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RESEARCH PROTOCOL

For an updated version, see
Basic Methods of Medical Research, Fourth Edition
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Protocol is the backbone that supports research in all steps of its execution. Thus sufficient thought must be given to its preparation. Many times it gradually evolves as more information becomes available and progressively examined for its adequacy. Most important aspect of protocol is the statement of the problem, objectives, and hypotheses. This deserves a separate discussion.

THE PROBLEM, OBJECTIVES, AND HYPOTHESES

It is colloquially said that a research is half done when the problem is clearly visualised. There is some truth in this assertion. Thus do not shy away from devoting time in the beginning on identifying the problem, on understanding thoroughly its various aspects, and on choosing the specifics that you would like to investigate.

THE PROBLEM

A problem is a perceived difficulty, a feeling of discomfort about the way the things are, presence of a discrepancy between the existing situation and what it should be, a question about why a discrepancy is present, existence of two or more plausible answers to the same question, etc. (Fisher and Foreit 2002). Among countless problems identifying one suitable for research is not always easy. Researchability of course is a prime consideration but rationale and feasibility are also important. Once these are established, the next important step is determining the focus. Review existing information to establish the parameters of the problem and use biological knowledge to refine its focus. Specify exactly what new the world is likely know through this research.

Statement of problem is not just the title. It is a comprehensive statement regarding the basis for selecting the problem, details of gaps in knowledge, a reflection on its importance, and comments on its applicability and relevance. The focus should be sharp. For example if the problem area is dietary role in cancers, the focus may be on how consumption of meat affects occurrence of pancreatic cancer in males residing in a particular area. For further focus, the study may be restricted to only nonsmoking males to eliminate the effect of smoking. For depth, meat can be specified as red or white. Further depth could be about how much red and how much white meat is consumed, and for how many years. Role of other correlates that promote or inhibit the effect of meat can also be studied. The actual depth would depend on the availability of relevant subjects on one hand and the availability of time, resources, and expertise on the other. Such sharp focus is very helpful in specifying the objectives and hypotheses, in developing an appropriate research design, and in conducting the investigation.

Justification of the problem is crucial to get the support from faculty, institution, and other agencies. Explain rationale of the problem with convincing arguments. Juxtapose it in the context of local health care framework and convince others that the problem is important for health improvement. Include considerations such as timeliness, the segment of population affected, relationship with the ongoing health care activities or an ongoing research, kind of concern it generates among medical profession, etc.

OBJECTIVES

Even the focused area of the problem may have several smaller components. Formulating objectives is breaking down the problem into a parsimonious set of questions to which answers would be sought. These questions are reworded as objectives in a measurable format. A primary medical research can have two types of broad objectives. One is to describe features of a condition such as clinical profile of a disease, prevalence in various segments of population, and the levels of medical parameters seen in different types of cases. The second type of objective is to study associations and cause-effect type of relationships. This is called analytical, and involves comparison of two or more groups. The broad objective would determine the methodology to be followed.

A broad objective would generally encompass several dimensions of the problem. These dimensions are spelt out in specific objectives. For example, the broad objective may be to assess whether a new diagnostic modality is better than the existing one. The specific objectives in this case could be separately stated on its (i) positive and negative predictivity, (ii) safety in case it is an invasive procedure, (iii) feasibility under a variety of settings such as field, clinic, and hospital, (iv) acceptability by the medical community and the patients, and (v) cost-effectiveness. Another specific objective could be to evaluate its efficacy in different age-gender or disease-severity groups so that the kinds of cases where it works well are identified. Specific objectives relate to the specific activities and they identify the key indicators of interest. Do not use umbrella type of terms such as 'To study the role of …' Instead say direct, for example, 'To estimate the relative risk of …'

Keep the specific objectives as few and focused as possible. Do not try to answer too many questions by a single study especially if its size is small. Too many objectives can render the study difficult to manage. Whatever objectives are set, stick to them all through the study as much as possible. Changing them mid-way or at the time of report writing signals that enough thinking was not done at the time of protocol development.

