Review Article

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Elements of medical research

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Most medical research is empirical based on evidence rather than hunches or preferences. It follows a series of specific steps. There are no short cuts. Collection of evidence and its analysis should follow a carefully drawn protocol. Most of the modern medical research requires biostatistical tools to reach to a valid and reliable conclusion. Researcher must have an adequate knowledge and skill to be really effective. The endeavours should be consistent with the accepted medical and research ethics. Medical research can provide immense satisfaction when conducted on scientific lines, and can be occasionally frustrating when years of efforts fail to produce expected results. This article focuses on aspects that can increase the credibility of research. It is addressed to all interested in medical research, and seeking answers to questions such as what actually is research, what are its types, what specific steps should be followed, what a research protocol should contain, and what makes research credible *etc*.

Key words Medical empiricism - medical ethics - research credibility - research protocol

Research is a foray into the unknown. It is search for new information and knowledge. Research is either discovery of new facts, enunciation of new principles, or fresh interpretation of the known facts or principles. It is an attempt to reveal to the world something that was either never thought of, or was in the domain of the conjectures—at best being looked at with suspicion. It is a systematic investigation to develop or contribute to generalizable knowledge. The basic function of research is to answer why and how of a phenomenon, but searching answers to what, when, how much, *etc.*, is also part of research efforts. All these questions have relevance to any discipline but medicine seems to have special appetite for such enquiries. The goal of medical research is to improve health, and the purpose is to learn how various systems in human body work, why we get sick, and how to get back to health and stay fit. Research is the very foundation of improved medical care. It can also provide evidence for policies and decisions on health and development.

Much of human biology is still speculative, and its interaction with environment is intricate. Thus medical science has enormous potential for useful research. At the same time it has its own risks as well. This is evident from some of the studies published in 2002. Popular breast cancer therapy tamoxifen was found to carry increased risk of endometrial cancer[1]. Menopausal women who took estrogen for long time were also found to be at higher risk of getting ovarian cancer[2]. Arthroscopic surgery for osteoarthritis of knee was found no better than placebo[3].

Medicine is a delicate science. It is concerned with vitalities of life such as health, disease and death. Thus, it brooks no error. Ironically, no theories are available that can make it infalliable. There are no lemmas and no theorems. It must per force depend on evidence provided by observations and experience. Medicine is largely an inductive science and has very little space, if any, for deductive methods. The past experience and present evidence provide an insight in to the future. This empiricism is the backbone of medical science. Very often it works wonderfully well but sometimes it does not. There is no assurance. Miscues reported in the year 2002[1-3] are examples of such errors.

Empiricism has no conflict with rationalism. The observations must stand up to the reason, and should have adequate rational explanation. After all it is the logic of reasoning that separates humans from other species. Research results are more acceptable when the accompanying evidence is compelling and inspiring.

All scientific results are susceptible to error but uncertainty is an integral part of medical framework because of its empirical nature. The realization of enormity of uncertainty in medicine may be recent but the fact is age-old. No two biological entities have ever been exactly alike; neither would they be so in future (How about cloning!). Also our knowledge about biological processes still is extremely limited. These two aspects—first variation, and second limitation of knowledge—throw an apparently indomitable challenge. But the medical science has not only survived but is ticking with full vigour. The silver lining is the ability of some experts to learn quickly from their own and other's experience, and to discern signals from noise, waves from turbulence, trend from chaos. Biostatistical methods play a key role in this endeavour. It is due to this learning that death rates have steeply declined and life expectancy is showing a relentless rise in almost all countries around the world. Burden of disease is steadily but surely declining across the nations per thousand population[4].

Types of medical research

Medical research encompasses a whole gamut of endeavours that ultimately help to improve the health of people. Functionally, it can be divided into basic and applied types. Basic, also termed as 'pure', research involves advancing the knowledge base without any specific focus on its application. The results of such research are utilized somewhere in future when that new knowledge is required. Applied research, on the other hand, is problem-oriented, and is specifically directed to solve an existing problem. In medicine, basic research is generally at the cellular level for studying various biological processes. Applied medical research could be on the diagnostic and therapeutic modalities, on agent-host-environment interactions, or health assessments.

