**Principles of Writing Research Protocol**

Research may be defined as an attempt to find out / discover facts in a systematic and scientific manner with statistical support.

Medical Research may be defined as the research conducted to aid the body of knowledge in the field of medicine and related disciplines. When an activity involving patients is undertaken with the prime purpose of testing a hypothesis and permitting conclusions to be drawn with the intention of contributing to medical knowledge, it becomes MEDICAL RESEARCH. Medical research is the formal, experimental study of human health and disease processes. If the research is done on patients it is either for Diagnosis, Treatment or Prognosis. It may be for finding out better and more valid and possibly less costlier methods for diagnosis of the disease. If the research is on Treatment, it is for finding out new, more effective and possibly less expensive methods of treatment modality like, new drugs or a new surgical method. This area of study is known as Clinical Trials. Prognosis is usually done as part of the clinical trial to find out the recovery rate, improvement rate, progression free survival rates or survival rate with the disease in case of chronic diseases like cancer and HIV.

Medical research need not be restricted to only Patients. Apart from research on patients, Medical research also deals with the estimation of magnitudes of various diseases and health conditions in terms of prevalence and incidence rates (prevalence rate of blindness in Kerala) and to identify the possible causative factors. This area of study is called ‘Epidemiology’ and the methods used for the same is called ‘Epidemiological methods’. Medical Research also deals with the general health of the people in terms of prevention of diseases through appropriate vaccination /immunization, health education on diet & excersise, maintenance of good health and promotion of health through good nutrition and life style. Experiments on Animals & Tis-sues, experiments in Basic medical sciences (Anatomy, Biochemistry & Physiology), Para-medical sciences (Microbiology, Pathology, Pharmacology, Bio-physics, Bio-medical engineering, Forensic Medicine) also are included under medical research. It also deals with Mathematical and Biostatistical modelling, Bioinformatics and Computer Software development for finding out efficient, quick and powerful methods involving a large number of variables and thus helping the medical personnel in better diagnosis, treatment and prognosis.

What ever may be the research area and problem preparation of a good protocol is a must for conducting any research. Certain important steps are to be followed in preparing a good research protocol and they are listed below:

1. **Problem Identification**
   The first step is to identify a research problem on which the researcher is interested to do research. This could be a rough problem for a student who has to do a thesis work. They may have already identified a problem in the concerned area during their graduate course or at any time before joining for the PG course. They should firm up this problem in consultation with their guide(s) in the concerned Department. This could be a very rough idea of the research problem. For example, the problem on finding an appropriate modality of treatment for cataract or controlling the incidence of cataract through the known safe guards and investigating on its effect on it.

2. **Literature Review**
   Once the research problem is identified a thorough review of literature has to be done to locate the lacunae, i.e.; what is missing in the literature on the identified area of study.

   If the research is being planned on a problem which is already done earlier, continue the previous study with the left out objective, if any or with the question(s) posed from it. For example, in the clinical trial conducted earlier for comparing the efficacy of a new drug in comparison to the standard drug, a particular dosage or a particular group of patients could not be included due to some practical problem. The new study may be planned on these aspects.

   If the research is planned on a new problem, screen the literature thoroughly to locate the gaps in the problem of interest pick up those gaps which are feasible, meaningful and relevant and develop the research questions based on the areas in which there are gaps. For example, in the earlier clinical trial the recovery rate obtained with the drugs used was not satisfactory or the sample size was inadequate to arrive at a valid conclusion and hence the same study may be repeated on a much larger sample size with adequate power (will be explained in a later issue).

   Review of literature will help not only in locating the lacunae and to define your research problems, but also, in many other aspects. It helps to get a complete picture of the studies already done in the selected area of the study, to prevent duplication of work, to refine the statement of the problem, to get familiar with the relevant research methodologies and to justify the new research Study.

   Possible sources of literature are: Journals (Indexed & Non-
indexed), books, unpublished material like letters, reports of research and educational institutions and hospitals, medical records, data-base, personal communications etc. In the modern world internet is an easy and widely used source of literature.

Once a thorough literature review has been done the researcher can define his/her research problem in terms of research question(s).

(3) Research Question

There is always an uncertainty about something in the population/among patients/in biological aspects/statistical or mathematical models which requires a thorough investigation. For example, estimation of the current prevalence rate of complete blindness in Kerala or in India and the possible risk factors for the same. In fact there is no shortage of research questions in any field. Even if we succeed in answering a question, we remain surrounded by many other related questions.

