



Continuing Education



Applications of evidence-based medicine: Overview of evidence-based medicine

Learning Objectives

Define evidence-based medicine and describe its key components

Discuss ways to incorporate EBM into call strategy

Identify key aspects of clinical trials

Describe the drug development process

Identify sources of funding for drug development

This first article in a three-part series provides an overview of evidence-based medicine and pharmaceutical research. Topics include evidence-based medicine and its components, integrating EBM into call strategy, clinical trials, the drug development process and funding sources for drug development.

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Evidence-based medicine (EBM) is the use of valid, rigorous clinical evidence, integrated with clinicians' own training and clinical expertise, to improve individual patient care.

The three key components of EBM are:

Sound, relevant research The foundation of EBM is clinical investigation that explores an issue in one of several categories: etiology (the causes of disease), prevention, screening, diagnosis, treatment and prognosis. In your discussions with clinicians, you may address issues related to research in each of these areas. However, you will usually find yourself focusing on the efficacy and safety of treatments – specifically pharmaceutical interventions. Most of the approved reprints you carry address this category. Be sure to become familiar with the details of your clinical trials. This will help you present a convincing case to clinicians for integrating your product into a disease management approach for diverse patient populations.

Clinical expertise EBM complements the practitioner's clinical expertise; therefore, a perceptive healthcare representative will apply good listening skills to understand how practitioners assess, diagnose and treat each patient. Doing so will reveal specific opportunities for discussing how you can use the evidence from clinical trials to support your product in the context of the clinician's approach. Alternatively, your understanding of the challenges clinicians commonly face in daily interactions with patients will uncover opportunities to introduce product information that is grounded in EBM and will enhance clinicians' ability to provide quality healthcare.

Patient-centric healthcare management Because of the unique values and circumstances of each patient, the patient has long been the focus of most care models. Patient-centric healthcare management starts with each patient and the information the patient provides. In patient-centric care, clinicians use communication strategies that invite the

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Example of a shift in call strategy

The following table illustrates the comparison of a typical selling strategy and an evidence-based strategy.

Segment of call strategy	Current selling strategy	Evidence-based strategy
Pre-call plan	Provide X number of sample boxes of product Z	Review reprint on product Z with clinician, highlighting findings relevant to the clinicians' patient populations
Main call objective	To increase the number of prescriptions written for product Z	To review the clinical evidence that supports the integration of product Z in the treatment of patients with a particular disease or disorder
Objection handling	My patients report unpleasant side-effects associated with product Z	Review patient profiles for whom the EBM results and product reprint suggest contraindications for use
Close	Ask clinician to call to request more samples	Elicit feedback from clinician on his/her reaction to the review of the reprint
Post-call notes	Schedule a next visit to restock samples	Schedule brief appointment with clinician to identify any changes in their clinical behaviors following exposure to the clinical evidence supporting product Z

Applying EBM to interactions with clinicians

The following table summarizes important information about the application of EBM in interactions between clinicians and healthcare representatives.

- Healthcare representatives should be aware of conflicts and limitations to topics that can be discussed with clinicians due to regulatory restrictions of product Z
- EBM provides healthcare representatives with another tool for use in their interactions with clinicians that can change clinical practice behaviors and result in improved patient outcomes and appropriate use of the representative's products

patient to discuss issues and concerns, listen actively while the patient speaks, and summarize what they heard while offering the opportunity to correct discrepancies. The clinical assessment and diagnostic tools complement this exchange of information. Then the practitioner relies on clinical expertise to make treatment decisions that strive for improved patient outcomes. The process also ends with patients, as their progress is followed and evaluated and their treatment plan adjusted accordingly.

EBM call strategy

Given the diverse challenges clinicians face, it is important for healthcare representatives to shift their call strategy toward a clinical support model of selling that integrates the process of EBM. The goal is to help clinicians quickly identify and evaluate relevant and current resources that will answer their patient-management questions.

Due to regulatory guidelines, most healthcare representatives are permitted to discuss only clinical issues within the boundaries of the product monograph for the patient types and disease states (and other conditions) for which a product has been indicated. Furthermore, representatives must limit discussion of articles in peer-reviewed journals to the specific approved reprints they are authorized to carry and distribute.

