

Types of studies and research design

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ABSTRACT

Medical research has evolved, from individual expert described opinions and techniques, to scientifically designed methodology-based studies. Evidence-based medicine (EBM) was established to re-evaluate medical facts and remove various myths in clinical practice. Research methodology is now protocol based with predefined steps. Studies were classified based on the method of collection and evaluation of data. Clinical study methodology now needs to comply to strict ethical, moral, truth, and transparency standards, ensuring that no conflict of interest is involved. A medical research pyramid has been designed to grade the quality of evidence and help physicians determine the value of the research. Randomised controlled trials (RCTs) have become gold standards for quality research. EBM now scales systemic reviews and meta-analyses at a level higher than RCTs to overcome deficiencies in the randomised trials due to errors in methodology and analyses.

Key words: Clinical trials, evidence-based medicine, medical research, meta-analysis

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INTRODUCTION

Expert opinion, experience, and authoritarian judgement were the norm in clinical medical practice. At scientific meetings, one often heard senior professionals emphatically expressing 'In my experience,..... what I have said is correct!' In 1981, articles published by Sackett *et al.* introduced 'critical appraisal' as they felt a need to teach methods of understanding scientific literature and its application at the bedside.^[1] To improve clinical outcomes, clinical expertise must be complemented by the best external evidence.^[2] Conversely, without clinical expertise, good external evidence may be used inappropriately [Figure 1]. Practice gets outdated, if not updated with current evidence, depriving the clientele of the best available therapy.

EVIDENCE-BASED MEDICINE

In 1971, in his book 'Effectiveness and Efficiency', Archibald Cochrane highlighted the lack of reliable evidence behind many accepted health-care interventions.^[3] This triggered re-evaluation of many established 'supposed' scientific facts and awakened physicians to the need for evidence in medicine. Evidence-based medicine (EBM) thus evolved, which was defined as 'the conscientious, explicit and

judicious use of the current best evidence in making decisions about the care of individual patients.'^[2]

The goal of EBM was scientific endowment to achieve consistency, efficiency, effectiveness, quality, safety, reduction in dilemma and limitation of idiosyncrasies in clinical practice.^[4] EBM required the physician to diligently assess the therapy, make clinical adjustments using the best available external evidence, ensure awareness of current research and discover clinical pathways to ensure best patient outcomes.^[5]

With widespread internet use, phenomenally large number of publications, training and media resources are available but determining the quality of this literature is difficult for a busy physician. Abstracts are available freely on the internet, but full-text articles require a subscription. To complicate issues, contradictory studies are published making

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decision-making difficult.^[6] Publication bias, especially against negative studies, makes matters worse.

In 1993, the Cochrane Collaboration was founded by Ian Chalmers and others to create and disseminate up-to-date review of randomised controlled trials (RCTs) to help health-care professionals make informed decisions.^[7] In 1995, the American College of Physicians and the British Medical Journal Publishing Group collaborated to publish the journal 'Evidence-based medicine', leading to the evolution of EBM in all spheres of medicine.

MEDICAL RESEARCH

Medical research needs to be conducted to increase knowledge about the human species, its social/natural

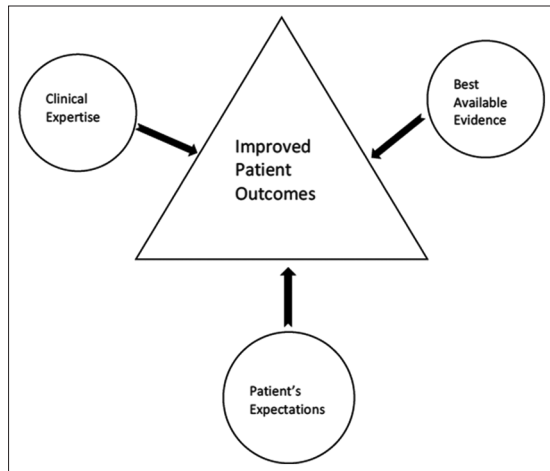


Figure 1: Triad of evidence-based medicine

environment and to combat disease/infirmity in humans. Research should be conducted in a manner conducive to and consistent with dignity and well-being of the participant; in a professional and transparent manner; and ensuring minimal risk.^[8] Research thus must be subjected to careful evaluation at all stages, i.e., research design/experimentation; results and their implications; the objective of the research sought; anticipated benefits/dangers; potential uses/abuses of the experiment and its results; and on ensuring the safety of human life. Table 1 lists the principles any research should follow.^[8]

Types of study design

Medical research is classified into primary and secondary research. Clinical/experimental studies are performed in primary research, whereas secondary research consolidates available studies as reviews, systematic reviews and meta-analyses. Three main areas in primary research are basic medical research, clinical research and epidemiological research [Figure 2]. Basic research includes fundamental research in fields shown in Figure 2. In almost all studies, at least one independent variable is varied, whereas the effects on the dependent variables are investigated. Clinical studies include observational studies and interventional studies and are subclassified as in Figure 2.

