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Protocol Writing in Clinical Research

Dentistry Section

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ABSTRACT

Writing a research proposal is probably one of the most challenging and difficult task as research is a new area for the majority of postgraduates and new researchers. The purpose of this article is to summarize the most important steps and necessary guidelines for producing a standard research protocol. Academic and administrative success of any project is usually determined by acquiring a grant for the related field of research. Hence, the quality of a protocol is primarily required to achieve success in this scientific competition.

Keywords: Academia, Grant, Higher Education, Researcher

WHAT IS A PROTOCOL?

Clinical research is conducted according to a plan (a protocol) or an action plan. The protocol demonstrates the guidelines for conducting the trial. It illustrates what will be made in the study by explaining each essential part of it and how it is carried out. It also describes the eligibility of the participants, the length of the study, the medications and the related tests.

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

Purpose of a Research Proposal

[Table/Fig-1] outlines the key aims of the protocol.

Aims
1) To raise the question to be researched and clarify its importance. 2) To collect existing knowledge and discuss the efforts of other researchers who have worked on the related questions (Literature review). 3) To formulate a hypothesis and objectives. 4) To clarify ethical considerations. 5) To suggest the methodology required for solving the question and achieving the objectives. 6) To discuss the requirements and limitations in achieving the objectives.

[Table/Fig-1]: Aims of the protocol.

Benefits of the Proposal to a Researcher

[Table/Fig-2] outlines the key benefits of the protocol.

Benefits
Allows the researcher to plan and review the project's steps. Serves as a guide throughout the research. Forces time and budget estimates.

[Table/Fig-2]: Benefits of the protocol.

The key points of the proposal should include justification for the need of the project and a detailed plan for the investigation [1,2]:

What is the question? (Hypothesis) What is it to be investigated?

- Why is the study important? (Significance)
- Where and when it will take place?
- What is the methodology? (Procedures and methods to be used).
- How are you going to do it? (Research design)
- Proposed time table and budget.
- Resources required (technical, scientific, and financial).

Drafting the protocol correctly will increase the likelihood that the conclusions drawn from the research are scientifically sound. Recommendations and suggestions should be sought from colleagues and experts so that researchers can develop their plans. However, once the study is launched, the protocol should not be altered during the progression of the study or trials. If the changes during progress of study are minor, then that part of the study should be excluded from the analysis. Unless unexpected complications occur during the conduct of the trial, it is advisable to reconsider and rewrite the protocol where the whole process is started again provided that the original research topic is still considered to be relevant. If complications are anticipated, it is suitable to run a pilot study, to check the feasibility of the study and find answers to the potential areas of the trial.

WHAT IS A PROTOCOL REVIEW?

Clinical trials must be approved and monitored by an Institutional Review Board that ensures that the risks are negligible and are worth any potential benefits. It is an independent committee that consists of physicians, dentists, statisticians, and members of the community.

The committee ensures that clinical trials are ethical and that the rights of all participants are protected. The board must initially approve and periodically review the research.

Components of a Research Protocol: The topics that should be covered in a protocol are shown in [Table/Fig-3] [3,4].

WRITING THE PROTOCOL

Protocol writing allows the researcher to review and critically evaluate the published literature on the interested topic, plan and review the project steps and serves as a guide throughout the investigation. The proposal is an inevitable document that enables the researcher to monitor the progress of the project [5].

1) Title of the Study: Title of proposal should be accurate, short, concise, and identify [2,6].

What is the study about, **Who** are the targets, **Where** is the setting of the study and **When** it is launched, if applicable-

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 problem. 7) Methodology: Study design, study population and methods of recruitment, variables list, sample size, methods of data collection, data collection tools, plan of analysis (analysis of data) 8) Project management: Work plan (Timeline - proposed schedule) 9) Strengths and limitations of the study 10) Issues for ethical review and approvals

[Table/Fig-3]: The components of the protocol.