We would like to classify applied medical research into two major categories although this is not a universally accepted classification. First is the conventional research that includes descriptive studies such as surveys, case-series, and census, as also analytical studies such as case-control studies and clinical trials. The second category includes unconventional research, which is quite common these days, that includes operations research (prioritization, optimization, simulation, *etc.*), evaluation of health systems (assessing quality and adequacy), economic studies (cost-benefit, cost-effectiveness, *etc.*), qualitative research (focus group discussion), and research synthesis (reviews and meta-analysis). This article is confined to the methods used in conventional studies that still form the bulk of modern research (Fig.). Several manuals/books on research methodology for operations research are available, such as for research methods in health[5], health systems research[6], for economic studies[7,8], for qualitative research[9,10], and for reviews and meta-analysis[11-13]. For training guide in health research methods, a WHO Manual[14] is available.

Levels of medical research: The first level of medical research is encountered at the time of investigations carried out for a Master's thesis. The primary objective of such an investigation is to provide training to the students in research methodology but the results sometimes have larger implications that can be shared with the medical community and the society. Generally this is a small-scale investigation. The written report is termed as thesis because the nature of most such investigation is to put forward a hypothesis that could be tested by further study. Results of such research are seldom conclusive.

The next is at the level of Doctoral dissertation. This reseach is expected to generate a new result that was not known earlier. A dissertation is a detailed discourse or treatise on a particular topic that provides a new

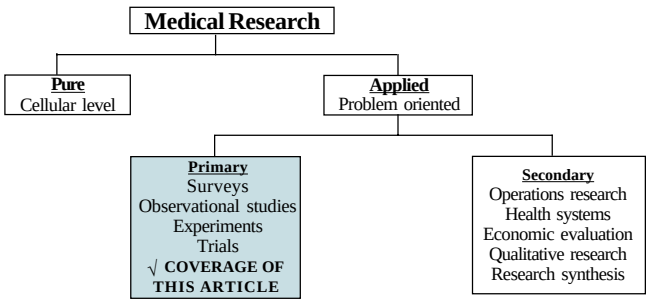

Fig. Types of medical research and coverage of this article.

perspective to a phenomenon. Since conducted by one person mostly within limited institutional resources, this level of research also is rarely able to make headlines.

The third is at the level of the institution. Many organizations are able to produce research that commands respect and becomes a topic of discussion among researchers. Some of it does change the way the medicine is practised.

Because of profound variations and uncertainties in many cases, sometimes it becomes necessary to conduct a large-scale multicentric study following a common protocol. This is the fourth level of research. The observations are pooled to come to a reliable conclusion. This could be organized either at the national or international level. Such research does attract a lot of attention because of its size but there is no evidence that it produces path-breaking results more often than organization-level research.

The basics of medical research for all levels are same as discussed in this article. Advanced methods would differ according to the focus area.

Steps in medical research

Science is known to be a systematic study that follows a pattern and produces testable results. Thus scientific research must follow a step by step approach. These steps are much more elaborate for medical research than for many other researches because of enormous uncertainties inherent in this field, and implication in human health. Because of empirical base, investigations are *sin-qua-non* for a medical research of the conventional type that is being discussed in this article. An outline of the preinvestigation, parainvestigation and post-investigation steps is as follows :

Preinvestigation steps

However odd it may sound, the preparation and plan for the investigation would be more critical than possibly the actual investigation. The following needs to be considered :

Identify the problem: The first step of course is to identify a problem area (research question) that needs investigation. An alert researcher can easily find a large number of issues floating around that need investigation. One paradigm is that, notwithstanding knowledge explosion in the past century, the unknown segment of the universe is much larger than the known segment. Thus it is necessary to match the research area to (i) relevance and applicability; (ii) interest and expertise; and (iii) the feasibility. These three aspects should considerably narrow down the problem area. Then the problem is converted to specific questions to which answers are proposed to be sought. Even when this is done with apparently sufficient specificity, it may be found during the course of the investigation that those questions were not so specific after all. Further steps as given below may help to attain focus and clarity.

Collect and evaluate existing information: After the problem is specified, the next step is to collect as much information on that problem as possible. One major source is the literature. But the potency of other sources should not be underestimated. There might be secondary data available in various organizations that can help to enhance the focus of the problem. Subject experts can provide a very useful insight to the problem that they imbibe through years of experience of working in that area. Experts might lead to the hitherto unexplored literature and, more importantly, to the work other agencies or institutions are doing in that area. The objective of all this exercise should be to identify the specific information and data gaps, and to examine how the problem fits into the medical jigsaw puzzle. In some cases it is possible that no or very little baseline information is available. In such cases, it is desirable to carry out an exploratory study as a first step.

