

Building upon existing evidence to shape future research endeavors

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Scholarly investigations, if not well constructed, cannot adequately answer research questions or resolve clinical dilemmas. Research design, planning, and conduct may require substantial resources. While Ralph Waldo Emerson undoubtedly reflected on endeavors beyond scholarly investigations, his premise certainly applies to pharmacy research, as we all strive to improve previous efforts. Identifying the missteps of others may facilitate planning and efficiency in carrying out subsequent investigations. The critical factors in this process include reviewing the biomedical literature to refine the research question and identifying pertinent background information to assist in perfecting one's own study design. Regardless of the nature of the research, an effective literature search, retrieval, and synthesis are critical in developing and refining study design.

Culling the literature

Proficiency in searching, procuring, and assessing the biomedical literature is vital in the course of patient care. However, these are also the same skills needed to carve out

Purpose. The identification, retrieval, and critical evaluation of biomedical literature to inform the development of future research efforts are discussed.

Summary. A literature search should be designed with the consideration of the desired scope of the information, discipline, or therapeutic area; the nature of the publication or presentation; the ease of full-text documents; and the frequency of updates. Published literature, as well as research abstracts and clinical trial registries, are good sources of information for investigators. Building upon the past efforts of others may give insight into study design techniques that are of particular value, areas in which the literature is lacking, and potential research pitfalls that should be avoided. Early research efforts are often susceptible to methodological flaws, small sample sizes, or poor reporting approaches. Reviewing the research literature can uncover these and other suboptimal study approaches. Variables that can influence study results, such as sex, age, health

status, concomitant diseases and medications, medical history, economic status, and disease severity, should be anticipated and minimized. The acronym PICO (patients, intervention, comparison, and outcomes) is commonly used to describe the integral steps of constructing a study. Alterations that may need to be made to improve the study may include broadening inclusion criteria, prolonging the length of the enrollment period, increasing sample size or number of study centers, and lengthening the follow-up period.

Conclusion. A thorough review and analysis of the literature can aid one in avoiding duplication of completed or current research projects. A survey of the research landscape can also ensure the novelty of the research question, as well as determine methods that may be adapted to meet the study design needs.

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a research plan. A literature search should be designed with the consideration of the desired scope of information, discipline, or therapeutic area; the nature of the publication or presentation; the ease of retrieval of full-text documents; and the

frequency of updates. Many products are openly accessible, but some databases require a subscription for access. Despite the extensive database access that most academic centers and health systems provide, falling into a routine and cursory literature

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The Research Fundamentals section comprises a series of articles on important topics in pharmacy research. These include valid research design, appropriate data collection and analysis, application of research findings in practice, and publication of research results. Articles in this series have been solicited and reviewed by guest editors Lee Vermeulen, M.S., and Almut Winterstein, Ph.D.

search pattern is common. Busy practitioners may be tempted to only search resources that provide full-text information rather than engage in multiple searches and retrieval steps. This may result in the omission of relevant information. Therefore, knowing where to find information, as well as the scope of information desired, is an important first step.

Original research manuscripts are commonly sought when planning a new investigation, but poster and presentation abstracts may also be useful sources of data. Not all research projects progress to full publication, perhaps because of investigator research fatigue or publication bias. A 2005 investigation revealed the potential impact of publication bias.¹ Nearly 80 studies of professional meeting abstracts, totaling more than 29,000 individual entries, were systematically reviewed for publication of full results within two years of first presentation. Abstracts with significant findings, results favoring the experimental treatment, or those associated with randomized or controlled clinical trials were published more often than investigations lacking those characteristics. A time lag was also often associated with publication of full results. Clinical trials that demonstrated statistically significant results favoring the experimental treatment were more commonly published within four to five years.² Investigations that resulted in other findings (e.g., favorable effects of control group) generally went unpublished for about six to eight years following completion. Failing

to recognize these factors may lead to conclusions that a literature gap exists, an intervention holds promise because its shortcomings have yet to be demonstrated, or other missteps. One must conduct a thorough search of many segments of professional literature to overcome these potential errors.

Biomedical research databases.

Following the identification of the scope of the information desired (e.g., published research manuscripts, abstracts of poster presentations), corresponding literature sources should be analyzed for pertinent records. Rather than scanning the volumes of primary literature (i.e., original research reports), the investigator should begin a search of the relevant information through a secondary literature review. Secondary references, or search engines, provide access to primary literature via abstract or index format, as well as many tertiary references (e.g., review articles, practice guidelines). Secondary literature is an essential and efficient source to gain a depth and breadth of information and serves as a gateway to everything from broad overviews to manuscripts of original research. Table 1 summarizes the core features of secondary databases that should be searched when preparing a research project.

MEDLINE, the primary biomedical database of the National Library of Medicine, is among the world's most prominent secondary resources. The database uses a structured, controlled vocabulary to categorize records in a hierarchical fashion. Efficient searching of MEDLINE generally necessitates an introduction to its basic structure and suggested search techniques, as described by Schrimsher and Kendrach.³ However, there are a number of other databases that should be considered as potential sources of information. An assessment of controlled clinical trials referenced in secondary databases revealed that Excerpta Medica

Database (EMBASE) yielded 85% of published trials, compared with 73% found in MEDLINE.⁴ These and other findings support the notion that multiple resources should be included to produce a more comprehensive search.