While practicing EBM, clinicians may lead discussions into two sensitive areas:

- Off-label use of a pharmaceutical product
- Clinical articles that representatives are not authorized to discuss

It is important that representatives respond appropriately to clinician statements and questions while adhering to legal and regulatory guidelines. In most cases, this involves referring the clinician to an approved resource, such as a research database

that addresses the issue in greater detail. Other good resources include clinical guidelines issued by professional societies or a clinical specialist within your organization who is authorized to discuss off-label use or unapproved clinical articles.

In addition, copies of the product information brochure can be provided to clinicians, allowing you to review the approved indications for your products and clarify questions about adverse events, contraindications and other issues related to patient care. Copies of the package insert can also be provided for clinicians to distribute to their patients to educate them about the therapeutic regimen that has been recommended.

EBM can be used as a strategy to change clinician behaviors regarding the optimal management of specific diseases or health conditions rather than simply influencing prescribing habits. If clinical information is presented with “fair balance” that acknowledges possible biases or limitations, clinicians will be more receptive to the role you can play in the process of clinical decision-making. A “fair balance” presentation of EBM about your product enhances impressions of the validity of the evidence and increases your personal credibility.

Clinical trials

A clinical trial is a research study designed to answer specific health-science questions to discover better ways to improve patient outcomes. In EBM, results from studies that comprise the research and development process are evaluated for their relevance to specific questions about medical interventions.

For healthcare representatives, information about issues such as trial types, protocol and enrollment are important when discussing evidence that supports specific therapies in patient management.

Clinical trials are generally divided into two categories: interventional trials and observational studies. Specific types of investigation within these two categories include:

- *Prevention trials*, which explore ways to reduce the incidence of disease through medicines, vitamins, vaccines or lifestyle changes
- *Diagnostic trials*, which investigate new methods, procedures or tests that have the potential to identify diseases or conditions earlier or more accurately
- *Treatment trials*, which evaluate the effect of interventions involving new drugs (or combinations of drugs), surgical procedures, radiation therapy and other types of therapeutic interventions
- *Genetic trials*, which explore how gene transfer therapy or a patient’s genetic makeup can be leveraged to detect, diagnose and treat diseases
- *Quality-of-life trials*, which investigate ways to improve quality of life for patients suffering from chronic or terminal illness.

Article summary

- **Evidence-based medicine (EBM) integrates clinicians’ training and clinical expertise with the most valid, rigorous clinical evidence to optimize individual patient care.**
 - The three key components of EBM are sound, relevant research; clinical expertise; and patient-centric healthcare management.
- **It is important for healthcare representatives to shift their call strategy toward a clinical support model of selling that integrates the process of EBM.**
 - EBM can be used as a strategy to change clinician behaviors regarding the optimal management of specific health conditions rather than simply influencing prescribing habits.
- **A clinical trial is a research study designed to answer specific health-science questions to discover better ways to improve patient outcomes.**
 - For healthcare representatives, information about issues such as trial types, protocol, and enrollment are important when discussing evidence that supports specific therapies in patient management.
- **Clinical research for a new drug is conducted in a sequence of steps progressing from preclinical stages to clinical trials (phases I, II, and III) to postmarketing surveillance (phase IV).**
- **Drug development is funded by many sources, mainly the federal government, the pharmaceutical industry, and private voluntary agencies.**

Every trial adheres to a trial protocol, which defines a set of rules designed to standardize procedures for the conduct of research and enhance communication among all investigators. The trial protocol describes the background, objectives, design, organization and methods of the study.

Primary and secondary endpoints are established before an investigation begins. Every trial has at least one primary study endpoint, which is a measurable outcome that indicates the effectiveness of a drug or intervention. Primary endpoints are designed to answer the research question originally generated as the rationale for the trial. Secondary endpoints are other possible outcomes that can help researchers interpret the results of the trial.