Formulate research objectives and hypotheses: Critical evaluation of the literature and other data on the identified problem will greatly assist in focusing thoughts regarding what exactly should be investigated. These should be translated into the research objectives. The objectives must match with the perceived utility of the results. For example, for interventions, the objectives could be to find efficacy, effectiveness, affordability, efficiency, safety, acceptability, *etc.* One has to be clear about what specific aspect to concentrate on, and formulate the research objectives accordingly. They should be amenable to evaluation, and should be realistic, clearly phrased and stated in logical sequence.

From objectives emanate hypotheses. A hypothesis is a carefully worded statement regarding the anticipated status of a phenomenon. For example, it may be hypothesized that recurrence of eclampsia in pregnant women is more common in those that have family history of hypertension. The hypothesis should be biologically plausible and supported by reasoning.

Identify the study subjects: The definition of the subject of study and the target population should be clearly spelt out. For example, iodine deficiency can be diagnosed either on the basis of the palpable or visible goiter, or on the basis of urine iodine concentration <100 µg/l. Borderline hypertension can be defined as BP ≥130/85 or BP ≥140/90 mm Hg. Besides inclusion criteria, the exclusion criteria should also be clearly stated so that the cases are not excluded mid-way through the study. For this, anticipate the type of cases that can become ineligible later on after inclusion.

Think of a design: Now, think of a strategy to get valid and reliable answer to the questions, or to get a solution of the problem. This strategy would be in terms of collection of data in a manner that inspires confidence. This calls for identifying all sources of uncertainty in that set up, and developing a design that can keep them under control. In effect, this means (i) deciding on the specifies of intervention if any; (ii) determining the variables on which the data will be collected—these should form a valid set to provide correct answers; (iii) method to obtain valid and unbiased data on those variables—a feasible yet robust method that stands to scientific scrutiny; (iv) tools to be used to record the information in a manner that makes it easier to note and analyze; (v) strategy to handle any ethical problem that might arise during the course of the investigation; (vi) the number of cases or subjects that should be included in this kind of investigation; and (vii) the method of selection. Biostatistical expertise is a big help in many of these aspects.

Write the protocol: All the hard work put into the preceding steps culminates into the draft of the research protocol that incorporates all the information regarding the research in a concise manner. This is just about the most important step in conducting a research. When the thoughts are put on a paper, they crystallize and concretize. Since protocol is a written commitment, further deliberations may be needed for example to make the objectives and hypothesis more specific and to justify all the strategy. It incorporates the work plan and identifies the resources required for the project, including the time-line. The latter will state the time point when each step is proposed to be initiated and how much time will this take to complete. Work on two or more steps can go together, and this time-line will indicate this overlap also.

Develop the tools: Tools for medical research are of two types. First is the recording questionnaire, schedule or proforma that is uniformly followed throughout the investigation. Second are the measurement and investigation tools such as a scoring system and Holter test. Development of tools also encompasses arranging investigations such as for imaging and those to be done in a laboratory. They may require procuring kits, and taking help of external facilities that are not in your control. Arrangement may have to be made also to procure drugs, including life saving drugs, to meet any contigency. Modality for help from outside agencies may have to be worked out whose help may be needed, either routinely, or in case of exigency. For a large-scale investigation, instruction manual may be needed. The staff may have to be trained in interview, examination or laboratory methods so that valid and uniform data are generated.

Investigation steps

Note that preinvestigation steps are complex, and major component of them is the thought process. Then is the time to conduct the actual investigation. This also requires some preliminary steps before actually embarking upon the real study.

Pretest and do pilot study: No matter how thoughtful one has been in developing the tools of the investigation, there is always a need to pretest them for their performance in actual conditions. Experience suggests that almost invariably some deficiency is detected, and the tools or their implementation is found to require some modification. Thus one should not shy away from this exercise. Similarly, a pilot study, which is a small forerunner of the actual investigation, also generally provides useful inputs regarding changes required in the measurements to be taken, in the interview or

examination method, in the laboratory or imaging investigations, in the recording system, *etc.*

Collect the data: Although the objective of this step is collection of the relevant data but it actually entails administering the intervention such as a drug if any, and observing the subjects. As always in a medical set up, the data are obtained either by interview or examination or laboratory/imaging investigations, or a combination of these data-eliciting methods. Continuous vigil may have to be maintained to ensure that the data remain of good quality, that is they are correctly obtained for each subject without favour or fervour, and honestly recorded. The data forms should be legibly filled, and they should be fully completed.

