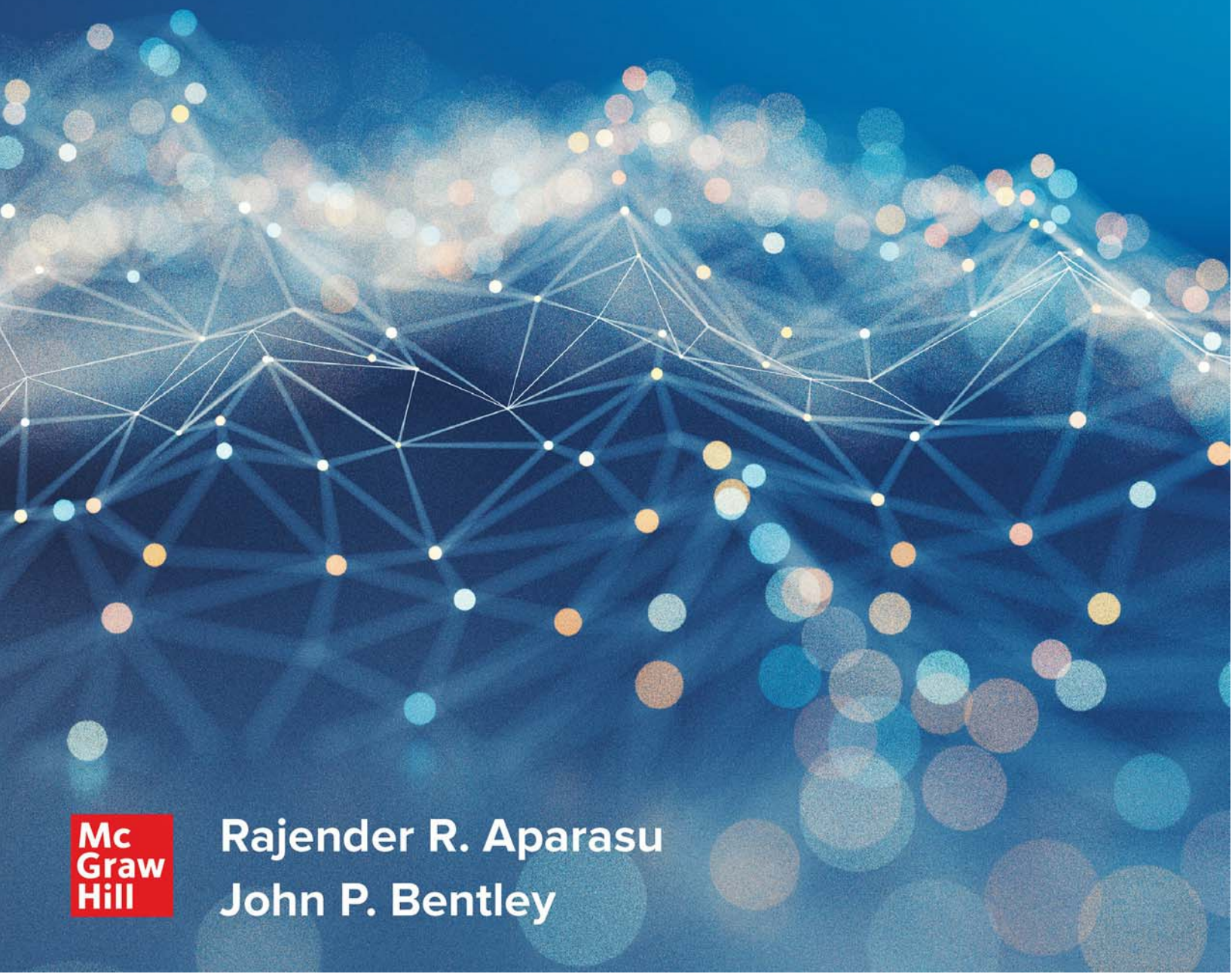
Second Edition

PRINCIPLES OF

Research Design and Drug Literature Evaluation



Rajender R. Aparasu
John P. Bentley

Mc Graw Hill

Principles of Research Design and Drug Literature Evaluation

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Principles of Research Design and Drug Literature Evaluation

Second Edition

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To my dear wife, Anu, and to my lovely kids, Shravya and Saureesh
—Aparasu

To my wife and partner, Sandy, and to Lon Larson and Mickey Smith, two incredible teachers, mentors, and friends
—Bentley

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About the Editors

Rajender R. Aparasu, MPharm, PhD, FAPhA, is a Professor and Chair in the Department of Pharmaceutical Health Outcomes and Policy at the University of Houston College of Pharmacy. He has more than 20 years of experience in teaching and research in the field of pharmaceutical outcomes and policy. He has taught various professional and graduate courses in colleges of pharmacy. Dr. Aparasu is a recognized educational leader and scholar in pharmaceutical outcomes and policy. He was instrumental in the growth of graduate programs at the University of Houston to train the next generation of pharmacy leaders. He led the creation of one of the largest MS/Residency programs in the country in collaboration with six Texas Medical Center institutions in Houston. He has trained over 30 graduate students and post-doctoral fellows in pharmaceutical outcomes research. Dr. Aparasu has received continuous Federal and non-Federal funding to address a broad array of quality of pharmaceutical care issues, especially among the elderly. The goal of his research is to provide real-word evidence for practice and policy decisions using available data sources based on novel methodological and analytical approaches for causal inference in observational outcomes research. He has served on national level patient safety and medication therapy management task forces.

Dr. Aparasu has more than 200 presentations in national/international meetings and more than 100 peer-reviewed publications. He is a peer reviewer for numerous pharmacy and medical journals and has been recognized as an Exceptional Peer Reviewer by several journals. He serves on the editorial boards of several pharmacy and healthcare journals including *Drugs & Aging* and *Research in Social and Administrative Pharmacy.* Dr. Aparasu is a grant reviewer for the American Heart Association, the Patient-Centered Outcomes Research Institute, and National Institutes of Health. He is the Editor-in-Chief of *Drug, Healthcare and Patient Safety* and has edited a book for graduate students titled *Research Methods for Pharmaceutical Practice and Policy.* He was recognized by his peers as a 2012 Fellow of the American Pharmacists Association for his exemplary professional achievements in practice and outstanding service to the pharmacy profession. In 2016, he was selected for the Fulbright Specialist Roster after receiving the endorsement from the U.S. Department of State's Bureau of Educational and Cultural Affairs and the Institute of International Education's Council for International Exchange of Scholars.