Developing a Research Question

For the established researchers continuity of the research problems w.r.t. a variety of factors and fields itself will give them lots of opportunities for further research. For a new researcher a good way to start is to master the published literature in a specific area of study and develop that problem into a research protocol. In fact, no amount of reading can substitute first hand experience. Essential strategy for a young researcher is to apprentice himself/herself to a GOOD, EXPERIENCED, DEDICATED, SINCERE and HELPFUL mentor. Choice of an appropriate mentor is the MOST IMPORTANT decision for a new researcher. The researcher should always be alert to new ideas. Besides reviewing medical literature, participating in Journal clubs and Scientific meetings & Seminars is very useful in developing research questions. Careful observation of patients has historically been one of the major sources of selecting problems for research. Teaching is also an excellent source of inspiration (during preparation, delivery of lectures and discussion). One should keep the imagination roaming. Some creative ideas may come to mind in the canteen, while traveling, showering or just simply sitting or idling. There are basically three categories of research questions:

(1) Confirms OR Refutes previous findings

(2) Extends previous findings

(3) Provides New findings. Any research would normally fall in any of these three categories.

Characteristics of a Good research question (FINER)

It is ideal that a good research question should satisfy the FINER Qualities. FINER stands for – Feasibility, Interesting, Novel, Ethical and Relevant.

Feasibility

The researcher should know the practical limits and problems of studying the chosen area of research before finalising the research protocol in terms of availability of adequate number of subjects, technical expertise, cost, time and scope.

Interesting

The selected research area should be interesting. Though the researcher may have many motivations in terms of financial support, availability of expertise and study subjects if the research question is not interesting it may be a negative point in doing research. Hence it would be better to choose an interesting problem for research so that the interest and enthusiasm can be sustained till the end.

Novel

A Good research question should be novel. A study that merely reiterates what is already established is not worth the effort and the cost. On the other hand, a research question need not be totally original. Replication of previous studies, whether applicable to a different group of subjects, or conditions or with improved measurement techniques or different doses of drugs tested earlier could be novel. A confirmatory study is particularly useful if it avoids weaknesses of previous studies.

Ethical

A good research question must be ethically acceptable. Informed consent process and Community acceptance & agreement should be ensured. Risk of research should be acceptable in relation to the likely benefits. Non-exploitation of patients or other study subjects including animals and privacy and confidentiality of information given by the participants in the study should be ensured. Clearance of the research protocol should be obtained from the Institutional Ethics Committee.

Relevant

Research problem selected should be relevant in the present context. A good way to decide about relevance is to imagine the various outcomes that are likely to occur and consider how each possibility might advance scientific knowledge, influence clinical management and health policy or guide further research.

Primary and Secondary Questions

It is always recommended that the research questions should not be given in serial order running into many questions. For practical purposes the research questions should be given under primary and secondary questions. Most important one, two or three primary questions may be included and other related questions may be included under
secondary questions. Normally required minimum sample size is computed w.r.t. the primary questions. If possible and feasible sample size may be computed w.r.t. the secondary questions also. But, primary questions should be given higher importance w.r.t. the estimation of required minimum sample size. For example, the primary question of a research study could be to estimate the prevalence of complete and partial blindness in Kerala and the secondary question could be to identify its possible risk factors.

Problems and Solutions in Developing the Research Questions

Not Feasible: Specify a smaller set of basic and study variables. Narrow down the questions.

Not enough subjects available: Expanding / modifying the inclusion and exclusion criteria, adding extra sources of study subjects and lengthening the time frame for entry into the study could be adopted if there is shortage of study subjects in the population. Also, strategies for decreasing the sample size by altering the required confidence and power (will be explained in later issues) could be tried.

Methods beyond the skills of the investigator: Collaborating with colleagues who have the skills or consulting the experts available nearby could be adopted for solving this problem. In a research study on glaucoma the expertise on pathology may be necessary. It would be ideal to locate a expert in Pathology for the study. If possible the researcher himself / herself should acquire the required skills in other fields and learn the required skills.

Too expensive: Reduce sample size at the cost of precision and accuracy of the estimates, reduce the number of study variables including only the important variables or reduce the number of follow-ups, if it is logical and scientifically acceptable.