Handle the nonresponse and ethical issues: In a science such as medicine, it is difficult to complete the investigation in all the selected subjects. Some will invariably drop out during the course of the investigation, and some may refuse to participate. Such nonresponse is to be anticipated and kept at the minimal level so that the results do not become biased. All efforts should be made to extract at least the basic information. Even when informed consent is taken, medical ethics requires that the intervention and data generation or collection should not subjugate the interest of the patient.

Scrutinize the data: Despite all the care that is exercised at the time of taking history of patients, at the time of physical examination; and at the time of laboratory/ imaging investigation, it would not be uncommon that errors occur. Most of these can be detected by scrutinizing the data for internal consistency and external validity.

Postinvestigation steps

After the data are collected, which should be adequate in terms of quality and quantity, they need to be exploited to their full potential to draw conclusions. This requires the following steps:

Analyze the data: Analysis of data is an umbrella term that incorporates a large number of mini-steps. First is preparing a master chart by tabulating the data in a manner that all the information on one subject constitutes one record. In an Excel format, this really means that there is only one row of data for each person. Also each field (column in Excel) must contain only one piece of information. If an AIDS patient has chronic parotinitis, toxoplasmosis and kaposi sarcoma, with codes 7, 12 and 14 respectively, these three should be entered in separate fields, and not as 7, 12, 14 in one field.

Second step is to summarize the data. This is done in terms of mean, standard deviation, proportion, rate and more importantly in medicine in terms of sensitivity, specificity, odds ratio and relative risk. Such summaries tend to delineate the uncertainty levels in the results. They are very helpful in grasping the essential features of data that set the tone for in-depth statistical analysis.

Third step in data analysis is exploring the data in terms of their pattern. For example, it may be necessary to examine whether some selected variables are really following a Gaussian pattern or not. That will decide that parametric tests of statistical significance should be used or nonparametric. For exploring relationship among various measurements, scatter plots can be immensely useful. These will indicate where and what type of relationship (linear or nonlinear) should be explored.

The next step is grinding the data through the rigours of statistical analysis[15]. This involves obtaining confidence intervals, performing statistical tests to assess the significance of differences, obtaining the structure of relationships such as regression and their significance, assessing trends and agreements, *etc.*

Interpret the results: Whereas statistical analysis is mostly computer-based, interpretation of the results requires critical thinking. First is to verify that various results are consistent with one-another and a proper explanation is available for the inconsistent ones. Second, check that all the potential biases have been either ruled out by design, or the results are properly adjusted for the biases. Thirdly, check that the results have adequate reliability. Fourth is to confirm that a convincing biological explanation is available that makes results plausible. Fifth is to conduct sensitivity analysis and uncertainty analysis of the results so that they are shown to be robust to the systematic variations. Sixth is to examine that the final conclusions are further development of the previous knowledge, or that they brook an entirely new ground that was not explored earlier. In short, not only that the

researcher should be convinced about the correctness of the conclusions but also there should be enough reasons to convince others.

Write the report: Report is a generic term that includes a thesis, a dissertation, an article, a paper, and a project report. Frankly, this could be the most important step in a research endeavour because this provides interface with the world. It is through this that the world is informed about the new conclusions, and a feedback regarding both inadequacies and the plus points is obtained. One has to get a clear idea about the users of the results, and accordingly disseminate the findings.

The report should be sufficiently detailed that can remove any doubt a reader might have about any aspect of the results. It should be properly worded, with a clear demarcation of the evidence-based results, and your opinions on various aspects under research. The report should be adequately illustrated by diagrams where they can enhance the clarity. Numerical results can be summarized in the form of tables. All the limitations need to be described candidly. No result has universal applicability, and the scientific community is fully aware of this fact. Thus the limitations should be stated without inhibition.

The format of the report needs to be geared to meet the expectations of the audience. A scientific paper would concisely state a particular aspect of the research in a paragraph that would take several pages in a thesis or a dissertation. The language for the press release would be very different than for a scientific paper. A report prepared for a funding agency may have a slightly different focus to fit their requirement.

Monitor the reactions: Research is a continuous process. It can be improved upon by systematically monitoring the reactions of the users of the results. It is not uncommon in research journals to publish comments and the author's rejoinder. They help to crystallize thought, and to improve in a subsequent endeavour. Also monitor whether or not the results are being utilized.