It should make the main objective clear, convey the main purpose of the research and mention the target population. Carry maximum information about the topic in a few words; it is a good practice to keep the title to within 12-15 words. It should convey the idea about the area of research and what methods are going to be used in a compact, relevant, accurate, attractive, easy to understand, and informative way.

2) Administrative Details: The following administrative details and a protocol content summary should follow the title page:

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

3) Project Summary: The summary should be distinctive, concise and should sum up all the essentials of the protocol.

4) Introduction (Background): The background to the project should be concise and refer to the subject straight forwardly. In writing the review, attention should be drawn to the positives, negatives and limitations of the studies quoted [7-9]. Introduction is concluded by explaining how the present study will benefit the community. The literature review should logically lead to the statement of the aims of the proposed project and end with the aims and objectives of the study. The review should include the most recent publications in the field and the topic of the research is selected only after completing the literature review and finding some gaps in it.

Introduction should briefly answer the importance of the topic, the gaps/lacunae in the literature, the purpose of the study and benefits for the society, from the study.

The research question should be described precisely and concisely. It is going to be the basis of designing the project. The definition of the problem should be clear so that a reader can straight forwardly recognize the real meaning of it.

5) Study Objectives (Aims): The aims should be explicitly stated. These should be confined to the intention of the project and they should arise from the literature review. State the goal you need to achieve.

The study aims or objectives emerge from the study questions/ hypothesis. They are answers to what are the possible responses to the research question or hypothesis under analysis and measure. Aims should be logical and coherent, feasible, concise, realistic, considering local conditions, phrased to clearly meet the purpose of the study and related to what the specific research is intended to accomplish. For example, to evaluate knowledge level regarding dental caries in primary school children in KSA (this is not detailed). The following should be added: Causes, treatment, preventive measures, etc.

The objectives should be (SMART objective): Specific, Measurable, Achievable, Relevant and Time based [10].

Specific Aims: Details of each objective that will finally lead to the achievement of the goal should be stated. Specific aims one by one should be listed concisely. It is good practice not to include too many aims in the study (2-5 best); too many objectives often lead to inaccurate and poorly defined results. Furthermore, aims should be achievable, realistic and specific with no general and ambiguous statements. They should be stated in action verbs that illustrate their purpose: i.e., "to determine, to compare, to verify, to calculate, to reduce, to describe, etc."

Secondary Objectives (Optional): These are referred to as ancillary and minor objectives that could be studied during the course of the study.

The formulation of objectives helps to focus the study and to avoid the collection of any unnecessary data and hence organize the study in clear and distinct stages.

Hypothesis: It is a statement based on sound scientific theory that recognizes the predicted correlation between two or additional assessable variables [11]. It is always developed in response to the purpose statement or to answer the research questions posed. Furthermore, hypothesis transforms research questions into a format amendable to testing or into a statement that predicts an expected outcome.

Types of hypothesis statements:

- **Null hypothesis:** A null hypothesis is a statement that there is no actual relationship between variables (H0 or HN). It may be read as there is no difference between the groups to be compared and no relationship between the exposure and outcome under investigation. H0 states the contradictory of what the researchers expect. The final conclusion of the investigators will either keep a null hypothesis or reject it in support of an alternative hypothesis. It does not essentially mean that H0 is accurate when not rejecting it as there might not be an adequate proof against it.
- **Alternative hypothesis:** An alternative hypothesis is a statement that suggests a potential outcome that the researcher may expect (H1 or HA). This hypothesis is derived from previous studies where an evident difference between the groups to be compared is present. It is recognized only when a null hypothesis is rejected. Practically, hypotheses are stated in the null form, because they have their inferential statistics. Such hypotheses of no difference will be challenged by researchers and the result of the statistical testing gives the probability that the hypothesis of no difference is true or false [12].

Aims should be logically linked and arranged according to the tested hypothesis statement.

Example:

- Research question: Is there a difference in fluoride release between the Compomer and Glass- ionomer cement?
- Null Hypothesis: There is no difference in fluoride release between the Compomer and Glass- ionomer cement.
- Alternate Hypothesis: There is a difference in fluoride release between the Compomer and Glass-ionomer cement.