HYPOTHESES

Hypothesis is a precise expression of the expected results regarding state of a phenomenon in the target population. Research is about replacing the existing 'hypotheses' by the new ones that are more plausible. In medical research, hypotheses could purport to explain the etiology of diseases, prevention strategies, screening and diagnostic modalities, distribution of occurrence in different segments of population, the strategies to treat or to manage a disease, to prevent the recurrence or adverse sequelae, etc. Consider which of these types of hypotheses can be investigated by the proposed research.

Hypotheses are not guesses but reflect the depth of knowledge of the topic of research. They must be stated in a manner that can be tested by collecting evidence. The hypothesis that dietary pattern affects the occurrence of cancer is not testable unless the specifics of diet and the type of cancer are specified. Antecedents and outcome variables, or other relevant variables, should be exactly specified in a hypothesis. Generate a separate hypothesis for each major expected relationship.

The hypotheses must correspond to the general and specific objectives of the study. Thus carefully examine each objective and assess which of these generate a new hypothesis. Whereas objectives define the key variables of interest, hypotheses are guide to the strategies to analyse the data.

PROTOCOL CONTENT

Protocol is the focal document for any medical research. It is a comprehensive yet concise statement regarding the proposal. Protocol is generally prepared on a structured format with headings such as **introduction** containing background that exposes the gaps needing research, **review of literature** with details of various views and findings of others on the issue including those that are in conflict, a clear-worded set of **objectives and the hypotheses** under test, the **methodology** for collection of valid and reliable observations, a statement about methods of **data analysis**, and the process of drawing conclusions. These components are listed more systematically in Box 1.4.

Administrative aspects such as sharing of responsibilities should also be mentioned. In any case a protocol would contain the name of the investigator, his qualification, institutional affiliation, and the hierarchy such as guides in the case of Master's and Doctoral work. The place of the study such as the department and institution should also be mentioned. The year the proposal was framed is also required. Appendix at the end includes the form of data collection, the consent form, etc. The main body of a protocol must address the following questions with convincing justification.

Title

1. What is actually intended to be studied—whether the title of the study is sufficiently specific?

Introduction

2. How the problem arose? In what context?
3. What is the need of the study—what new is expected that is not known so far? Is it worth investigating? Is the study exploratory in nature, or definitive conclusions are expected?
4. To what segment of population or to what type of cases the problem is addressed?

Review of literature

5. What is the status of the present knowledge? What are the lacunae? Are there any conflicting reports? How the problem has been approached so far? With what results?

Objectives and hypotheses

6. What is the broad objective and what are the specific questions or hypotheses to be addressed by the study—are these clearly defined, realistic, and evaluable?

Methodology

7. What are the subjects, what is the target population, what is the source of subjects, how are they going to be selected, how many in each group, and what is the justification? What are the inclusion and exclusion criteria? Is there any possibility of selection bias, and how is this to be handled?
8. What exactly is the intervention, if any—its duration, dosage, frequency, etc. What instructions and material are to be given to the subjects at any time?
9. Is there any comparison group? Why is it needed and how will it be chosen? How will it provide valid comparison?
10. What are the possible confounders? How these and other possible sources of bias are to be handled? What is the method of allocation of subjects to different groups? If any blinding, how will it be implemented? Is there any matching?

11. On what characteristics would the subjects be assessed—what are the antecedents and outcomes of interest? When these assessments would be made? Who will assess them? Whether these assessments are necessary and sufficient to answer the proposed questions?
12. What is the operational definition of various assessments? What methods of assessment are to be used—are they sufficiently valid and reliable? What information will be obtained by inspecting records, what by interview, what by laboratory and radiological investigations, and what by physical examination? Is there any system of continuous monitoring in place? What mechanism is to be adopted for quality control of measurements?
13. What form is to be used for eliciting and recording the data? (Attach it as Appendix) Who will record? Whether or nor it will contain the instructions?
14. What is to be done in case of contingencies such as dropout of subjects or nonavailability of the kit or the regimen, or development of complications in some subjects? What safeguards are provided to protect the health of the participants? Also, when to stop the study if a conclusion emerges before the full course of the sample?
15. What is the period of the study and the time-line? (See Figure 1)