John P. Bentley, RPh, PhD, FAPhA, FNAP, is a Professor of Pharmacy Administration and a Research Professor in the Research Institute of Pharmaceutical Sciences at The University of Mississippi School of Pharmacy, with a joint appointment in the Department of Marketing in the School of Business Administration. He serves as the Chair of the Department of Pharmacy Administration and Program Coordinator for the University's Graduate Minor in Applied Statistics. In the professional pharmacy curriculum, Dr. Bentley teaches elements of research design, biostatistics, epidemiology, and drug literature evaluation. At the graduate level, he teaches several applied statistics courses, including general linear models, multivariate statistics, and elective courses focusing on the application of modern longitudinal data analysis methods and principles of statistical mediation and moderation. He has conducted research projects in a variety of areas, including: patient-reported outcomes; medication adherence; medication use, misuse, and outcomes; pharmaceutical marketing and patient behavior; patients' evaluation of health-care providers; pharmacy practice management; tobacco use, control, and cessation among college students; and ethics and professionalism. His statistics research interests include longitudinal data analysis and statistical mediation and moderation analysis.

Dr. Bentley has been a member of many interdisciplinary research teams, consulted with numerous researchers concerning statistical analysis, and served on the MS or PhD committees of over 140 students from various disciplines. He was named a Fellow of the American Pharmacists Association in 2009 and the National Academies of Practice in 2019. He has been recognized as a Thelma Cerniglia Distinguished Teaching Scholar at The University of Mississippi School of Pharmacy and has received the Excellence in Graduate Teaching and Mentoring Award from the University of Mississippi Graduate School, the University of Mississippi's Faculty Achievement Award for Outstanding Teaching and Scholarship, and the Outstanding Article of the Year Award for a paper published in *Quality of Life Research*. He has served as a peer reviewer for many journals and as an Associate Editor for the *Journal of the American Pharmacists Association*. Dr. Bentley received his BS in pharmacy and MBA from Drake University, his MS and PhD in pharmacy administration from The University of Mississippi, and his MS and PhD in biostatistics from The University of Alabama at Birmingham.

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Preface

We are delighted to offer the second edition of our popular book under the highly accessible McGraw-Hill Pharmacy Educational Series. The first edition, released in 2015, was well-received by pharmacy students, residents, fellows, and faculty. The very positive feedback from the academy, especially from fellow educators, and increased emphasis on evidence-based pharmaceutical care, motivated us to update our book. The second edition includes:

1. Revised and updated chapters to reflect changing research and practice paradigms;
2. A new chapter (Chapter 20) on the application and evaluation of qualitative research;
3. Updated examples in the chapters with new clinical research studies; and
4. Revision of certain content based on feedback from instructors.
5. Revised online and journal resources.
6. Student learning resources at McGraw-Hill AccessPharmacy

The structure of the book in the form of three sections has remained the same for ease of use: Section 1: Principles of Clinical Research; Section 2: Statistical Principles and Data Analysis; and Section 3: Principles of Drug Literature Evaluation. We sincerely hope that the new edition will provide students and faculty with strong foundational principles of clinical research and drug literature evaluation techniques to provide evidence-based pharmaceutical care. We believe that all knowledge is considered as work in progress, like the contents of this book. Therefore, we are open to any feedback from students and faculty for future editions.

—July 2019

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Preface to the First Edition

With the increasing emphasis on evidence-based practices, there is a greater need for pharmacists to understand clinical research, evaluate scientific findings, and translate evidence to support patient-care decisions. This requires a comprehensive understanding of the principles and practice of drug literature evaluation with a strong grounding in research design and statistical methods. Most available texts emphasize statistical approaches and/or scientific literature evaluation techniques. Although there may be comprehensive books in other health professions, it is challenging to find a pharmacy textbook that covers all critical research design and evaluation elements to translate evidence into practice. We decided to edit this book to provide a balanced approach to the principles of clinical research and statistics for evaluating pharmacy literature to implement evidence-based pharmacotherapy.

Most pharmacy schools offer a course in the pharmacy professional program that covers fundamentals of research design, biostatistics, and evaluation of pharmacy literature, as required by the Accreditation Council for Pharmacy Education (ACPE). Consequently, this book is divided into three sections to provide comprehensive course content to meet and exceed these curriculum standards set by the ACPE. Section 1 of the book covers principles of scientific research with an emphasis on clinical research designs ranging from randomized controlled trials to case reports. Section 2 of the book provides the foundation necessary to understand statistics and to critically evaluate results from statistical analyses reported in the medical literature with a focus on common statistical methods. Section 3 of the book covers principles of evidence-based medicine, drug literature sources and evaluation techniques, and application of evidence to patient care. There are seven chapters in each section of the book.

Chapter 1 defines basic, applied, clinical, and translational research, and describes the steps in scientific research and evidence-based medicine. Chapter 2 explains the guiding ethical principles in clinical research and discusses the regulatory framework governing clinical research. Chapter 3 provides the basics of designing clinical research, with an emphasis on common clinical research designs and methodologies. Chapter 4 discusses the design considerations associated with randomized controlled trials, including common clinical designs and analytical framework. Chapters 5 and 6 provide observational approaches for conducting clinical research. Chapter 5 describes case-control and cohort designs and includes a discussion of common biases and analytical approaches to minimize such biases. Chapter 6 provides an overview of cross-sectional studies, pre- and post-observational studies, ecological studies, and time series evaluations. Chapter 7 presents the key steps in designing a case report and case series studies along with tools to critically evaluate these designs.

Chapter 8 discusses the summarizing, organizing, and presenting functions of statistics, commonly referred to as descriptive statistics, and also introduces the different kinds of data that are collected in clinical research. Chapter 9 provides the general foundation for applying basic tools of statistical inference, focusing on the related mechanisms of estimation and hypothesis testing. Given that many studies in the drug literature involve the comparison of two or more groups, Chapter 10 discusses commonly used statistical procedures that are used to answer research questions involving group comparisons; in addition, it describes the statistical methods for assessing the correlation between two variables. Chapters 11 and 12 provide an overview of regression analysis methods that can be used to account and/or adjust for variables that cannot be handled at the design stage of an experiment. Chapter 11 describes simple linear and multiple regression approaches to address a number of research problems, such as confounding and effect modification. Chapter 12 introduces logistic regression and Cox regression methods to analyze binary and time-to-event outcomes, respectively. Chapter 13 introduces the statistical principles underlying sample size calculation. Chapter 14 presents the elements of the systematic review process and describes meta-analysis as a method to quantitatively synthesize evidence from studies identified in a systematic review.

