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The Basics of Medical Research

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Basic Methods of Medical Research, Fourth Edition
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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 generalisable knowledge. Research is a step in relentless search for truth – it is an organized and systematic way of finding better answers to questions. 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 endeavours. 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 systems in human body work, why we get sick, and how to get back to health and stay fit. It is a systematic process to better determine etiology, patho-physiology, diagnosis, therapy and prognosis. Research is the very foundation of improved medical care. It can also provide evidence for policies and decisions on health development.

Sometimes an established regimen is used in a new setting or on a new kind of subjects to test its applicability to the new environment. This kind of confirmatory work is not hardcore research but is accepted for postgraduate thesis because the objective is training. Large number of medical theses is based on such research.

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 illustrated by the reports questioning established modalities. Tamoxifen, a selective estrogen modifying agent and a popular breast cancer therapy for women, was found to carry an increased risk of endometrial cancer. Menopausal women who took estrogen for long time were also found to be at higher risk of getting ovarian cancer. Arthroscopic surgery for osteoarthritis of knee was found an unhelpful procedure. These are not isolated examples. There are many instances when established medical practices were overturned. Some recent advances have indeed been bivalent—potentially useful as well as potentially harmful.

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 infallible. There are no lemmas and no theorems. It must depend on evidence provided by observations and experience. Medicine is largely an inductive science and has very little space, if any, for deductive methods. If a treatment regimen has worked in

Mr. Somebody and nine others of his clan, there is a high likelihood that it would work in the eleventh also of that type. The past experience and present evidence provide an insight in to the future. Such **empiricism** (Box 1) is the backbone of medical science. In dealing with a new case, or an old case with a new set of conditions, past knowledge and experience is applied, and it is hoped that they would work in the new setup also. Very often they do but sometimes they do not. There is no assurance. Miscues cited earlier are examples of such errors.

Box 1: What is empiricism?

Empiricism is a system based on observations and experience. These two together form the evidence. Evidence could arise from experiments, trials, natural occurrences, experiences, records, etc. It refers to the actual facts as currently present or occurred in the past. Empiricism emphasizes the tentative and probabilistic nature of knowledge. In contrast, mathematics and some other physical sciences are based on theories and theorems. They are deductive and not empirical. Deductive science holds that mind can directly perceive truths without going through the process of sensual experience. Empiricism is based on induction from sensual learning.

Empiricism has no conflict with rationalism. The observations must stand upto 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 that stands to the reason and inspires confidence.

POSTGRADUATE THESIS

Almost all universities in India awarding Medicinae Doctor (MD) and Master of Surgery (MS) degrees require students to devote at least one full year in conducting a small-scale research and collating and presenting results as a thesis. See also Box 2. The primary purpose is *training* of the students in research methodology.

There are pros and cons of this provision. Students get training and prepare for research career. It helps in fine-tuning the thought process and inculcates the ability to critically evaluate the evidence including review of literature. If the students go for teaching they are better prepared to supervisor MD/MS students. In Supervisor, they have a mentor who can provide effective recommendations for a job. Institution gets credit for research and sometimes the mankind is benefited by discovery of improved procedure.

On the down side is one extra year needed to complete the education, and sometimes being treated as assistant to the supervisor. Sometime the supervisor is not well-versed and adds to the confusion instead of clarity. He or she may lack time and the institution may not have adequate infra-structure. Some students tend to learn how to fudge the data, and copy-paste previous texts or results.

CHALLENGES OF MEDICAL RESEARCH

Any research on diagnostic, prophylactic, and therapeutic modalities or on risk assessment is empirical. Experience on one or two patients can help in special cases but generally investigation of a large group of subjects is needed to come to a definitive conclusion. Study of groups brings in the epidemiological perspective. In many researches this perspective is prominent although sometimes not realized by the researcher. On the other hard, some researches are sharply focused on clinical aspects.

All scientific results are susceptible to error but uncertainty is an integral part of medical framework. The realisation 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. 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. 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 others' experience, and to discern signals from noise, waves from turbulence, trends from chaos. It is due to this learning that death rates have steeply declined in the past 50 years and life expectancy is showing a relentless rise in almost all nations around the world. Burden of disease is steadily but surely declining in most countries.

