Review Article

Research in Clinical Sciences

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ABSTRACT

The scope and spectrum of medical research, including that in clinical sciences has tremendously expanded. It now extends from simple clinical observations to gathering of epidemiological data to the study of molecular mechanisms of diseases to evaluation of effects of therapeutic interventions. It is more meaningful to engage in multi-disciplinary and collaborative arrangements for the better achievements in health research. Translational approach involves the direct application of results of laboratory experiments to clinical use for benefit of patients. Besides clinical and experimental research, it is equally important to strengthen operational research for efficient implementation of health programmes and policies in the hospitals as well as in the community.

There are several difficulties and constraints related to ethical principles, patient's safety, confidentiality and costs. It is critically important to adhere to ethical principles and guidelines to maintain the moral and social perspectives. It is equally important to follow the scientific research methodology for the maximum gains from research experiments and projects. Interpretation of results of clinical experiments are hardly ever unequivocal, hence, there is a need for repetitive studies, systematic reviews and meta-analyses to reach definitive conclusions.

It is important for busy physicians to adopt a scientific temper of logic and engage themselves in searching for answers to different research questions. It is always gainful to spare some time and resources for research out of a busy clinical practice. It is also worthwhile to go through a formal training programme in research methodology to improve capacity and competence to conduct meaningful research. **[Indian J Chest Dis Allied Sci 2011;53:175-182]**

Key words: Clinical science, Therapeutic, Translational research, Healthcare, Tuberculosis, Research methodology.

INTRODUCTION

Research is a continuous and ongoing process of searching for answers to unanswered questions that are already there, or to develop further questions from the answers in existence. Although search as an essential function of mind has existed since the evolution of life, it is only in the modern era that research has emerged in more precise terms — the search for truth and a tool of development. It is no more a phenomenon of chance but a planned activity with definite goals in mind.[1] It has been defined as the gathering of data, information and facts for the advancement of knowledge; a process of steps to collect and analyse information; or an inquiry "aimed at discovery and interpretation of facts, revision of accepted laws in the light of new facts, or practical application of such new or revised theories or laws".[2,3]

Research in the last Century has come to stay as an essential component of progress and development. The research in physical and other basic sciences has a long tradition. On the other hand, the history of research in medical sciences, especially as an organised activity is relatively recent. The modern face of medical research was completely changed following addition of an experimental approach in the eighteenth century.[4] Robert Koch's introduction of the postulates stressed the importance of the sound principles of reason to prove (or disprove) an association between a cause and an infective disease.[5] The use of new methods of microbial detection have made these postulates as limited and less relevant; new postulates based on nucleic acid findings are now suggested.[6]

The medical research today is one of the fastest growing and attractive but difficult field of science. Research into clinical sciences in particular remains a subject of concern, controversy and debate in the public domain. It deals with the safety and efficacy of drugs, devices, diagnostic methods, treatment regimens and other aspects of health, disease and death in humans. There is an immediate and direct impact of results of clinical research.

WHY DO RESEARCH?

Research in the past was a passion with an element of

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obsession for an inquisitive mind. There are numerous examples in history with investigators going to great risks to see the success of an experiment. Anatomists during the medieval era were known to dig out buried corpses from the graves at nights for human anatomy. Andreas Vesalius stole the body of an executed criminal and took it to his house for dissection.[7] Forssmann[8] who introduced the first prototype for cardiac catheterisation in 1929, first inserted a ureteral catheter into his own right heart though a vein in his arm and walked up stairs to the x-ray department for confirmation. He had ignored the advice of his department superior and tied his assistant to an operating table to avoid her interference; he was later awarded the Nobel Prize in 1956. Edward Jenner[9] had tested his hypothesis on immunity from smallpox by taking pus from the blisters of milkmaids suffering from cow pox and inoculating the 8-year-old son of his gardener (James Phipps).