Chapter 15 identifies the steps involved in evidence-based medicine along with the discussion of its strengths and limitations. Chapter 16 discusses the sources and use of primary, secondary, and tertiary literature to identify clinical evidence for evidence-based medicine. Chapters 17, 18, and 19 discuss approaches to appraise published primary literature for patient care. Chapter 17 provides a stepwise approach to appraise published literature with an emphasis on evaluating the study objectives, methods and design, statistics, results, and discussion. Chapter 18 describes the key considerations for evaluating methodological rigor in randomized controlled trials using an example. Chapter 19 describes and applies formal criteria to evaluate observational studies using an example. Chapter 20 discusses general principles of applying evidence to patient care with an emphasis on evidence from clinical trials and practice guidelines. Finally, Chapter 21 describes the general format of a journal club and examines the characteristics of an effective journal club.

This book is designed for professional pharmacy (PharmD) students. Instructors teaching principles of research and drug

literature evaluation can design the professional course primarily based on this book or can supplement this book with research articles. The contents of the book can be delivered in one or two semesters. Chapters are written by expert authors specializing in pharmacy practice and research. Each chapter includes the following elements:

- *Learning Objectives* present the chapter's desired outcomes to the reader.
- *Key Terminology* helps the reader quickly identify critical new terms.
- *Review Questions* allow readers to apply what has been learned in the chapter and assess their understanding of the content.
- *Online Resources* direct students to web sites relevant to the content.

The chapters are designed to provide the knowledge base and application techniques for research design and drug literature evaluation. In addition to figures and tables, numerous pharmacy examples and case studies are provided to aid student learning. Additional readings from pharmacy journals and a drug literature evaluation project can improve the critical thinking skills of pharmacy students. The online sources and chapter references can be used to supplement the content. This book can also be an excellent resource for students in residency and fellowship training programs. In addition, this book can be beneficial to pharmacy practitioners and professionals, especially those involved in training students, residents, and fellows.

We would greatly appreciate feedback from students and faculty for future editions. All knowledge is considered as work in progress, including the contents of this book.

—March 2014

Acknowledgments

Many individuals have contributed to the fruition of this book. The concepts and vision for this book have evolved over 20 years of teaching professional courses in research design, biostatistics, and drug literature evaluation. Feedback from pharmacy students and regular discussions with colleagues, especially Dr. Rebecca Baer at South Dakota State University (Aparasu) and Dr. Kim Adcock at the University of Mississippi (Bentley), were instrumental in developing the master plan for this book. Sincere thanks to all of the authors for patiently working with us in developing the chapter content and updating the chapters, and most importantly for contributing their expertise to this book. The feedback from the reviewers was also very helpful in improving the content and formatting of the book. The insight and support of Drs. Albert Wertheimer and Shane Desselle was instrumental in undertaking this book.

We greatly appreciate Dr. Jeffrey Sherer for helping us to recruit the authors for the third section of the book and overseeing the development of initial chapter outlines. Our gratitude also goes to several of our graduate students, who offered input from a student's perspective on several chapters. Several individuals provided valuable feedback to us following the publication of the first edition of the book; we would like to especially acknowledge Dr. Lourdes Planas, a faculty member at the College of Pharmacy at the University of Oklahoma Health Sciences Center, for her kind words, encouragement, and suggestions for improvement. We appreciate the editorial assistance of Dr. Satabdi Chatterjee for the second edition. We also would like to thank our respective university and college/school faculty colleagues and administration teams for providing us the time and encouragement to complete this project. Finally, we are grateful to the publishing team at McGraw-Hill Education, especially Michael Weitz and Peter Boyle their help and support. The editorial assistance of the production staff of McGraw-Hill Education is also very much appreciated and we would like to specifically acknowledge the efforts and support of Apoorva Mathur with Cenveo Publisher Services.

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SECTION 1

Principles of Clinical Research

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1

The Scientific Approach to Research and Practice

Rajender R. Aparasu, MPharm, PhD, FAPhA • Satabdi Chatterjee, MS, PhD

CHAPTER OBJECTIVES

- Define basic, applied, clinical, and translational research
- Understand the principles of scientific inquiry
- Describe the steps in scientific research and evidence-based practice
- Discuss the scientific basis of professional education

KEY TERMINOLOGY

Abstract
Analytical research
Applied research
Basic research
Biomedical research
Clinical research
Comparative effectiveness research
Descriptive research
Development
Discussion section
Empiricism
Ethics
Evidence-based medicine
Hypothesis
Implementation science
Introduction section
Journal article
Method section
Objectivity
Patient-centered outcomes research
Pharmaceutical practice and policy research
Positivism
Poster
Practice-based research network
Primary methods
Quality
Research
Research and development
Research design
Research methodology
Research report
Results section
Secondary methods
Theory
Translational research

INTRODUCTION

Pharmacists are a vital component of healthcare delivery and biomedical systems. Medications and clinical services are integral to the myriad roles pharmacists play in the healthcare system. Pharmaceutical research and development (R&D) is instrumental in the discovery of new medications and pharmaceutical formulations. There are more than 10,000 prescription products and 300,000 over-the-counter products in the marketplace.[1] This is mainly attributed to R&D in basic sciences like biology, chemistry, biochemistry, and microbiology, and applied sciences like pharmacology, pharmaceutics, and pharmacotherapy. During the past few decades, there has been significant growth of clinical pharmacy services to meet the complexities of delivering pharmaceutical care in diverse healthcare settings. Pharmacists provide a broad range of outpatient services, such as medication therapy management, immunizations, and health screenings, and inpatient services

range from nutrition to therapeutic drug monitoring in institutional settings. High quality research is vital to develop new medications and clinical services; it also provides the knowledge base to effectively use these products and services.

Pharmacists have an important role in creating and applying scientific evidence. Although pharmacists are mostly consumers of research information, they contribute immensely to the growing scientific knowledge base relevant to the pharmacy profession. Pharmacists involved in research make a vital difference by providing evidence that others can use. This knowledge is also important in academia to train the next generation of pharmacists. In recent years, practice-based innovations have created new models in delivering pharmaceutical care. With increasing role of evidence-based paradigms, there is a greater need to critically apply and evaluate research for pharmaceutical practice and policy. Both creating and applying research evidence require an understanding of the principles of research design. This chapter defines biomedical research and evolving clinical research paradigms relevant to the pharmacy profession. It discusses the principles of research design and steps involved in scientific research inquiry. Finally, the concept of evidence-based medicine (EBM) is introduced to effectively translate scientific evidence to patient care.