Box 2: Levels of medical research

FIRST LEVEL OF RESEARCH – MASTER'S THESIS

- Generally a small-scale investigation that puts forward a hypo*thesis* to be tested by further study
- Objective is to provide training to the student in research methodology—thus process is more important than outcome
- Seldom provides results that can be immediately implemented in health care
- Duration is generally 12-18 months and it is part fulfillment of the degree
- The guide is called Supervisor whose intellectual resources are extensively utilised
- Almost invariably based on institutional resources without support of any funding agency
- There is no public defense of the findings
- Volume is nearly 100 pages

SECOND LEVEL OF RESEARCH – DOCTORAL DISSERTATION

- A detailed discourse or treatise on a particular topic that provides a new result or new perspective—must be capable of publication in a reputed journal
- It must provide evidence of critical thinking of the candidate on the topic of research
- Many times provides results that can be immediately implemented in health care
- Duration is mostly three to four years and thesis itself is enough for the degree
- The guide is generally called Advisor and the work is mostly based on the candidate's own intellectual contribution.
- Mostly based on institutional resources but can be part of a large-scale research funded by some agency.
- Required to be publicly defended.
- Volume is generally 200 pages or more.

THIRD LEVEL OF RESEARCH – INSTITUTIONAL STUDY

- Generally conducted in only one location.

- A large-scale investigation that culminates into a full-fledged project report and mostly published in a reputed journal in concise form
- Expected to provide a path-breaking result that can be immediately implemented in health care
- Mostly based on specially marked funds

FOURTH LEVEL OF RESEARCH – MULTICENTRIC STUDY

- Conducted in several locations with common protocol to check replicability in a variety of settings
- Necessarily a large-scale investigation for which a full-fledged report is prepared and almost invariably finds a place in a reputed journal in a concise form
- Attracts attention because of its size but there is no evidence yet that this level of research produces path-breaking results more often than institutional level research
- Invariably based on specially marked funds.

Management of uncertainty requires a science that understands randomness, instability and variation. Biostatistics is the subject that deals specifically with these aspects. This is supportive science all through this book. Instead of relating it to conventional statistical methods such as test of hypothesis and regression, it is presented as aid to solve problems of medical research. In doing so, we deliberately avoid mathematical intricacies. This text should be light and enjoyable for the medical fraternity so that medical research is perceived as a delightful experience, and not as a burden.

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 pathway that foster clarity and avoids the problem of multiplicity. These steps are much more elaborate for research in medicine than for other disciplines because of enormous uncertainties inherent in medical field and the implication is human health. Jenicek (2006) has provided a layout of modern argument in medical research. This involves processes that go on from what is in your mind to searching external evidence (e.g., literature) for or against, making a qualified claim, then conducting the study, leading to the results with limitations such as probabilities and applicability. Because of empirical base, investigations are sin-qua-non for a primary medical research. An outline of the preinvestigation, investigation and postinvestigation steps is given next. The details are in the followings chapters.

PREINVESTIGATION STEPS

However odd it may sound, the preparation and plan for the investigation would be more critical than possibly the actual investigation. Preinvestigation steps are as follows.

IDENTIFY THE PROBLEM

The first step in research is to identify a problem area to work on. One paradigm is that, notwithstanding knowledge explosion in the past century, the unknown segment of the universe is much larger than the known segment. An alert researcher will find a large number of issues floating around. For selection, match the research area to (i) relevance

and applicability for improving health in one way or the other, (ii) interest and expertise of you and your collaborators, and (iii) the feasibility of completing the work with available resources, time, subjects, tools, etc. These three aspects should considerably narrow down the problem area. If the situation permits, select a topic that is in debate or meets a current demand.

Choose a topic that is in need of development, verification or refutation. It must be well-defined and focused. It should fit your caliber and should be ethically sound. For postgraduate thesis, it is advisable to consider several topics and choose the one that looks promising. Don't feel shy if it does not work out.

. Convert the problem to specific questions that require answer. The question must pass the "so what?" test. Even when this is done with apparently sufficient specificity, the course of the investigation may reveal that those questions were not so specific after all. Further steps as given below may help to attain focus and clarity.

A good research question is backed up by theoretical considerations. If you are investigating the role of a particular type of diet in esophagus cancer, it is helpful to consider why that type of diet can alter the risk of this cancer. Biological plausibility gives a definite edge. Nevertheless, associations may exits for which sufficient causative mechanism is not understood – perhaps it emerges later on. Research on such poorly understood pulsations too are perfectly valid problems

COLLECT AND EVALUATE EXISTING INFORMATION

The next step is to collect as much information on the identified problem as possible and evaluate it critically. One major source is the literature. But do not underestimate the potency of other sources. Secondary data might be available in various organisations that can enhance the focus of the problem. Thesis guide and the subject-experts can provide useful insight that they imbibe through years of experience of working in that area. Talk to them without inhibition. Do not think that your limited knowledge will be a hindrance. In fact this limitation is propelling you to explore this problem. Experts might lead to the hitherto unexplored literature and, more importantly, to the work other agencies or institutions are doing in that area. Make sure that a reasonable answer to the proposed question is not already available. The objective of all this exercise should be to identify the specific information gaps, and to examine how the problem fits into the medical jigsaw puzzle. Assess if the problem is really worth pursuing. If none or very little baseline information is available, consider carrying out an exploratory study as a first step.