Interventional clinical study is performed with the purpose of studying or demonstrating clinical or pharmacological properties of drugs/devices, their side

Table 1: General principles of medical research

Principle	Definition/Details
Essentiality	Entailing the research is absolutely essential after considering all alternatives in light of the existing knowledge
Voluntariness, informed consent and community agreement	Research participants are fully apprised of the research and the impact and risk of such research
Non-exploitation	Research participants are remunerated for their involvement in the research or experiment
Privacy and confidentiality	Identity and records of human participants of the research or experiment are as far as possible kept confidential
Precaution and risk minimisation	Due care and caution are taken at all stages of the research and experiment
Professional competence	Research is conducted at all times by competent and qualified persons who act with total integrity and impartiality
Accountability and transparency	Research or experiment is conducted in a fair, honest, impartial and transparent manner after full disclosure is made by those associated
Maximisation of public interest and distributive justice	Research or experiment and its application are conducted and used to benefit all humankind
Institutional arrangements	All procedures required should be complied with and all institutional arrangements required are duly made in a bona fide and transparent manner
Public domain	Research and any further research emanating from such research are brought into the public domain
Totality of responsibility	Professional and moral responsibility for the due observance of all the principles, guidelines or prescriptions laid down
Compliance	Duty on all persons, conducting, use of a human participant to ensure that guidelines, as well as any other norms, directions and guidelines are followed

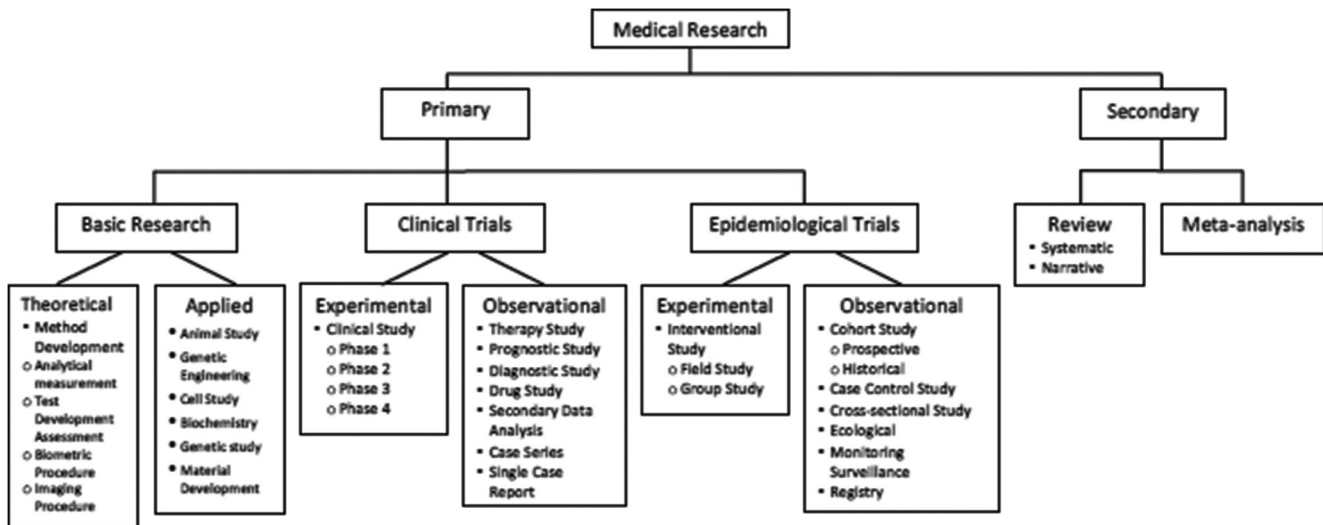


Figure 2: Classification of types of medical research

effects and to establish their efficacy or safety. They also include studies in which surgical, physical or psychotherapeutic procedures are examined.^[9] Studies on drugs/devices are subject to legal and ethical requirements including the Drug Controller General India (DCGI) directives. They require the approval of DCGI recognized Ethics Committee and must be performed in accordance with the rules of 'Good Clinical Practice'.^[10] Further details are available under 'Methodology for research II' section in this issue of IJA. In 2004, the World Health Organization advised registration of all clinical trials in a public registry. In India, the Clinical Trials Registry of India was launched in 2007 (www.ctri.nic.in). The International Committee of Medical Journal Editors (ICMJE) mandates its member journals to publish only registered trials.^[11]

Observational clinical study is a study in which knowledge from treatment of persons with drugs is analysed using epidemiological methods. In these studies, the diagnosis, treatment and monitoring are performed exclusively according to medical practice and not according to a specified study protocol.^[9] They are subclassified as per Figure 2.

Epidemiological studies have two basic approaches, the interventional and observational. Clinicians are more familiar with interventional research, whereas epidemiologists usually perform observational research.

Interventional studies are experimental in character and are subdivided into field and group studies, for example, iodine supplementation of cooking salt to

prevent hypothyroidism. Many interventions are unsuitable for RCTs, as the exposure may be harmful to the subjects.

Observational studies can be subdivided into cohort, case-control, cross-sectional and ecological studies.