Data analysis

16. What estimations, comparisons and trend assessments are to be done at the time of data analysis? Whether the quality and quantity of available data would be adequate for these estimations, comparisons, and trend assessments?
17. What statistical indices are to be used to summarise the data—are these indices sufficiently valid and reliable?
18. How the data analysis is to be done—what statistical methods would be used and whether these methods are really appropriate for the type of data, and to provide correct answer to the questions? What level of significance or the level of confidence is to be used? How the missing data, noncompliance, and nonresponse are to be handled?
19. What is the expected reliability of the conclusions? What are the limitations of the study, if any, with regard to generalisability or applicability?

Administration

20. What resources are required, and how are they to be arranged?
21. How the responsibilities are to be shared between investigators, supporting units (e.g., pathology, radiology, biostatistics), hospital administration, funding agency, etc.?

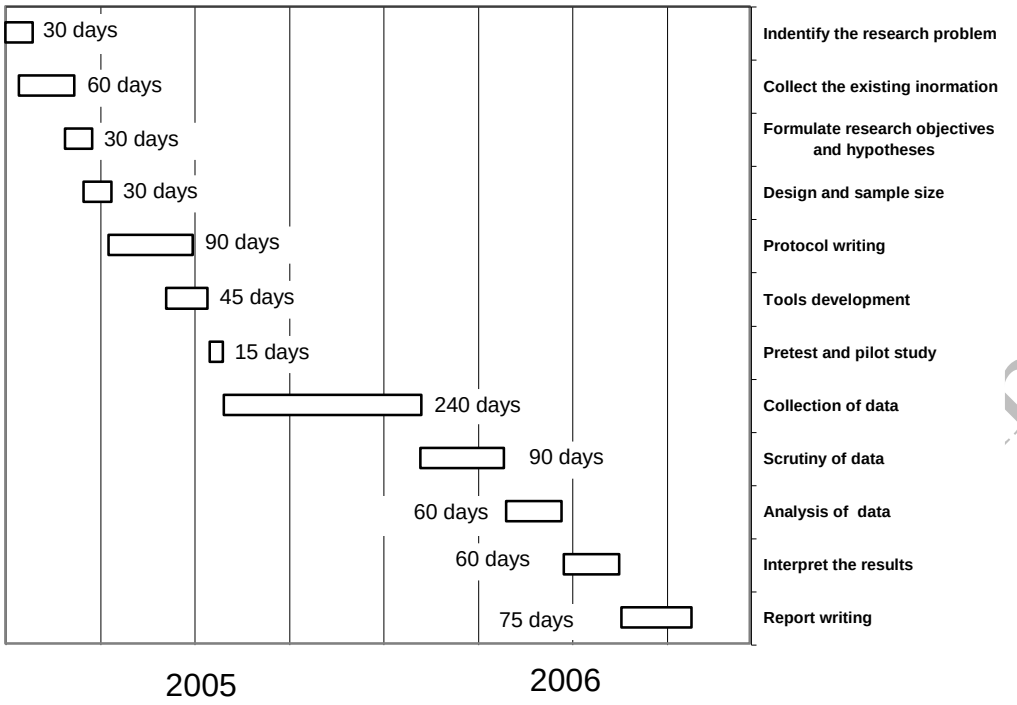

Figure 1: An example of a time-line (Gnatt chart) for a medical research project

In short, the protocol should be able to convince the reader that the topic is important, the data collected would be reliable and valid for that topic, and that contradictions, if any, would be satisfactorily resolved. Present it before a critical but positive audience and get their feedback. You may be creative and may be in a position to argue with conviction, but skepticism in science is regularly practiced. In fact it is welcome. The method and results would be continuously scrutinised for possible errors. Protocol is the most important document to evaluate the scientific merit of the research proposal by the funding agencies as well as by the accepting agencies (the teaching faculty in case of postgraduate research). Peer validation is a rule rather than exception in scientific pursuits. A good research is the one that is robust to such reviews.