FORMULATE RESEARCH OBJECTIVES AND HYPOTHESES

Critical evaluation of the literature and other data on the problem will greatly assist in focusing thoughts regarding what exactly to investigate. Translate these to 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. Clearly identify the 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. The objectives should be consistent with meaningful decisions taken in actual practice. They should not focus on trivial issues that can be addressed without research.

Consider whether you expect to come up with entirely novel findings or just confirm previous work that left some doubt, or would address the present conflict (Brand 2003).

From objectives emanate hypotheses. A hypothesis is a carefully worded statement regarding the anticipated status of a phenomenon. For example, one may hypothesise 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. It should be restricted to the research under plan. Further details about objectives and hypotheses are described in the next section.

IDENTIFY THE STUDY SUBJECTS

The definition of the subject of study and the target population should be clearly spelt out. Iodine deficiency can be diagnosed either on the basis of the palpable or visible goiter, or now on the basis of urine iodine concentration <100 µg/l. Borderline hypertension may be defined to start from 135/85 mmHg or from 140/90 mmHg. Choose a definition that is consistent with the objectives and justify it. 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. If there are two or more groups, define them.

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. The strategy would be in terms of collection of data in a manner that inspires confidence. This requires identifying all sources of uncertainty, and developing a design that can keep them under control (Chapter 3, 4 and 5), In effect, this means (i) sample design for survey; (ii) prospective, retrospective or cross-sectional strategy for observational study; (iii) deciding on the specifics of intervention if any; (iv) determining the variables on which the data would be collected: the variables that are valid to provide the correct answer; (v) the mode to obtain valid data on those variables – feasible yet robust methods that can stand scientific scrutiny; (vi) tools for easy recording of information; (vii) the strategy to handle any ethical problem that might arise during the course of that investigation; (viii) the number of cases or subjects that should be included in this kind of investigation; (ix) the method of selection of the subjects of the study; (x) the method of randomization, blinding, matching, etc., and (xi) the method of statistical analysis of data. Most medical professionals do need expert advice from a biostatistician to develop an appropriate design. If needed, catch him at early phase of planning and seek his collaboration for all phases of the study. Do not aim at methodological overkill. Marginally improved results at a substantially higher cost may not be worth.

WRITE THE PROTOCOL

All the hard work put into the preceding steps culminates into the draft of a research protocol. It incorporates all the information regarding the plan of research in a concise manner. Developing a protocol is just about the most important step in conducting a research. For this reason, we are devoting a full section in this chapter on this aspect alone. When the thoughts are put together on a paper, they crystalise and concretise. Since protocol is a written commitment, further deliberations may be needed for

example to make the objectives and hypotheses more specific and to justify the strategy to be adopted. Protocol contains much more information. For example, it states the work plan and identifies the resources required for the project, including the time-line. The latter comprises the time point when each step is to be initiated and how much time this will take to complete. Work on two or more steps of research 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. For some this may require procuring kits with the help of external facilities. Arrangements may also have to be made to procure drugs, including life saving drugs, to meet any contingency. Work out the modality for getting help from outside agencies when needed 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 their major component is the thought process. After these steps comes 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 you have been in developing the tools of the investigation, there is always a need to pretest them for their performance in actual conditions on the same kind of subjects as the main study. Experience suggests that almost invariably some deficiency is detected, and the tools or their implementation are found to require some modification. Thus do not shy away from this exercise. Similarly, a pilot study, which is a small forerunner of the actual investigation, also 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 setup, the data are obtained by inspecting the records, by conducting interview or physical examination or laboratory/ imaging investigations, or by a combination of these data-eliciting methods. Continuous vigil is 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 methods earlier decided should be strictly followed. If the past history is to be obtained by interview, do not

replace it by records available with the patients. 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 planned subjects. Some subjects will invariably drop out during the course of the investigation. Anticipate such nonresponse and keep it at the minimal level to avoid bias in the results. Make all efforts to extract at least the basic information that can help in adjusting for any bias.

Then there are ethical issues that need to be constantly monitored, particularly if the research involves an intervention such as a therapeutic maneuvre. 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.