BIOMEDICAL RESEARCH

Pharmaceuticals and pharmacists are vital for healthcare delivery. Research drives the increasing role of pharmaceuticals and pharmaceutical services in disease state management. The National Science Foundation (NSF) has defined **research** as "systematic study directed toward fuller scientific knowledge or understanding of the subject studied."[2] **Biomedical research** is a broad area that deals with research in biological and medical sciences to understand and improve the health of patients and populations. Biomedical research can be further classified as *basic* or *applied* based on the goals of the research. **Basic research** is defined as "systematic study directed toward fuller knowledge or understanding of the fundamental aspects of phenomena and of observable facts without specific applications toward processes or products in mind."[2] It is usually conducted in laboratories to provide knowledge and understanding of natural phenomena. Some areas of inquiry in basic biomedical research are biology, physiology, biochemistry, and genetics. Although scientists involved in basic research are only focused on generalized knowledge, this knowledge is critical for applied research that is product or application-oriented.

Applied research is defined as "systematic study to gain knowledge or understanding necessary to determine the means by which a recognized and specific need may be met."[2] It focuses on applying the basic knowledge for the purpose of developing a product or an application such as a new medication, drug regimen, or service. It has a practical orientation rather than the explanation focus that is inherent in basic research. It is conducted in animals and other living systems to solve a practical problem or to create a product. Some areas of inquiry in applied biomedical research are pharmacology, medicinal chemistry, and pharmaceutics. R&D involves applied biomedical research and is considered as the engine for pharmaceutical industry.

Drug development is specifically focused on developing new drug products. **Development** is defined as "systematic application of knowledge or understanding, directed toward the production of useful materials, devices, and systems or methods."[2] **Research and development** refers to "creative work undertaken on a systematic basis in order to increase the stock of knowledge, including knowledge of man, culture, and society, and the use of this stock of knowledge to devise new applications." In pharmaceutical industry, R&D is an expensive and time consuming process. It takes an average of 15 years for a new product to enter the market at an average cost of $1.2 billion due to complex development, testing, legal, and regulatory considerations.[3]

Clinical research plays a vital role in the drug development process as approval of a drug by the Food and Drug Administration (FDA) requires randomized controlled trials to demonstrate the safety and efficacy of pharmaceutical products. The National Institutes of Health (NIH) has defined **clinical research** as "research that either directly involves a particular person or group of people or uses materials from humans, such as their behavior or samples of their tissue."[4] Specifically, it is "any investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy."[5] Clinical research helps in understanding and applying knowledge for products or processes in prevention, diagnosis, prognosis, treatment, and cure of diseases in humans. It is conducted in laboratories, healthcare settings, and other specialized locations in accordance with the regulatory guidelines.

Clinical research includes patient-oriented research, epidemiological and behavioral research, and health services research.[4] Patient-oriented research examines the mechanisms of human diseases, effects of drug therapies and other interventions, and use of technologies and devices in humans. Epidemiological and behavioral research evaluates the distribution of and factors associated with diseases, health behavior, and health in general. Health services research evaluates the effectiveness and efficiency of treatment, interventions, and services in real-world practice. All facets of clinical research are important to improve the health of patients. Clinical research involving pharmaceuticals and pharmacy services is vital to improve the quality of pharmaceutical care.

Pharmaceutical practice and policy research is a component of health services research that deals with issues related to pharmaceuticals, pharmacist services, and pharmacy systems. It is defined as a "multidisciplinary field of scientific investigation that examines cost, access, and quality of pharmaceutical care from clinical, sociobehavioral, economic, organizational, and technological perspectives."[6] The goal of pharmaceutical practice and policy research is to increase knowledge and understanding of pharmaceuticals, pharmacist services, and pharmacy systems for individuals and populations. New areas such as pharmacoepidemiology, pharmacoeconomics, pharmaceutical outcomes research, and pharmacy practice-based research are evolving and expanding the research frontiers of pharmaceutical practice and policy research. This evidence

base is critical to expand the scope and role of pharmacists and pharmacy systems.

EVOLVING RESEARCH PARADIGMS

Translational research is the new clinical research paradigm for transferring knowledge across the research and practice continuum. According to the NIH, **translational research** includes "two areas of translation. The first area is the process of applying discoveries generated during research in the laboratory, and in pre-clinical studies, to the development of trials and studies in humans. The second area of translation concerns research aimed at enhancing the adoption of best practices in the community."[7] The first area of translation is designed to improve the trajectory of research from laboratory to patient care. This is critical for diseases such as cancer and acquired immune deficiency syndrome (AIDS) which are in need of products that treat or cure devastating diseases. The second area of translation is gaining support of scientists, clinicians, educators, and funding agencies to rapidly adopt evidence-based patient care practices. According to the Institute of Medicine (IOM), there is a significant gap between what patients are receiving and what they should receive, leading to a quality chasm in healthcare.[8] Translational research and EBM can be instrumental in bridging this quality gap.

In recent years, there is significant interest in comparative effectiveness research due to limited data comparing two therapies, interventions, or devices. The demand for comparative effectiveness data is apparent as most clinicians want such data for clinical decisions. The efficacy data derived from placebo-controlled randomized trials are designed for the drug approval process. Comparative effectiveness research is based on the concepts of evaluation of alternatives so that the research can be used to select appropriate agents among the alternatives to optimize patient outcomes. **Comparative effectiveness research** is the "generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve delivery of care."[9] The goal of comparative research is to provide information to decision makers at both individual and population levels.

With increasing focus on patient-centered care, a new type of clinical research called patient-centered outcomes research has evolved. The **patient-centered outcomes research** (PCOR) is designed to incorporate patients' inputs in the research process and to provide relevant information to providers and patients for deciding on healthcare choices. The PCOR "helps people and their caregivers to communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options."[10] For pharmaceutical products and services, the goal of the PCOR is to "assess the benefits and harms of preventive, diagnostic, therapeutic, or health delivery system interventions to inform decision making, highlighting comparisons and outcomes that matter to people."[11] The incorporation of patient relevant outcomes is a new phenomenon as traditional clinical research, until now, emphasized outcomes from clinicians' perspective. In an effort to generate evidence for patient-oriented outcomes, the Federal Government has created the Patient-Centered Outcomes Research Institute (PCORI), which will fund research on 1) assessing prevention, diagnosis, and treatment options, 2) improving access and care in healthcare systems, 3) communicating and disseminating research for shared decision making, 4) addressing disparities in prevention, diagnosis, or treatment effectiveness, and 5) accelerating PCOR and methodological research.[11]

DETERMINANTS OF SCIENTIFIC METHODOLOGY

All scientific research is bound by principles of scientific inquiry. These include empiricism, objectivity, theory, and ethical standards.[6] **Empiricism** refers to the collection of information based on human experience. It is based on the philosophy of **positivism** that states that all information derived from sensory experience is empirical evidence of science. All aspects of science should be observed and measured to be considered as scientific evidence. All clinical outcomes in research are explicitly defined and measured to be considered as evidence to evaluate the safety and effectiveness of medications. Measurement and quantification are vital for scientific research. **Objectivity** means that there is no subjectivity or bias in any aspect of research including definition, measurement, design, and analysis. In clinical research, not only the measures to define effectiveness, such as blood pressure and blood glucose, are objective, the measurement process is often blinded to minimize any kind of subjectivity. All biases in research are minimized to increase the strength of scientific evidence.