The statement of the problem should provide a summary of exactly what the project is trying to achieve.

- What exactly do you want to study?
- Why is it worth studying?
- Does the proposed study have theoretical and/or practical significance?
- Does it contribute to a new understanding of a phenomenon? (i.e., Does it address new or little known material or does it treat familiar material in a new way or does it challenge an existing understanding or extend existing knowledge?)

The justification of the research should be a convincing statement for the need to do it:

- How does the research relate to the priorities of the region and the country?
- What knowledge and information will be obtained?
- What is the ultimate purpose that the knowledge obtained from the study will serve?
- How will the results be disseminated?

- How will the results be used, and who will be the beneficiaries?

6) Methods and Materials: It should describe in detail the 'Where', 'Who', 'How' the research will be conducted. It explains the study design and procedures and techniques used to achieve the proposed objectives. It defines the variables and demonstrates in detail how the variables will be measured. It details the proposed methodology for data gathering and processing.

Methodology composes an important part of the protocol. It assures that the hypothesis will be confirmed or rejected. It also refers to a thorough strategy to attain the objectives [13].

The methods and materials are divided into various subheadings:

a) Study design (cross-sectional, case-control, intervention study, RCT, etc.): Proper explanation should be given as to why a particular design was chosen (on the basis of proposed objectives and availability of resources).

A study design is in fact the researcher's general plan to acquire the answer (s) to the hypothesis being tested. Here, strategies will be applied to develop balanced, correct, objective and meaningful information [14]. It explains the methods that will be used to collect and analyze data. Proper selection of the study design is important to attain reliable and valid scientific results.

Ethics, logistic concerns, economic features and scientific thoroughness will determine the design of the study. Here, a chief concern is given to the legality of the results including potential bias mystifying issues.

Randomized controlled clinical trial is the best to document a causal relationship between an exposure and its outcome [Table/Fig-4].

b) Study population (Study subjects): Where are you going to do the research and who is the study population (why doing research in this place and why selecting this population?).

It describes in detail about the study subjects, all aspects of the selection procedure and sample size calculation. Proper definition of eligibility, inclusion, exclusion and discontinuation criteria of the study subjects should be stated. Allocation of subjects to study arms should be explained and described in details bearing in mind the concealment and randomization process [15,16].

c) Sample size: Sample size calculation is recommended for economical and ethical reasons [16-18]. The calculation of the sample size must be explained including the power of the sample. The sampling technique should be mentioned, e.g., randomization that will be used in order to obtain a representative sample for your target population. Each step involved in the recruitment of the study subjects should be described according to the selection criteria (inclusion and exclusion criteria).

"Informed consent" should be mentioned (Permission granted in full knowledge of the possible consequences).

d) Proposed intervention: Full 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 scientific and brand name should be mentioned followed by the name of the manufacturing company, city, and country. Drug route, dosage, frequency of administration, and total duration of treatment with the drug should be mentioned.
- When using apparatus its name should be given followed by the name of the manufacturer, city and country.

Purpose	Study Design
To determine frequency and burden of a disease	* Cross-sectional survey (Prevalence) * Cohort study (Incidence)
To identify the risk factors	* Cohort study * Case-Control study
To determine prognosis of a disease	* Cohort study
To determine efficacy/effectiveness of a new treatment	* Clinical trials * Community intervention
To evaluate community programs	* Evaluation

[Table/Fig-4]: Suitable research design depends on the purpose of the study.

Involved personnel should precisely define:

- Who will be responsible for the interventions?
- What activities each personnel will perform and with what frequency and intensity?

e) Data collection methods, instruments used:

Data collection tools are:

- Retrospective data (medical records) [19]
- Questionnaires [20]
- Interviews (Structured, Semi-Structured)
- Laboratory test (literature or personal knowledge should be referenced, if established test, or description should be provided in details, if not established)
- Clinical examinations
- Description of instruments, tools used for data collection, as well as the methods used to test the validity and reliability of the instrument should be provided [21].