A protocol should consist of full details with no short cuts yet should be concise. It should be to the point, and coherent. The reader, who may not be fully familiar with the topic, should be made absolutely clear about why, what, and how of the proposed research. To the extent possible, it should embody the interest of the sponsor, the investigator, the patients, and the society. It also is a reference source for the members of research team whenever needed. It should be complete and easy to implement.

Protocol is a big help at the time of writing of the report or a paper. Introduction and methods section remains much the same as in the protocol, although in an elaborate format. The objectives as stated in the protocol help to retain the focus in the report. Much of the literature review done at the time of protocol writing also proves handy at the time of report writing.

Whereas all other aspects as detailed in Box 1 may be clear by themselves, or would be clear as we go along in this text, we would like to emphasise on the impartiality in review of literature. Do not be selective to include only those pieces of literature that support your hypotheses. Include those also that are inconsistent with or opposed to the hypotheses. Justify the rationale of research with reasons that effectively counter the opposite or indifferent view. *Research is a step in relentless search for truth, and it must pass the litmus test put forward by conflicting or competing facts.*

Box 1: Elements of a medical research protocol

Title — Clearly worded but concise title that aptly describes the gist of the study

Investigator — Name, qualification, affiliation, supervisor/advisor, degree, year, etc.

Introduction — Identification of the problem area, background information including lacunae and gap in knowledge, and why is it important to fill this gap

Review of literature — Critical appraisal of the findings of others that could have bearing on this research; this may have global overtones but must be focused on local environment so that the relevance is clearly established; confine it to the topic and include latest developments

Objectives and hypotheses — Clear-worded short statement of what exactly is purported to be achieved by this research, and for what segments of population or patients would it apply; statement of what hypothesis is under test

Methodology — Inclusion and exclusion criteria for subjects (Box 1.5), specification of various groups, number of subjects to be included in each group with justification, method of selection of subjects, method of allocation of subjects to different groups, blinding and other strategies to reduce bias, matching criteria with justification, specification of intervention if any and the treatment schedule, definition of variables to be assessed, assessment of compliance, identification of confounders and their control, method of eliciting information, validity and reliability of devices, and time-sequence of collecting data and their frequency; also feasibility of the study within the time frame and resources; various possible contingencies and how they would be handled

Ethics — List of ethical problems and how are they proposed to be resolved, including protocol deviations, and safeguards for the participants

Statistical evaluation — Methods to be used for various estimations, to test various hypotheses, to detect trends, etc., as dictated by the objectives. Comment on internal validity and external generalisability of the results, include strategies for handling missing data, confounding, and biases.

Limitations — Conditions or groups to which the results would not apply

Administration — Arrangement of resources, assignment of duties, and sharing of responsibilities

References — Those cited in the text of the protocol and possibly a bibliography of other literature on the topic that could be of interest to the reader

Appendix — Forms such as questionnaire, schedule, or proforma to be used: structured or open, precoded or not, and pretested or not; the consent form; letter of support; etc.

Box 2: Inclusion and exclusion criteria

Inclusion criteria — The set of characteristics such as age-group, type of disease, and severity of disease that are necessary for subject to be considered as eligible for inclusion in the study. Whether or not such a subject is actually included will depend on the selection procedure. Some of these may become ineligible when exclusion criteria are imposed.

Exclusion criteria — The set of conditions presence of which will exclude an otherwise eligible subject from the study. Generally these conditions are indicative of severe form of disease or complications that render a subject unsuitable for that research.

Inclusion and exclusion criteria are part of the case definition that delineates the target population.

REFERENCES

Fisher AA, Foreit JR. Designing HIV/AIDS Intervention Studies: An Operations Research Handbook. New York: Population Council, 2002:p8.