Theory provides an understanding or explanation of a natural phenomenon. Theories evolve over years or decades to explain natural phenomena. In pharmaceutical research, theories are often based on pathophysiology of a disease and pharmacology of a medication to investigate medication effects. Sociobehavioral theories are often used to understand patient and provider behaviors in pharmaceutical practice and policy research. Theories are also useful in developing a research hypothesis. They provide the rationale and logic for research questions and hypotheses. Research findings are used to strengthen or dispute a theory. **Ethics** provide the moral societal standards for responsible research conduct. These standards are based on respect, fairness, and well-being of research participants.[12] The standards are often governed by the institutional review board, state, and federal regulations. To reflect all these principles in research, Kerlinger has defined scientific research as a "systematic, controlled, empirical, and critical investigation guided by theory and hypothesis about presumed relationships among such phenomena."[13]

PROCESS OF SCIENTIFIC INQUIRY

The scientific research process involves the following steps: 1) pose a research question and hypothesis, 2) develop and implement a research plan, 3) perform data collection and analysis, and 4) prepare a research report.[6] Each of these steps is critical for scientific inquiry. The research question or hypothesis dictates the research plans and data collection. Often practical and scientific considerations necessitate overlap of these steps of research process. The following description uses clinical and translational research framework to explain the research steps: (**Figure 1-1**).

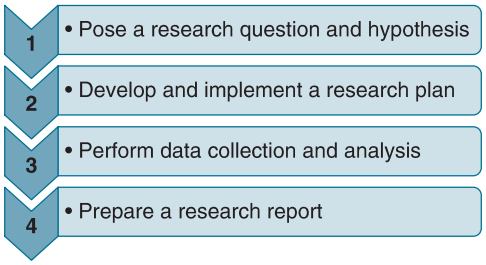

FIGURE 1-1: Steps in the Scientific Research Process.

The first step in the scientific research process is to pose a research question and a hypothesis. It is important to develop a research question that needs empirical investigation. The commonly used sources for a research question are clinical practice, policy, current issue, literature, or theory. The desirable characteristics of a research question are that it is feasible, interesting, novel, ethical, and relevant (FINER).[14] Practical considerations, such as funding, expertise, environment, and access to patient care data, are also important to address the feasibility of the research. The novelty aspect of the research question can be evaluated by conducting a literature review. The goal of the research is to add something new to the existing evidence base. The ethical principles of research are governed by local institutional review boards and federal regulations. This requires appropriate regulatory approvals to conduct clinical research. Research relevant to the pharmacy profession should have strong implications for pharmaceutical practice and policy. Research that is not relevant will have limited value to stakeholders such as patients, providers, payers, and policy makers. These considerations will not only help formulate a good research question but also ensure a valuable contribution is made to evidence-based practice and policy (**Box 1-1**).

The population, intervention, comparator, outcomes, timeline, and setting (PICOTS) framework is often used to develop a good clinical question. This framework is ideal to compare interventions such as medications, devices, clinical services, policies, and programs. It also provides the components of a research question.[15,16]

BOX 1-1

RESEARCH QUESTION AND HYPOTHESIS

Question: In patients with diabetes, do clinical services by pharmacists improve short-term clinical outcomes compared with traditional care in outpatient setting?

Hypothesis: Clinical services by pharmacists will improve short-term clinical outcomes in outpatients with diabetes compared with traditional care.

Sources: Irons BK, Lenz RJ, Anderson SL, et al. A retrospective cohort analysis of the clinical effectiveness of a physician-pharmacist collaborative drug therapy management diabetes clinic. Pharmacotherapy. 2002;22:1294–1300.

Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11:253–260.

The PICOTS framework requires the research question to identify: population to be studied, intervention to be applied, comparator to be used, outcomes to be evaluated, timeline to evaluate the outcomes, and healthcare setting of interest (**Figure 1-2**).

The population of interest can be grouped based on age, disease, or location. The intervention is usually a pharmaceutical product or service. The comparator can be an active medication/service or a placebo based on the goals of the research. The economic, clinical, and humanistic outcomes (ECHO) are usually evaluated in pharmaceutical practice and policy research.[17] Costs of direct and indirect medical care are often included as economic outcomes. Clinical outcomes include morbidity and mortality measures that represent safety and effectiveness of treatment. Humanistic outcomes include patient-reported outcomes such as health-related quality of life and functional status. The timeline for research can be short-term or long-term based on the expected impact of pharmaceutical products or services.

In addition to comparative research framework, research can be classified as descriptive or analytical. **Descriptive research** describes or explores characteristics of a population such as the prevalence of a disease. **Analytical research** evaluates the relationship between two or more variables. **Hypothesis** specifies an expected relationship that is being evaluated between intervention/and outcome, or two or more variables. The hypothesis is often based on existing theories. The pathophysiology of the disease and pharmacology of the medication provide the rationale for expected effects of the pharmaceutical product. The expected relationship between clinical intervention and outcomes is usually postulated based on sociobehavioral theories. Research hypothesis is not usually specified in descriptive or exploratory research.

Developing and implementing a research plan requires a strong understanding of the principles of clinical research. Research plans include specific details of research design and methodology. Grant proposals have other requirements, such as timeline and funding details, in addition to research plans. These plans are implemented after the necessary approvals by the local institutional review boards. **Research design** refers to the overall plan that allows researchers to address study questions and test study hypotheses.[18] The research designs can be broadly categorized into two types—experimental and observational designs. Experimental designs such as randomized controlled trials are the strongest study designs to test research hypotheses. The randomized designs are considered the gold standard in clinical research and are used to evaluate drug safety and efficacy. Observational research such as cohort or cross-sectional studies provides the evidence of associations or relationship. The evidence from observational research is generally weaker than that of randomized controlled trials due to scientific considerations such as confounding and biases. Study design provides a structural framework for experimental or observational research.[6] Various other study designs are available to address the research question; the goal is to select the best design that fits the research question.