7) Data Management and Analysis Plan: This section should be written following statistical advice from a statistician. The analysis plan and which statistical tests will be used to check the significance to the research question/hypothesis with appropriate references should be described. Names of variables that will be used in the analyses and the name of statistical analysis that will be performed to assess the outcome should be listed [22-25].

If computer programs are to be applied, it is important to mention the software used and its version.

8) Project Management: Work plan-A work plan is an outline of activities of all the phases of the research to be carried out according to an anticipated time schedule.

Proper time table for accomplishing each major step of the study should be defined. Assigning time frame to each step in the trial will be helpful in organizing the structure of the research trial. The personnel (investigators, assistants, laboratory technicians etc.) involved in the study or data collection should be properly trained.

9) Strengths and Limitations: It is important to mention the strengths or limitations of the study, i.e., what study can achieve or cannot achieve is important, so as to prevent wasteful allocation of resources.

10) Ethical Considerations (Issues for Ethical Review and Approvals): It should indicate whether the procedures to be followed are in accord with the Declaration of Helsinki. In any case, study should not start unless approval from ethics committee is received [26].

The following points should be explained:

- The benefits and risks for the subjects involved. The physical, social and psychological implications of the research.
- Details of the information to be given to the study patients including alternative treatments/approaches.
- Information should be provided on the free informed 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 freedom to withdraw from the study whenever they wish to. Confidentiality indicates how the personal information obtained from the patient will be kept secret (Data safety).

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

12) Reference System: Referencing is the regular method of recognizing information taken from other researchers' work. A proper citation will enable the readers to follow-up any reference of interest. Plagiarism refers to claiming and acquiring someone else's ideas, an action that is considered a criminal action.

Failure to reference an idea that you have found in your research, or to acknowledge the work of other team members in a team assignment falls under the category of plagiarism. Therefore referencing is an extremely important aspect of the research protocol. The two most commonly used citation systems in clinical writing are the Vancouver system and the Harvard system [27, 28]. The choice of referencing system is dependent upon the funding organizations where the research protocol is being submitted. These frequently identify their preferred system of referencing and this should be strictly adhered to. The most common style used in the dental literature is Vancouver style.

13) Annexure:

The following annexes are to be attached at the end of the protocol:

1. Informed consent form.
2. Letters from ethics committees.
3. Study questionnaire (copies of any questionnaires or draft questionnaires).
4. Case Record Forms (CRFs).
5. Budget details.
6. Curriculum Vitae (CV) of the chief investigator and co-investigator and their role in the study. It will ensure that the role of each investigator is well defined.

HOW TO JUDGE A GOOD PROTOCOL?

The protocol should adequately answer the research question. The research design must be sound enough to yield the expected knowledge. It should provide enough detail (methodology) that can allow another investigator to do the study and arrive at comparable conclusions. Here, the proposed number of participants is reasonably justified and the scientific design is adequately described.

COMMON MISTAKES (COMMON PITFALLS TO AVOID)

Incorporating insufficient elements regarding proposed studies and inadequate explanation for the implication of the problem must be shunned as well as suggesting far more work than can be practically done during the study period. Furthermore, underpowered sample size should be justified, invalid or unreliable instrumentation should be tested and improper statistics should be adequately analyzed.

CONCLUSION

The most difficult stage of conducting a research project is the preparation of a protocol that results in a short yet comprehensive document that clearly summarizes the project. Such proposal is considered successful when it is clear, free of typographical errors, accurate and easy to read.

It is important to understand the steps in developing a research protocol in order to perform an appropriate study and obtain reliable results. Extra time spent to write a good protocol will save failures at a later stage besides helping analysis. If the protocol is poorly prepared and not adhered to, it is unlikely that the project will yield the information that you hope for and in all probability the chances of selling your idea to the reviewers of a granting agency would be less.

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