There are numerous other examples of self-experimentation in medicine.[10,11] In respiratory medicine, Roger Altounyan[12] who discovered sodium cromoglycate for asthma had experimented on himself with "Khella" - a traditional Middle Eastern remedy. Such experiments cannot be imagined in today's world with current rigid safety standards, ethical and legal regulations in force. Research has now almost become a profession, though the passion still remains the strength for all clinical investigators.

The primary goal of research in clinical sciences reflects an amalgamation of multiple objectives (Table 1), any of which may dominate over the others for a particular investigator. Research being an organised activity, several individuals may have different roles in the same plan or project. Therefore, objectives of different participants are also guided by the roles they play in a single activity.

Table 1. Goals of research in medical science

Personal gratification: satisfaction of a curiosity
Academic challenge – new knowledge
Professional achievements – career development
Improved disease – management and health-care delivery
Financial interests and gains

Research for students of medicine is essentially of curricular importance for purposes of writing theses, and dissertations for their postgraduation or doctorate degrees. It is a mandatory requirement that they need to fulfil for completion of their courses. On the other hand, qualified doctors in practice consider research as an ungainful investment of time and resources. There is no real motive for them to indulge in any meaningful research work. Unfortunately in India, research as a subject of interest remains an issue of only marginal involvement even for teachers in medical colleges and other large hospitals, who are expected to guide students for their research work. Factually, it is considered as a wasteful expenditure of time and money by the teachers, as well as by the hospital and college managements. Majority of the theses are only a collection and presentation of data with little research component in the true sense of the word.

The onus of medical research, therefore, has come to rest on the shoulders of only a few people working in a few institutions. This is a rather worrisome and dangerous sign for the overall progress and development of medical sciences in the country. India cannot afford to be just a beneficiary of research carried out in other countries without making its own contributions. Dependence and reliance on results of external research and their extrapolation to Indian scenario is fraught with long-term risks.

DIFFICULTIES OF CLINICAL RESEARCH

Unlike in physical sciences, research in clinical sciences directly concerns the humans that imposes several restrictions and limitations.[13-15] Ethics of conducting an experiment constitute a most basic issue (Table 2). The principal questions of the "need", i.e. why an experiment should be done and "whether the experiment is required for the benefit of the individual on whom the experiment (an investigation) is being performed" require to be redressed. In any clinical study or trial, the potential benefits of research to the society can not override the benefits to and the safety of the individual. Some of the other ethical issues besides the "need" and the "safety", deal with the confidentiality, consent, costs and possible risks of the unintended-outcomes.

Table 2. Ethical issues in medical research

Infringement of privacy and confidentiality
Conflicts with personal, religious, societal, cultural beliefs, values and taboos
Medical risks and safety issues — physical and psychological
Issues of costs and time
Who is to bear the costs?
Compensation *versus* inducement
Risks of knowledge of disease
Obligations of treatment of diseases
Withholding of information to patients/families/others
Potential future applications of research
Research on stored materials (especially, genetic studies)
Ethics of reporting, publication and scientific crediting

Clinical research involves the whole organism — the human body.[16,17] It is a highly complex system whose parts cannot be isolated. Therefore, clinical research is integrative in approach.[18,19] It is difficult to conduct experiments and prove hypotheses. The

results are limited in their interpretations. Results of similar experiments may be highly variable and sometimes contradictory when conducted in different laboratories. It is, therefore, generally necessary to have multiple and repetitive experiments. Clinical research is also affected by a large number of intended and unintended variables. The experiments are influenced by technical, environmental and other background variations. There are also variations based on genetic, ethnic and other biological factors.

TYPES OF MEDICAL RESEARCH

Clinical research can be broadly classified as follows (Table 3).[20,21]

Table 3. Types and purposes of clinical research

Types	Purposes*
Basic research	Innovative
Patient oriented research	Developmental
Clinical trials	Curricular
Epidemiological research	Operational – implemental
Clinical observations	Promotional
Operational research	
Translational research	

*Each type of research can involve multiple purposes listed in the table.