Research methodology provides details of data collection and measurement techniques.[6] The definitions and the measurement process of intervention and outcomes are specified in the methods. Research methods are broadly grouped as primary methods and secondary methods. **Primary methods** collect data specifically

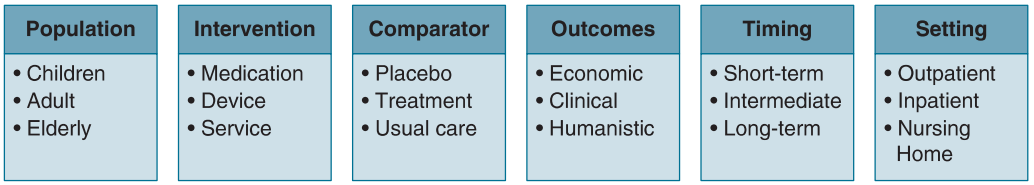

FIGURE 1-2: Components of a Scientific Research Question with Examples.

for the research question using techniques such as self-reported observations and biological assessments; examples include surveys and laboratory tests. These are often collected prospectively, that is, data are collected after the study onset. **Secondary methods** involve the use of data that was collected for other purposes such as patient care or reimbursement; examples include medical charts and medical claims. These are retrospective in nature which means data were collected based on past events or already existing sources. Prospective methods are generally considered superior to retrospective methods as the researcher controls the data collection methods. The goal of research methods is to collect research data that are reliable (consistent) and valid (accurate). Researchers have a choice of research methods; the goal is to select the most appropriate method to collect the data. (**Box 1-2**).

The research design and methodology define the data management and analysis plans. Data collected from all sources should be recorded at the patient level or other units of analysis to conduct appropriate statistical analyses. Data collected from surveys and laboratory tests should be gathered and coded accordingly. Similarly, data from secondary sources should also be extracted and coded in accordance with the analysis plan. Although data collection seems easy, it is often tedious and time consuming as any error can undermine the data integrity and subsequent steps in the research including statistical analyses. Statistical analysis provides the quantitative answers to the research question. It is a tool to organize, summarize, and analyze research data. Several descriptive and inferential statistics are used to analyze the data. The descriptive measures such as means, medians, and modes are often used to summarize study sample characteristics. Inferential statistics such as the *t*-test and analysis of variance are used to make inference or draw conclusions based on the data collected. The appropriate statistical test is selected based on the research question, research hypothesis, research design, and methods. (**Box 1-3**).

Research reports or journal articles are vital to communicate research findings to stakeholders such as patients, providers, payers, and policy makers. A **research report** or **journal article** is a detailed document that often includes the following sections: introduction, methods, results, and discussion (IMRaD).[19] It is generally peer-reviewed to ensure scientific discourse and scrutiny (**Figure 1-3**).

Research **abstract** is a structured summary of research which provides quick and easy-to-use information to readers. The **introduction section** of a research report or journal article includes relevant background information and covers existing

BOX 1-2

RESEARCH PLAN

Design:

- Choe HM et al. conducted a randomized controlled trial to evaluate the impact of clinical services by pharmacists on glycemic control and other process measures in diabetes patients.
- Irons BK et al. used a retrospective cohort design to evaluate the clinical effectiveness of clinical services by a pharmacist in primary care for patients with diabetes.

Methods:

- Choe HM et al. prospectively collected data on glycosylated hemoglobin using a high-performance liquid chromatography machine and other secondary outcomes were collected using chart review.
- Irons BK et al. used secondary data like medical charts to collect data related to glycosylated hemoglobin and other secondary outcomes for the study population.

Sources: Irons BK, Lenz RJ, Anderson SL, et al. A retrospective cohort analysis of the clinical effectiveness of a physician-pharmacist collaborative drug therapy management diabetes clinic. Pharmacotherapy. 2002;22:1294–1300.

Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11:253–260.

BOX 1-3

DATA COLLECTION AND ANALYSIS

- Choe HM et al. analyzed data collected using Wilcoxon Rank Sum Test and linear regression analysis. A level of $P < .05$ was set to define statistical significance.
- Irons BK et al. analyzed data collected using *t*-test, chi-square, analysis of variance, and Cox regression models. Two-sided tests were performed with *a priori* alpha level of 0.05.

Sources: Irons BK, Lenz RJ, Anderson SL, et al. A retrospective cohort analysis of the clinical effectiveness of a physician-pharmacist collaborative drug therapy management diabetes clinic. Pharmacotherapy. 2002;22:1294–1300.

Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11:253–260.

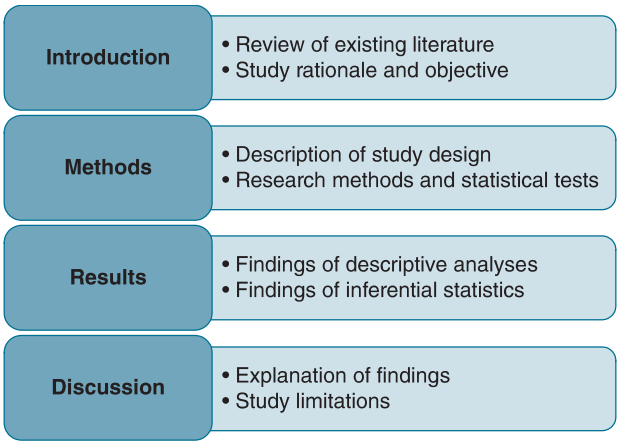

FIGURE 1-3: Components of a Research Report.

literature on the subject. It provides a rationale for conducting the research. It specifies the research objective or question and research hypothesis. The **method section** includes descriptions of research design, data collection methods, and statistical tests. The **results section** describes the research findings based on the statistical analyses. The study sample is often summarized using descriptive statistics and graphs. Inferential statistics usually include confidence intervals and probability or *p* values. The results section provides answers to the research question. This is the most objective and unbiased section of the research report. The **discussion section** provides the interpretation and explanation of the research findings using previous research or theory. It also addresses possible limitations and future directions of the research. Research **posters** are often used for graphic/visual presentation of research in scientific conferences usually employing the IMRaD format (**Box 1-4**).

BOX 1-4

KEY FINDINGS AND RESEARCH REPORT

- Choe HM et al. found a significant decrease (–2.1%) in glycosylated hemoglobin levels in the intervention group when compared to the decrease in the control group (–0.9%). Significant improvements were also seen in other process of care measures. The other results can be found in the research report.
- Irons BK et al. found no difference in glycosylated hemoglobin between the two groups. However, there was higher risk (5.19, 95% CI 2.62–10.26) of achieving clinical goal (A1C <7%) in the study group compared to the control group. The other results can be found in the research report.

