8.3 Appendix 3: Template Informed Consent Form for Adults without Capacity (For CTIMPS)

(Form to be on departmental headed paper)

Figure 1: Informed Consent Form

CONCLUSION

Standardization of procedures is critical during a clinical research study. Research which is not conducted in a standardized manner is unethical because it is going to put research participants in danger while yielding invalid data. All staff involved during a clinical study must be conversant in and must strictly adhere to, the procedures described within the research protocol.

The GCP guidelines of the International Council for Harmonization require a research protocol for any study that involves the human participants. Additionally, Title 21 Part 312 of the Code of Federal Regulations requires a research protocol for studies conducted under Investigational New Drug application.

A protocol amendment may be a change to some aspect of the study. Amendments must be approved by the IRB before they will be implemented, unless there is an instantaneous safety concern for participants.

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

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Source of Support: The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of Interest: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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