Basic Research

It implies to experiments and estimations in the laboratories on samples of secretions, excretions, tissue specimens and other materials obtained from patients and/or control subjects with the objective of understanding the underlying mechanism of disease causation. Such types of experiments are undertaken in laboratories of pre- and para-clinical sciences (Biochemistry, Microbiology, Pathology and allied areas). The scope has now further expanded to include experiments on materials not only obtained from the patients and volunteers, but also *in vitro* on materials developed in the laboratory, such as cell-lines, modified/engineered genes and clones (etc). Basic research while being seemingly safe from an individual's point of view, involves issues of confidentiality, conflict of interest, costs and commercial exploitation. Sometimes, even larger and potential issues related to morality and social impacts arise and long-term risks of genetic and cloning experiments may pose serious ethical questions.

Patient-oriented Research

It involves direct observations and investigations on patients including imaging and scanning procedures, endoscopic examinations; physiological, biochemical and haemodynamic measurements; biopsy and other tissue sampling techniques. Most of these investigations are generally invasive or semi-invasive in nature and carry potential risks to patients. Such investigations are often otherwise required for routine diagnostic work-up of patients in whom the experiments are to be undertaken. Specific justification and approvals are required in case these tests are being done on healthy subjects or on patients without indications.

Clinical Trials[22-24]

Trials primarily refer to the study of drugs for their effects on diseases in patients. These also include study of effects of other interventions (e.g., surgical and semi-surgical techniques, counselling, dietary modifications and other forms of therapies) used for the treatment of diseases. The "trial" involves the comparison of results in groups of patients (with and without the treatment under study). While essential on one hand, several pharmaceutical trials in recent times have generated major controversies regarding the ethical concerns with reference to commercial exploitation, safety of drugs and marketing policies. The "trials" may also include research on tests and techniques for diagnosis and assessment of diseases.

Epidemiological Research[25-29]

Epidemiology refers to the study of occurrence of disease in the community. It includes the study of prevalence and incidence of a disease, risk factor association, sub-group distribution and characterisation. It also includes the methods of community-diagnosis and interventions for treatment, management and prevention. The spectrum of epidemiological research extends from simple observational or "case-control studies" at one end to the longitudinal and experimental or interventional studies at the other end (Table 4).[27-29] Mixed types of "nested-case control" or "nested cohort studies" can also be undertaken. A nested case-control study involves a hybrid design in which the data are collected initially as a typical cohort but thereafter a group with the disease and a group of controls for analysis of risk factors are selected.

The scope of epidemiological research has expanded from interviews and questionnaires to include molecular and genetic methods to study the different aspects of a disease in the community. These are frequently employed to locate the source of origin and spread of an infection as well as to study the ethnic and geographical variations.

Table 4. Spectrum and types of epidemiological research

Observational Studies
Case-control studies: Backward design. Retrospective collection of information
Cohort studies: Forward, a longitudinal design. Prospective follow-up study of cohorts (groups of subjects with and without risk factor (for development of disease)
Nested or hybrid design
Initial cohort formation followed by grouping of subjects with disease and without disease
Retrospective cohort – historical prospective design
Interventional Studies
Oservations before and after and experiment or intervention (at the level of the community)
Molecular and Genetic Epidemiology

Clinical Observations

One of the most elementary type of clinical research is undertaken with the help of routine clinical observations made during the management of patients. Yet many such observations have marked the beginning of a whole new spectrum of a disease or a speciality. The reporting of '*pneumocystis carinii*' infection and of cytomegalovirus infection in homosexual men and of Kaposi's sarcoma laid the foundation for the discovey of "human immunodeficiency virus" disease.[30,31] Similarly, the observation of multiple purplish patches over the skin of hands and feet in 1877 and histological findings of epithelioid and giant cells on skin biopsy of similar lesions described as "multiple benign sarkoids of the skin" in 1899, subsequently led to the recognition of sarcoidosis.[32,33]