Sources: Irons BK, Lenz RJ, Anderson SL, et al. A retrospective cohort analysis of the clinical effectiveness of a physician-pharmacist collaborative drug therapy management diabetes clinic. Pharmacotherapy. 2002;22:1294–1300.

Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11:253–260.

EVIDENCE-BASED MEDICINE

The goal of clinical research is to provide scientific evidence to improve the health and functioning of people. The healthcare providers, payers, and policy makers are all interested in ensuring the delivery of the highest quality patient care. **Quality** in healthcare refers to "the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge."[20] According to the IOM, all stakeholders in healthcare should pursue the following six aims in the delivery of quality healthcare[8]: 1) safe: avoid harm to patients from the healthcare delivery; 2) effective: deliver care that benefits patients; 3) patient-centered: care that is individualized based on patient preferences and values; 4) timely: ensure timely, needed care and avoid delays; 5) efficient: care that maximizes use of healthcare resources; and 6) equitable: care that does not vary due to personal characteristics—race or ethnicity—and minimizes healthcare disparities at the individual and population level. To achieve these aims, patients and populations should receive healthcare that is based on the best scientific evidence. (**Figure 1-4**).

The core of **evidence-based medicine** is to translate scientific evidence to patient care. There are several definitions of EBM. Some have initially emphasized the translational aspect of evidence as a "process of systematically finding, appraising, and using contemporaneous research findings as the basis for clinical decisions."[21] Others have defined EBM holistically as "integration of best research evidence with clinical expertise and patient values."[22] The holistic definition is the most widely accepted and practiced as it not only emphasizes scientific evidence but also incorporates expertise of clinician and patient preferences. Clinical expertise includes the knowledge, skills, and experience of practitioners to integrate evidence with patient preferences. Any care that is not patient-centered will have limited value as treatment success is dependent on individualization. This holistic approach lends equal importance to evidence (scientific), expertise (provider), and values (patient) to achieve the desired patient outcomes.

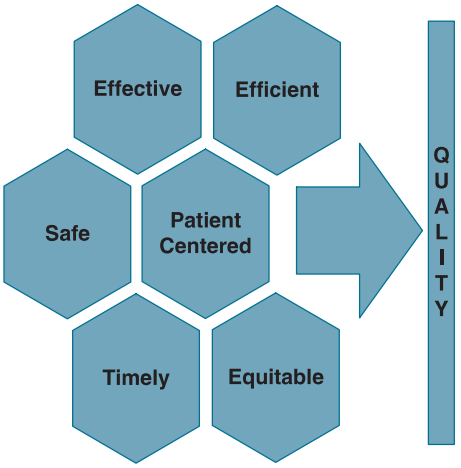

FIGURE 1-4: Six Aims of Quality Improvements.

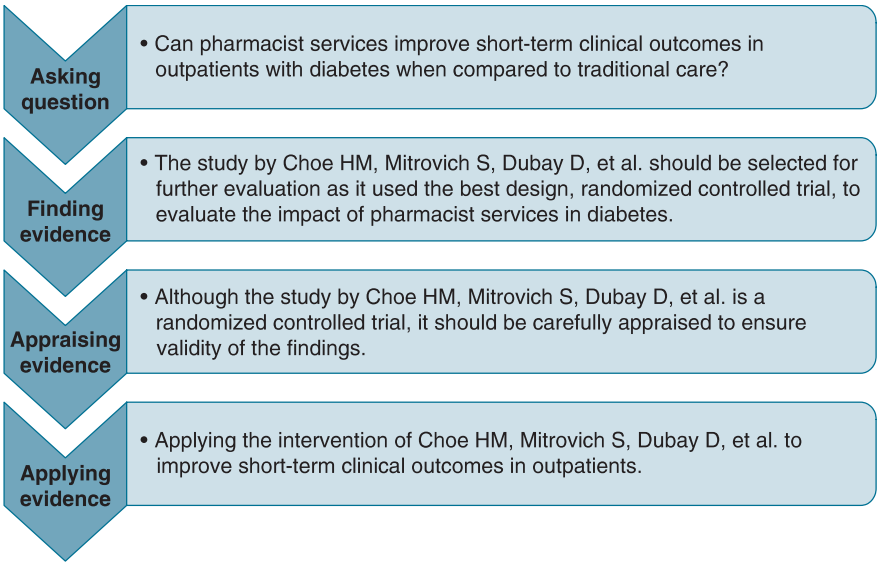

FIGURE 1-5: Example of Evidence-Based Medicine. (Choe HM, Mitrovich S, Dubay D, et al. Proactive case management of high-risk patients with type 2 diabetes mellitus by a clinical pharmacist: a randomized controlled trial. Am J Manag Care. 2005;11:253–260).

Since scientific evidence is the core of EBM, the following steps of EBM are evidence-centered: 1) asking an appropriate and answerable question, 2) finding evidence, 3) appraising evidence, and 4) applying evidence to practice.[22] A simplified example is presented in **Figure 1-5**.

Each step is important to ensure that relevant evidence is obtained and combined with clinical expertise and patient values to deliver EBM. An understanding of the scientific research process and value of research evidence is critical in implementing EBM. If the goal of pharmaceutical practice and policy research is to develop an evidence base for pharmaceuticals, pharmacist services, and pharmacy systems, then the goal of EBM is to use the relevant scientific evidence to provide the highest quality patient care.

The research problem or question is the starting point for research. Similarly, asking appropriate question is the starting point for providing EBM. The components of the question should include: patient, intervention, comparator, and outcome (PICO). The relevant evidence is obtained after scouting for the evidence from various sources. The most relevant research is then critically appraised to ensure the validity and applicability of the evidence to patient care. This is often a time consuming and critical process in EBM. Just because research is published in a peer-reviewed journal, it does not mean the research is relevant or applicable to patient care.

The understanding of scientific principles is important to ensure that relevant evidence is valid and applicable. Critical appraisal of the selected research will ensure that research findings are correct (internal validity) and are applicable to the clinician's patient population (external validity). The best available and valid evidence is applied to provide patient-centered care. Medical decision making is a complex process with critical consequences; therefore, it requires "conscientious use, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[23]

IMPLEMENTATION SCIENCE

Although evidence-based practices are effective in improving quality of care, there is often an extensive delay in incorporating EBM into practices. Several factors contribute to this delay in translating research into practice, including internal factors such as time and workflow and external factors such as payments and policies. A recent systematic review classified these implementation factors into external context, organization, professional, and intervention.[24] Context refers to external environmental structural and process factors such as healthcare structure, financial incentives, market dynamics, payment, and healthcare policies. Organizational factors include institutional infrastructure, governance, work flow, culture, and institutional policies and procedures. Professionals include providers of healthcare including physicians, pharmacists, nurses, and allied healthcare members. Since most healthcare delivery involves inter-profession collaboration, there is often a delay in incorporating evidence-based care due to issues in professional roles, philosophy of care, time, and competencies. Finally, evidence-based interventions that lead to their implementation in routine practice are the ones that promote ease of use, acceptance, and extent of benefit across various settings.