Research protocol

Protocol is a comprehensive yet concise statement regarding the proposed research. It is generally prepared on a structured format containing items such as the knowledge gaps needing research, 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 design for collection of valid and reliable observations, a statement about methods of analysis of data, and the process of drawing conclusions. In particular, the protocol must address the following questions with convincing justification :

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

2. 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?

3. What are the specific questions or hypotheses that are intended to be addressed by the study—are these clearly defined, realistic, and evaluable?

4. Are these questions consistent with the present knowledge and, if not, would the conflicts be satisfactorily resolved?

5. What is the period of the study, and the time-line?

6. 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? Is there any possibility of selection bias, and how is this proposed to be handled?

7. What exactly is the intervention, if any—its duration, dosage, frequency, *etc.*?

8. What are the possible confounders, and how these and other sources of bias are proposed to be handled?

9. 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?

10. Whether these assessments are necessary and sufficient to answer the proposed questions?

11. What methods of assessment are planned to be used—are they sufficiently valid and reliable? Is there any system of continuous monitoring in place? What mechanism is to be adopted for quality control of measurements?

12. What is proposed 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?

13. What estimations, comparisons and trend assessments are planned 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?

14. What summary measures are proposed to be used to describe the data—are these measures sufficiently valid and reliable?

15. How the data analysis is proposed 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? How the missing data—noncompliance and nonresponse—are proposed to be handled?

16. What is the expected reliability of the conclusions?

17. What are the limitations of the study, if any, with regard to generalizability or applicability?

18. What resources are required, and how are they proposed to be arranged?

19. How the administrative responsibilities are proposed to be shared?

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 appreciative audience and get their feedback. One 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 scrutinized for possible errors. A good research is the one that is robust to such reviews.

Pleasures and frustrations of medical research

Scientific enquiry is among the most challenging enterprises. Any research, more so medical research, is an occupation ridden with uncertainties. If successful in bringing out a path-breaking result, it may be idolized. If the research fails to produce expected results, the consequent frustration could be disastrous. Nobody can predict. If the result is predictable, it is not research after all. The only thing one can do is to ensure that full care is taken of possible biases by developing a good design, and the methods of measurement and analysis are valid and reliable. Medical research is becoming increasingly complex and expensive, and the monitoring these days is very close. A point has already been made about skepticism that is accepted as an integral part of all scientific activity. Make sure that the results stand up to third-party reviews. The key word is the credibility. The results can be positive or negative but they must be reliable and valid.

Errors in reporting research: Since the most critical issues in a research are credibility and integrity, we take this opportunity to describe three types of error that grip medical research across the world. The first is the honest error. This can occur despite best intentions. Most of such errors arise due to limitation of knowledge about a particular phenomenon. This limitation can reflect in the design of study that fails to address an unforeseen bias, or can be due to the acknowledged reliability and validity of tools that were later found inadequate. Almost nothing can be done to avoid such errors except to take appropriate care in future research. The second is the negligent error on aspects that are known to affect the results but are not properly accounted. These can be intentional but are mostly unintentional. Sometimes a

particular source of bias is ignored just to come to a positive conclusion. Lilienfeld[16] argued that asbestos industry was behind attempts to suppress information on the carcinogenicity of asbestos that affected millions of workers. On the other hand, unintentional errors are due to carelessness. Negligent errors of either type are not excusable, although they sometimes fail to attract attention as it happened for many years for carcinogenicity of asbestos. At the bottom is the third type of errors that can be branded as misconduct. This comprises deliberate acts of omission and commission to engineer the findings, and includes plagiarism, which means stealing the results of the others. Reporting inflated sample size, stating a methodology that was not actually used, stating results that were not actually obtained, *etc.*, come under this category. When a misconduct of this nature is detected, some sort of punishment is accorded. The journals blacklist the author, the university forfeits the thesis, and the industry fires the staff, *etc.* Misconduct affects the reputation not only of the person concerned but also of the institution and the community around him.

Fruits of medical research: On bright side are the fruits of medical research that is conducted with conscience and dedication. Sometimes the results can be so strong that they improve the well being of a large segment of a population. Although a research that improves the quality of life of even one patient is worth the efforts but that can be very expensive to the society. Thus efforts are concentrated more on aspects that benefit a large number of persons. Medical research, on the whole, has been very illuminating and has brought abundant pleasure and benefit to the individuals and the society. Considering major emphasis these days on methodological aspects, it is expected that the future research would be more efficient, and the benefits would be available to a larger segment of population at lower cost.

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