There are two other categories of collaborative medical research which are now defined as follows:

Operational Research[34-36]

It is concerned with the study of an 'operation', a programme or of a strategy involving the conduct and coordination of activities within a complex system. Operational research can help to decide on the 'alternate courses of actions' for solutions to problems and improve the performance of the system. Essentially, it deals with the methods and steps of implementation of a plan or a project. It can be more explicitly defined as "research into strategies, interventions, tools or knowledge that can enhance the quality, coverage, effectiveness and performance of health systems and programmes so that better care is delivered to patients and communities". The simple examples include operationalisation of National Health Programmes such as investigations into the different components of the Directly Observed Treatment, Short-course (DOTS) for tuberculosis (TB) or of DOTS-Plus for drug resistant TB meant to improve the efficiency of these programmes.[37] On the other hand, the safety or formulation of infection-control or antibiotic policy in an intensive care unit or in a hospital are equally good examples of operational research. Similarly, operational research may include investigations into a wide spectrum of tools for telemedicine as well as domiciliary care for diseases.[38,39]

Translational Research[40-42]

Translational research involves the translation (or application) of results of basic research into active clinical practice. It involves a coordinated "bench-to-bedside" activity from the laboratory to the management of diseases. It is a multi-disciplinary activity with different investigators/groups engaged in different aspects of a single subject. Translational research is a kind of 'participative science' and 'participative action research' in different domains of sciences, including in clinical medicine.

Translational research includes two basic components: (1) basic (fundamental or pure) research involves changes in the principles leading to 'breakthroughs' or 'paradigm-shifts' that happen over a long period; (2) applied research on the other hand involves the clinical practice leading to direct changes within a short period of time. Translational research in TB, for example, extends from the study of mycobacterial constituents and immunological responses, development of tests of diagnoses, therapeutic agents and vaccines by groups of biochemists, microbiologists and pharmacologists, to the clinical application of results and trials by the clinicians, all working together in tandem.

METHODOLOGY OF CLINICAL RESEARCH[43-45]

The methodology of research involves a step-wise approach in an organised manner (Table 5). It is always useful to start with a 'research question' than with a method, a technique or a database. The 'question' gives a clear direction to the investigator to proceed. Formulation of 'aims and objectives' should be done around the question. It is always advisable to limit the scope of the research-objectives commensurate with the time and other resources available for research. One must avoid ambitious plans, at least in the beginning.

The next steps consist of defining the variables, and the study-population; selecting the study-sample; identifying potential errors, biases and confounders in the study, and finalising the study-design. The prior identification of the important components of a research plan avoids pitfalls and ensures good collection and recording of data for subsequent statistical analyses and interpretation of results.

Table 5. Steps involved in medical research

Development of an idea — defining objectives and priorities
Defining the variables
Selection of the study population and sample technique
Identification of potential errors, biases and confounders
Defining the hypothesis
Selecting a study design
Preparation of the study protocol
Data collection and management
Pilot assessment
Analyses and interpretation
Report writing/Presentation/Publication and implementation

"Data does not collect itself". It is important to start experiments and collect data from the very start of the research project. Efficient management of data collection process helps to monitor the progress and trace the missing data. It is also useful to do a 'Pilot study' in the first few weeks/months and analyse the preliminary results. The pilot study will help to assess the practicality of the research protocol and estimate the rate of recruitment of subjects in the study.

Development of an Idea, Aims and Objectives[44-46]

Ideas and stimuli for research come from questioning the existing answers or by trying to find the gaps in explanations. It is rare that an idea is original or innovative. It is equally important to continue with new applications of already available results or to look into the 'next' question. One must critically think over the idea and discuss with colleagues for its viability and practicality. It is crucial to look into the time-factor required to study a particular research question. It is also important to adequately review the literature to see the previous work on the issue, including that in the related and allied fields. One must also decide on the methods of statistical analyses required for the study and discussion with a statistician is often worthwhile.