SCRUTINISE THE DATA

Despite all the care exercised at the time of taking history of patients, at the time of physical examination, and at the time of laboratory/imaging investigation, errors do occur. Most of these can be detected by scrutinising the data for internal consistency and external validity. For example, if a patient with hypertension has low cholesterol then sufficient reasons should be available within the record. A woman of age 23 years can not possibly have six children. Such errors look odd but they are practical occurrences particularly in a large-scale research. Some times called data cleaning, this step of scrutiny is considered essential for quality research.

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.

ANALYSE 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 peritonitis, 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 in data analysis is exploring the data for their pattern. Not many researchers appreciate the importance of this preliminary step. For example, pattern in geographical plot may reveal hidden mysteries in the medical phenomena you are studying. Outliers may reveal new relationships. Examine whether some selected variables are really following a Gaussian pattern or not. That will decide whether parametric tests of statistical significance should be used or nonparametric tests. For exploring relationship among various measurements, scatter plots can be immensely useful. These will indicate where and what type of relationship should be explored.

Third step is to use the data for assessing the parameters of health and disease that were outlined in the protocol. Various indicators and indices of health and disease such as waist-hip ratio and scores may have to be calculated to assess risk factors and outcomes of interest.

Fourth step is to summarise the data. This is done in terms of mean, standard deviation, proportion, rate, and more importantly in medicine in term of odds ratio and relative risk. Such summaries tend to delineate the uncertainty levels in the results and help in grasping the essential features of data. This step sets the tone for statistical analysis.

The next step is grinding the data through the process of statistical analysis. This involves performing statistical tests to assess the significance of differences, obtaining the structure of relationships such as regression and their significance, assessing trends and agreement, etc.

Wise researchers devote sufficient time to the examination of the data and to their analysis. Collecting quality data is important in itself but exploiting it fully is even more important. New results are sometimes missed despite availability of good data because they are not properly exploited.

INTERPRET THE RESULTS

Whereas statistical analysis is mostly computer-based, interpretation of the results requires critical thinking. A series of steps can be suggested. (i) Examine the results in the context of the questions that prompted the research. (ii) Verify that various results are consistent with one-another and a proper explanation is available for the inconsistent ones. (iii) Check that all the potential biases have been either ruled out by design, or the results are properly adjusted for the biases. (iv) Assess the reliability of the results. They must be reproducible. (v) Confirm that a convincing biological explanation is available. (vi) Show by sensitivity analysis and uncertainty analysis that the results are robust to the systematic variations. (vii) Ensure that the final conclusions are indeed a further development and not repeat of previous knowledge. In short, not only that you should be convinced about the correctness of the conclusions but also there should be enough reasons to convince others. Results should not be speculative, instead should be based on evidence as revealed by the data and other facts. If the results are too good to believe, reexamine them.

WRITE AND DISSEMINATE THE REPORT

Report is a generic term that includes a thesis, a dissertation, an article, a paper, and a project report. It should contain all the details in a concise manner. Then disseminate it to the intended audience. Dissemination could be the most fruitful step in a research endeavour. The world is informed about the new conclusions, and a feedback is obtained regarding quality of the conclusions. A clear idea about the users of results will help to decide how to disseminate findings to the stakeholders.

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 from opinions and comments. The report should be adequately illustrated by diagrams to enhance clarity. Numerical results can be summarized in the form of tables. Describe all the limitations 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 is geared to meet the expectation 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 different focus to fit their requirement.

MONITOR THE REACTIONS

Research is a continuous process. You might want to improve upon by learning from the reactions of the users of the research. For this it is necessary that all such reactions be systematically monitored. It is not uncommon in research journals to publish comments and the author's rejoinder. These help to crystalise thoughts, and to improve in a subsequent endeavour. Also monitor whether or not the results are being utilised.

PLEASURES AND FRUSTRATIONS OF MEDICAL RESEARCH

Scientific enquiry is among the most challenging enterprises. Any research, more so medical research, is an occupation riddled with uncertainties. If successful in bringing out a path-breaking result, it may be idolized. If it 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 you can do is to take full care of possible biases by developing a good design, and use valid and reliable methods of measurement and analysis. Medical research is becoming increasingly complex and expensive, and the monitoring these days is very close. Since skepticism is accepted as an integral part of all scientific activity, make sure that the results stand upto third-party reviews. The key concern is credibility. The results can be positive or negative but they must be reliable and valid.

ERRORS IN REPORTING RESEARCH

Most critical issues in a research are credibility and integrity. Three types of error 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 (1991) argued that asbestos industry in the U.S. 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 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. No one should ever indulge in such practices. 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 when 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 cheers 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. You could be an important contributor to these efforts by following the simple rules elaborated in this text.

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For details, see Basic Methods of Medical Research, Fourth Edition, 2012

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