- Cohort studies are suited to detect connections between exposure and development of disease. They are normally prospective studies of two healthy groups of subjects observed over time, in which one group is exposed to a specific substance, whereas the other is not. The occurrence of the disease can be determined in the two groups. Cohort studies can also be retrospective
- Case-control studies are retrospective analyses performed to establish the prevalence of a disease in two groups exposed to a factor or disease. The incidence rate cannot be calculated, and there is also a risk of selection bias and faulty recall.

Secondary research

Narrative review

An expert senior author writes about a particular field, condition or treatment, including an overview, and this information is fortified by his experience. The article is in a narrative format. Its limitation is that one cannot tell whether recommendations are based on author's clinical experience, available literature and why some studies were given more emphasis. It can be biased, with selective citation of reports that reinforce the authors' views of a topic.^[12]

Systematic review

Systematic reviews methodically and comprehensively identify studies focused on a specified topic, appraise their methodology, summate the results, identify key findings and reasons for differences across studies, and cite limitations of current knowledge.^[13] They adhere to reproducible methods and recommended guidelines.^[14] The methods used to compile data are explicit and transparent, allowing the reader to gauge the quality of the review and the potential for bias.^[15]

A systematic review can be presented in text or graphic form. In graphic form, data of different trials can be plotted with the point estimate and 95% confidence interval for each study, presented on an individual line. A properly conducted systematic review presents the best available research evidence for a focused clinical question. The review team may obtain information, not available in the original reports, from the primary authors. This ensures that findings are consistent and generalisable across populations, environment, therapies and groups.^[12] A systematic review attempts to reduce bias identification and studies selection for review, using a comprehensive search strategy and specifying inclusion criteria. The strength of a systematic review lies in the transparency of each phase and highlighting the merits of each decision made, while compiling information.

Meta-analysis

A review team compiles aggregate-level data in each primary study, and in some cases, data are solicited from each of the primary studies.^[16,17] Although difficult to perform, individual patient meta-analyses offer advantages over aggregate-level analyses.^[18] These mathematically pooled results are referred to as meta-analysis. Combining data from well-conducted primary studies provide a precise estimate of the “true effect.”^[19] Pooling the samples of individual studies increases overall sample size, enhances statistical analysis power, reduces confidence interval and thereby improves statistical value.

The structured process of Cochrane Collaboration systematic reviews has contributed to the improvement of their quality. For the meta-analysis to be definitive, the primary RCTs should have been conducted methodically. When the existing studies have important scientific and methodological limitations, such as smaller sized samples, the systematic review may identify where gaps exist in the available literature.^[20] RCTs and systematic review of several randomised

trials are less likely to mislead us, and thereby help judge whether an intervention is better.^[2] Practice guidelines supported by large RCTs and meta-analyses are considered as ‘gold standard’ in EBM. This issue of IJA is accompanied by an editorial on Importance of EBM on research and practice (Guyat and Sriganesh 471_16).^[21] The EBM pyramid grading the value of different types of research studies is shown in Figure 3.

In the last decade, a number of studies and guidelines brought about path-breaking changes in anaesthesiology and critical care. Some guidelines such as the ‘Surviving Sepsis Guidelines-2004’^[22] were later found to be flawed and biased. A number of large RCTs were rejected as their findings were erroneous. Another classic example is that of ENIGMA-I (Evaluation of Nitrous oxide In the Gas Mixture for Anaesthesia)^[23] which implicated nitrous oxide for poor outcomes, but ENIGMA-II^[24,25] conducted later, by the same investigators, declared it as safe. The rise and fall of the ‘tight glucose control’ regimen was similar.^[26]

SUMMARY

Although RCTs are considered ‘gold standard’ in research, their status is at crossroads today. RCTs have conflicting interests and thus must be evaluated with careful scrutiny. EBM can promote evidence reflected in RCTs and meta-analyses. However, it cannot promulgate evidence not reflected in RCTs. Flawed RCTs and meta-analyses may bring forth erroneous recommendations. EBM thus should not be restricted to RCTs and meta-analyses but must involve tracking down the best external evidence to answer our clinical questions.

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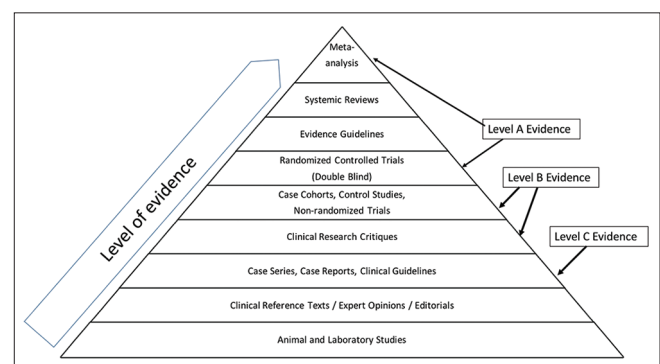


Figure 3: The evidence-based medicine pyramid

Conflicts of interest

There are no conflicts of interest.

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