Once the idea on the study-question is finalised, one should define and write the aim(s) and clearly pointed objective(s) (Figure 1). One or more experiments may be required for the study of each objective. Both the experiments and the objectives should also be prioritised appropriately, based on their relative importance to decide the sequence of performance.

Study Protocol[47-49]

Study-protocol is the written document on step-wise

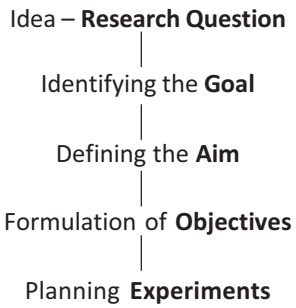

Figure 1. Step-wise downward approach from development of an idea to planning of experiments.

details of the research project. It should clearly state the objectives, the background information, the material (or patients) for the study, and the methods employed for the study. The protocol should also identify the source(s) of recruitment of patients, inclusion and exclusion criteria, the place and the method of recruitment, the ethical issues and other difficulties concerning the research "material". The written protocol is not required merely for submission of the plan, but for the investigator's own help to successfully proceed with the study. One is likely to feel lost in the absence of a clearly defined protocol for guidance.

Variables[50,51]

Variables are the factors or parameters to observe and record for each experiment for further analysis and interpretation at the end of the study. Typically, variables are classified as follows:

1. Independent. These are the factors which are not "influenced" by the experiment or other conditions. These are also called as the 'classification', 'presumed', the 'causal' variables or the 'risk-factors' depending upon the type of the study. Essentially speaking, independent variables are the baseline parameters related to the study before the experiment.

2. Dependent. These are the variables after/at the end of the experiment. Their values are dependent on the experiment, therefore also called the 'outcome', 'response' or 'effect' variables.

3. Extraneous. There are the "undesirable" factors that influence the intended results of an experiment. These constitute the background 'noises', 'biases' or 'effect modifiers'. It is always important to identify and possibly control all the potential extraneous variables for "true results" of an experiment.

Confounding Variables[51,52]

A large number of extraneous variables in clinical research are unavoidable. A confounder is defined as a factor that possesses a similar association/ relationship with both the causal (independent) and the outcome (dependent) variable. It, therefore,

modifies the results of an experiment, and is responsible for an erroneous interpretation. As an example, true association of the outcome (C) proved with a risk factor (B) may be erroneously attributed to the risk-factor (A); the risk factor A related to the true risk factor B is actually a confounder which may have been missed in the study (Figure 2).

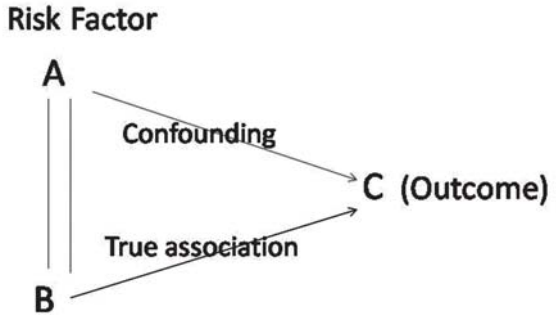

Figure 2. Risk factors A is non-causally related to risk factor B, therefore causing confounding in demonstrating a suspected causal link with the outcome, C.

Errors and Biases[51-53]

Clinical research is often fraught with numerous types of errors and biases that may make the results difficult to interpret. A good researcher is required to eliminate most, if not all of such errors. An "error" is the "distortion in the estimate of an association" between the causal and the outcome variables. Study biases (or errors) may occur anywhere from the stage of sampling and selection to the experimental and measurement stages. For example, the sample may be too small, non-representative and biased; the selection may be biased towards inclusion (or exclusion) of the symptomatic (or the affected) individuals; information that is provided may either be inadequate or exaggerated. Finally, confounding by the extraneous variables is an important bias in the study and may not be altogether visible or avoidable.