Summary

• All Research studies should have Research Questions.
• Thorough reviewing of published and unpublished literature on the selected and related topics should be done.
• Collaborating with the concerned experts in all the areas related to the research problem
• Focusing on one or two Primary Questions and a few relevant Secondary Questions
• Testing the research questions with FINER qualities

(4) Research (Statistical) Hypothesis

Research questions need to be stated in terms of statistical hypothesis for testing the statistical significance of the hypothesis and answering the research question.

Statistical Hypothesis

A declarative statement about the parameters (of population) or the distribution form of the variable in the population.

Examples

(1) Mean intra-ocular pressure value in cataract patients (M1) > mean intraocular pressure value in normals (M2) i.e. M1 > M2.

(2) Occurrence of cataract is positively associated with diabetes; i.e., Prevalence of cataract in those with Diabetes is greater than that in those without diabetes (P1 > P2). Statistical hypothesis has to be stated in terms of Null & Alternate hypotheses for testing the statistical significance of the difference in the values of any variable between groups or the association between a problem and its possible causative factor.

Null Hypothesis --- $H_0$

No difference in average values or percentages between two or several populations. i.e; M1=M2 or P1=P2

Alternative Hypothesis ($H_1$) --- two sided

There is difference in average values or percentages between two or several populations:

- $H_1$: M1 # M2 or P1 # P2

Alternative Hypothesis ($H_1$) --- one sided

- M1 > M2 or M2 > M1 or P1 > P2 or P2 > P1

One sided research hypothesis is stated when the direction of the difference is clearly known. For example, in studying the association of smoking with lung cancer, one sided test can be stated since it is well established that the prevalence of lung cancer will be statistically higher in smokers than in non-smokers. Advantages of one sided test is that the sample required will be comparatively less compared to two-sided tests.

Statistical Hypothesis & Research Question

Hypothesis is a statement of belief. Null hypothesis is either proved (accepted) or disproved (rejected) under the study conditions, limitations & practical considerations. Research Question is largely a matter of organizing one’s thoughts into a concise statement of what one intends to do based on the results observed in the earlier studies and from experience. This is the foundation for the further development of the study Problem.

(5) Goals/Objectives/Aims/Purposes

Though the wider meaning of all these terms may be the same, they may be differentiated as follows:
**Goals / Aims are** Long term expectations and **Objectives/Purposes are** Specific points of the current study

**Goal(s)**

Ultimate long term benefit(s) to the patients, Population and in general the country. It is the target planning to be achieved in the long run. The goal(s) of any study may not be achievable by a single study. Only a group of similar studies conducted over a period of time, probably with the relevant variations, the goal may be achieved. The goal of medical research is to find better ways to treat conditions, cure diseases or improve health. While Goals are normally broad and abstract and may not be possible to get validated easily from a single study, Objectives are narrow, specific, realistic, observable and precise and can be validated from a single study itself. Ideally in any study, both the goal(s) and the Objectives have to be stated. However, in case of Students’ thesis work, this is not necessary. It would be alright if only the objectives of the study are stated since there could be limitation w.r.t. time, finance and other factors.

The following steps in preparing a research protocol will be discussed in the next issue of the Journal:

1. Preliminary work done
2. Justification of the Study
3. Study Design
4. Estimation of minimum Sample Size and Method of selection
5. Research Tools: Questionnaire(s), Proforma(e) of Clinical Examination and Laboratory tests, Instruments & Equipments
6. Standardization of Research Tools
7. Data Collection Method(s)
8. Training Interviewers, Scientists & other Researchers who are involved in Data Collection
9. Logistics-Resources, Personnel, Facilities and Budget
10. Methods of Data entry, Data Editing, Cleaning & Verification (Inconsistency checking & Correction)
11. Data Analysis Plan: Manual / Computer, Dummy Tables and Statistical Software to be used for data analysis
12. Consent Form
13. Time Schedule
14. References

**Books / Guides for further reading:**

1. Practical guide for health researchers, WHO Regional publications, Eastern Mediterranean Series-30, Mahmoud F Fathalla, WHO, Regional office, Cairo, 2004

Prof Sundaram was previously the Head of Biostatistics at All India Institute of Medical Sciences. Currently he heads the Department of Biostatistics at Amrita Institute of Medical Sciences.