The importance of implementation of EBM as a scientific enquiry has been growing due to critical need to have widespread implementation of evidence-based practices. **Implementation science** is the "scientific study of methods to promote the systematic uptake of research findings and other evidence-based practices into routine practice, and, hence, to improve the quality and effectiveness of health services."[25] Implementation science requires collaboration and teamwork to incorporate evidence-based interventions into practice. Implementation science helps to change practices and improve the quality of healthcare. Pharmacists are in an ideal position to take an active role in implementation science due to their increasing role in patient care. With the rapid expansion of

pharmacy services and increasing inter-profession collaboration of care, there is greater need for pharmacists to get involved and take the lead in implementation science to advance the profession of pharmacy.

SCIENTIFIC BASIS OF PROFESSIONAL EDUCATION

Scientific contributions are critical for pharmacy education and the profession. The evidence base and scientific innovations immensely contribute to the knowledge base for pharmacist training and advancement of the pharmacy profession in the healthcare system. Pharmacy researchers, practitioners, and educators have an important role to play to generate and translate the evidence to patient care. Pharmacist involvement is needed across the research and practice continuum, from basic research to clinical and translation research to evidence-based practice (**Figure 1-6**).

Basic and clinical researchers are vital in developing the knowledge base relevant to the pharmacy profession. Scientific breakthroughs in the basic sciences such as biology, chemistry, biochemistry, genetics, and microbiology are critical in the development of applications in biomedical sciences. The research support by the NSF and the NIH have been instrumental in transforming the basic biomedical research landscape in the United States.[26] Pharmacists can indirectly or directly contribute to basic sciences as they have a broad understanding of basic and applied sciences relevant to pharmacy practice.

Applied scientists in pharmaceutical sciences such as medicinal chemistry, pharmaceutics, and pharmacology are instrumental in developing innovative healthcare products and services. The NIH and the pharmaceutical industry have played an important role in funding the applied biomedical sciences.[26] Foundations such as American Cancer Society (ACS) and American Heart Association (AHA) are also making a difference in advancing healthcare research. Pharmaceutical scientists have made immense contributions in developing and applying biomedical knowledge to products and services. Pharmacists have made enormous contributions to applied biomedical sciences and have great potential to influence the future landscape of pharmaceutical sciences. Although advanced training such as graduate degrees or fellowships are recommended to directly participate in applied research areas, pharmacists can make a difference in applied research owing to their broad understanding of basic and clinical sciences.

Clinical research is the pathway to evaluate the safety and effectiveness of products and services. With increasing patient care responsibilities, the pharmacists' role in clinical research has evolved. The 1975 Millis Commission Report recognized the importance of clinical scientists that are well versed in pharmacotherapy and biomedical research and recommended the development of training programs for clinical scientists.[27] National organizations, such as the American Association of Colleges of Pharmacy (AACP) and the American College of Clinical Pharmacy (ACCP) followed up on these recommendations and developed educational and training agenda for clinical scientists.

In 2008, the ACCP Taskforce report on research in the PharmD curriculum detailed research content areas and competencies.[28] It required pharmacy students to 1) identify problems and research gaps, 2) design research to test hypotheses within the regulatory and ethical framework, 3) conduct analyses, 4) disseminate research findings, and 5) apply study findings to practice. The latest curriculum standards by the Accreditation Council for Pharmacy Education (ACPE) require pharmacist education and training to incorporate 1) principles of research design and methodology, 2) regulatory and ethical principles of research, 3) methods in data management and statistical analyses, 4) principles of drug literature evaluation, and 5) practice implications of research.[29] These content areas not only emphasize the drug literature evaluation component, but also principles of research design. Sound understanding of the scientific basis of evidence creation and provision of patient care is essential for pharmacists to succeed in the highly competitive healthcare arena.

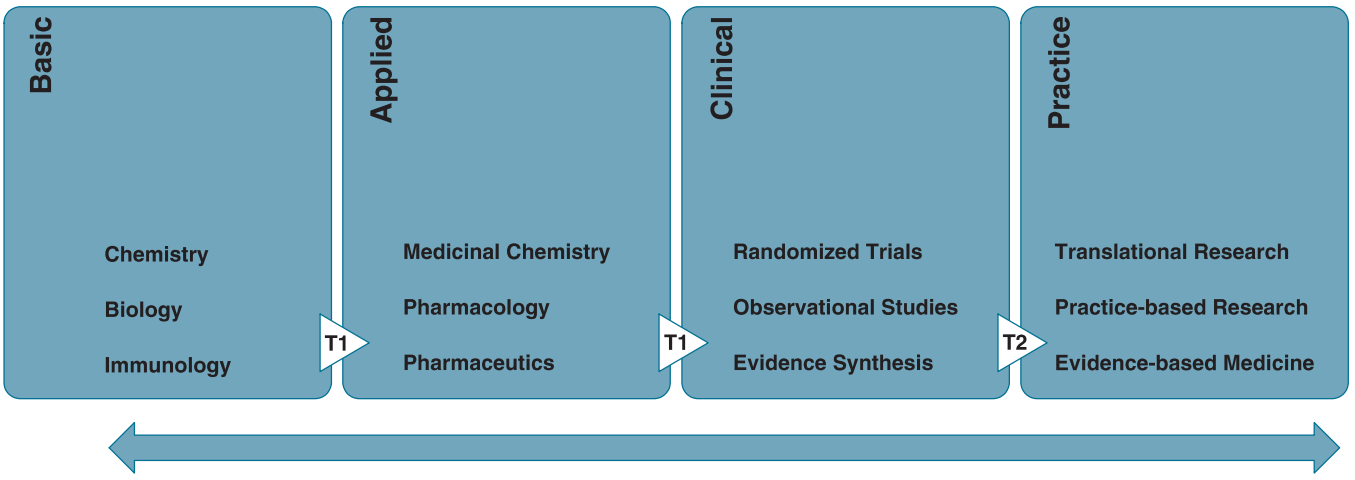

FIGURE 1-6: Research and Practice Continuum of Biomedical Sciences.