Results of a study are influenced by errors depending upon their types. Type I error relates to results that proves an association which in fact is not there. This type of "Yes for No" result is always considered as more serious. On the other hand, the type II error relates to "proving no association which in fact is there" i.e. "No for Yes" results. Type II error indicates the inadequacy or failure of the research experiment without any serious impact on the results.

Study Design

Design of a study depends upon the purpose of the study. It should be planned after formulation of objectives and identification of variables. Several different designs are possible to answer a research question. Different designs are proposed for different objects, with different strengths. There are three main types of designs: (i) descriptive, (ii) experimental, and (iii) observational.

Descriptive studies are used to describe the frequency or magnitude of a disease, distribution of different characteristics and observations on risk factors and other parameters. It is difficult to describe the associations of different variables, although a broader idea can sometimes be made on gross observations. Such descriptions are highly valuable in case of new observations.[30-33]

Experimental studies involve carefully planned designs to prove (or disprove) associations. An experimental design constitutes a powerful method of testing a causal or a presumed hypothesis. Experimental studies are carried out in laboratories on patients' specimens or in animals to study the disease pathogenesis or other hypotheses. In clinical medicine the efficacy and/or toxicity of a drug is best tested in clinical trials.[22-24,54,55] These may include 'double blind' designs in a simple-experiment (trial drug *versus* control), repeated measures or repeated measures with cross-over, experiments. The strength of an experiment increases as one proceeds from a 'simple' to a 'cross-over' design. Obviously, the cross-over design will also have greater operational difficulties of performance in clinical settings, increased costs and complex statistical analyses.

Observational studies are either epidemiological or quasi-experimental, and are especially helpful when experimental studies are not possible to undertake.[25-29] These primarily aim at the study or observation of "naturally occurring" events or changes in different variables.

Sampling[56-58]

It is almost impossible to study the whole population suffering from a disease in any clinical study. One, therefore, selects a sample out of the total eligible population. However, the sample should fairly represent the population for any meaningful interpretation. This goal can be achieved if the sample is 'adequate' in size and is randomly selected so that each member of the population has an equal chance of selection. Both randomisation and the size of the sample should follow the standard statistical methods. The non-random methods of convenience or cluster samples cannot be considered to represent the study-population.

Statistical Considerations[52,59-62]

Statistical analyses provide precise and understandable formats to the data. Statistical tests, appropriated to the objectives, depend upon the study-design, the type of sample and the variables collected in the project. Appropriateness of tests and

interpretation of the statistical results should not be left only to the statisticians. Any clinical research is almost meaningless without an adequate statistical analysis and interpretation. The statistical principles are not only useful at the completion of a study, but even at planning and execution stage. It is of little use to express results in mere 'percentages' even for descriptive studies.

Statistical analysis to determine the significance of differences in percentages are important for the purpose of interpretation. Advances in statistical analyses these days have made it possible to identify subtle differences and relationships. However, it is important to apply and understand the statistical results in different clinical settings. It is generally not possible for clinical research investigators to use the advanced statistical packages themselves. But they must understand the philosophy behind and the need for a particular test for a complete and correct interpretation of their results. The clinical investigators have an equal or more important role in the evaluation of results.

Analysis and Interpretation of Results

A whole lot of clinical data are known to gather dust in the laboratories and in the shelves of investigators for want of analyses. A large number of records and databases collected in different surveys and studies as well as the theses of postgraduate and doctoral students are never published. Stacked in the libraries, these hardly ever see the light of the day. Most often, it is the lack of the final steps, i.e. analysis interpretations and write-up that remain to be done.

It is important to devote an adequate time to the organisation of results and their analysis. This time period should be structured within the project timeline. Statistical analyses become easy if the data are regularly entered and managed with computer software. Finally, a clinical study is always limited in its interpretation and scope of application. As stated earlier, the results of a study often need substantiation by results from a large number of similar studies conducted elsewhere and under different circumstances.

Writing of the research report and papers for publication in journals are equally important both to earn credit for oneself and benefit others from the findings of research.

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