To ensure the safety of all people who volunteer for a trial, clinical investigations adhere to principles of Good Clinical Practice (GCP), which are the same ethical and legal codes that govern medical practice. Institutional review boards are affiliated with an investigator’s institution and provide oversight for all research activities to ensure that regulations for the protection of human subjects are followed.

Drug development process

Clinical research for a new drug is conducted in a sequence of steps progressing from preclinical stages to clinical trials (phases I, II and III) to postmarket-

ing surveillance (phase IV).

Preclinical During the first stage of drug development, thousands of chemicals may be screened for a particular chemical activity. Compounds that appear promising, known as “leads,” are followed through subsequent evaluations. Preclinical trials are then conducted in vitro and on living animals to assess the biological activity of the drug and discover any harmful effects on living organisms. Preclinical studies evaluate acute and subacute toxicities, carcinogenicity and effects on reproductive health in animals.

Clinical trials Clinical trials are conducted in three phases. A **phase I** trial is the first time the drug is administered to humans. A limited number of participants, usually between 20 and 100 healthy normal volunteers, are given increasing doses of the drug. Phase I trials assess the tolerability, pharmacokinetics, pharmacodynamics and safety of a drug. During **phase II**, controlled trials are conducted on patients for whom the drug is intended. The purpose

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is to determine evidence of efficacy of the drug, proper dosing levels and intervals, evidence of safety and tolerance in patients, and metabolism and excretion in patients with disease(s) for which the drug is indicated. **Phase III** trials involve several thousand patients from various demographic groups who are treated with the drug for longer periods of time to determine its long-term efficacy.

When a company is satisfied with its clinical trial results, it may submit a New Drug Application (NDA) to the FDA for approval to market the new drug. Upon receipt of FDA approval, the manufacturer can launch the product.

Postmarketing surveillance. **Phase IV** studies, commonly known as postmarketing surveillance, evaluate the use of a drug in uncontrolled clinical settings and among certain clinical situations, such as health maintenance organizations or certain patient populations (e.g., those in particular age groups). Postmarketing surveillance usually depends on reports from clinicians who prescribe the drug. In addition, information is acquired from large databases such as those maintained by Medicare, by managed care organizations or through insurance claims data. Postmarketing surveillance is critically important in our national effort to ensure the safety of pharmaceutical products.

Funding sources

Drug development is funded by many sources, mainly the federal government, the pharmaceutical industry, and private voluntary agencies. Each source of funding has different funding priorities.

Federal government agencies Congressional action is required before federal agencies can finance any type of health research. Most congressional appropriations for research are distributed to the National Institutes of Health (NIH), which consists of 27 Institutes and Centers. The majority of the NIH budget is awarded to scientists and doctors at research centers and universities throughout the country, who must compete for NIH grants. Although its budget has increased substantially over the years, the proportion of total health research and development expenditures by the federal government is significantly less than the investment by private industry.

Pharmaceutical industry In 2005, pharmaceutical companies spent an estimated \$39.4 billion on pharmaceutical R&D. The total NIH budget was \$28.6 billion, of which only a portion was devoted to pharmaceutical research.

Private voluntary agencies A large number of private, not-for-profit organizations, such as the American Cancer Society, American Diabetes Association and American Lung Association, also provide financial support for research on therapeutic interventions for specific diseases. Voluntary agencies are influential, not only in funding research directly but also in lobbying the government to appropriate research funds for specific healthcare issues.

Financial support for extramural research is usually awarded in one of two forms:

- **Grants** are allocations to be used in pursuit of a specified line of research; however, specific results or findings are not expected. When compared to contracts, grant recipients have more freedom with respect to research design, subject enrollment and collaboration with other institutions
- A **contract** is an allocation of funds intended to accomplish a specific research task. The specifications in the contract require the researcher to perform certain tasks to answer a specific question. Government, not-for-profit and industry funding sources may offer contracts to investigators to support research and development. When the pharmaceutical industry allocates funding to academic or private research institutions, it is almost always awarded as a contract. Contracts may be awarded to an institution, an academic department or an individual.

The next article in the series will discuss clinical trial designs and clinical reprints.