EMBASE, a fee-for-service reference that focuses on pharmacology and toxicology, is characterized as a bibliographic database that is more international in scope than MEDLINE.⁵ International Pharmaceutical Abstracts (IPA) is specific to the field of pharmacy.⁶ IPA, an original abstracting service, covers the broad scope of the profession, including clinical practice, operations, education, and legal aspects. State pharmacy journals and national pharmacy meeting abstracts are also included. Cumulative Index to Nursing and Allied Health Literature (CINAHL) is the premiere secondary database for the field of nursing, along with nearly 20 other allied health care disciplines.⁷ CINAHL, international in scope, provides a variety of information beyond clinical practice, including patient education; quality assessment within the scope of practice development; and patient care, education, and health services administration. Entries exceed the format of published journal articles, with a number of records devoted to textbooks, dissertations, software, and meeting proceedings. Allied and Complementary Medicine is a bibliographic listing of publications specific to alternative medicine and allied health care (e.g., acupuncture, homeopathy, herbal medicine). It has a deep grounding in European literature.⁸

The Cochrane Collaboration is a rich source of data. Its multiple databases are collectively referred to as the Cochrane Library.⁹ As a provider of systematic reviews of health care interventions, the nonprofit collaboration aims to assist professionals in health care decision-making based upon the best available evidence. To

Resource		Availability	Features	Scope of Content		
				Manuscripts ^a	Meeting Proceedings	Clinical Trials
AIDSinfo http://aidsinfo.nih.gov	Open access	Federally-supported content includes ongoing clinical trials	No	No	Yes	
Allied and Complementary Medicine www.bi.luk/collections/health/amed.html	Fee-for-service	Compiled by the British Library Large representation of European literature Focuses on alternatives to conventional medicine (e.g., acupuncture, herbal agents)	Conditional full-text ^b	No	No	
Biological Abstracts http://scientific.thomson.com/products/ba/	Fee-for-service	Primary focus on life sciences International coverage Pharmacy applications primarily within basic science or translational research	Conditional full-text	Available in Reports, Reviews and Meetings database component	No	
Chemical Abstracts and SciFinder www.cas.org/products/scifinder/index.html	Fee-for-service	Supported by the American Chemical Society International coverage Pharmacy applications primarily within basic science or translational research	No	Yes	No	
ClinicalTrials.gov http://clinicaltrials.gov	Open access	Registry of funded human research Developed in collaboration with FDA ^c Searchable by disease and condition, sponsor, status, or key words	No	No	Yes	
Cochrane Collaboration www.cochrane.org	Fee-for-service Abstract content freely available	Available through Wiley Interscience Includes original systematic reviews and critiques of published reviews Both clinical trials and economic assessments of health care interventions Contents also indexed in MEDLINE	Conditional full-text	Yes	No	
Computer Retrieval of Information on Scientific Projects http://crisp.cit.nih.gov	Open access	Maintained by NIH ^d Searchable database of clinical research funded by U.S. Department of Health and Human Services	No	No	Yes	
Cumulative Index to Nursing and Allied Health Literature www.cinahl.com	Fee-for-service	Premier database of nursing and 16 other allied health professions Primarily a domestic focus Practice, education, management, and quality-improvement literature	Conditional full-text, with limited full-text provided by database sponsor	Selected conference proceedings	No	

Table 1. Bibliographic Database and Clinical Trial Registries

Resource	Availability	Features	Scope of Content		
			Manuscripts ^a	Meeting Proceedings	Clinical Trials
Current Contents http://scientific/thomsonreuters.com/products/cc/	Fee-for-service	Contains tables of contents for journals and books Access to items ahead of print Users can subscribe to routine updates via e-mail	Conditional full-text	May be available as journal supplement	No
Current Controlled Trials www.controlled-trials.com/mrct	Open access	International register of clinical trials Assigns a unique number to each trial to facilitate tracking throughout trial's life cycle	None	No	Yes
Educational Resources Information Center www.eric.ed.gov	Fee-for-service	Focuses on educational literature, including higher and health professions education	Conditional full-text	Yes	No
Excerpta Medica Database www.embase.com	Fee-for-service	Electronic version of Excerpta Medica Greater focus on non-U.S. publications than MEDLINE	Conditional full-text	Yes	No
Google Scholar http://scholar.google.com/	Open access	Indexes many peer-reviewed publications, theses, and items before they go to publication Focuses on information from peer-reviewed or academic sources Not limited to biomedical topics Citation tracker feature	Full-text with some materials freely accessible	Yes	No
International Pharmaceutical Abstracts http://scientific.thomson.com/products/ipa/	Fee-for-service	Domestic and international pharmacy reports Research, practice, news, education, legal aspects	Conditional full-text	Abstracts of select pharmacy meetings (e.g., ASHP Midyear Clinical Meeting)	No
MEDLINE www.pubmed.gov/ (for PubMed)	Open access— PubMed via National Library of Medicine Fee-for-service via variety of vendors	Electronic version of Index Medicus Premiere biomedical database Structured vocabulary and corresponding hierarchy	Conditional full-text, with some materials freely accessible	No	No
National Cancer Institute Comprehensive Cancer Information www.cancer.gov	Open access	Massive clinical trial registry of ongoing and completed research protocols Includes information from ClinicalTrials.gov Highlights of American Society of Clinical Oncology Meeting Proceedings	None	Yes	Yes

Continued on next page

Table 1 (continued)

Resource	Availability	Features	Scope of Content		
			Manuscripts ^a	Meeting Proceedings	Clinical Trials
Web of Science http://scientific.thomson.com/webofknowledge	Fee-for-service	Component of Web of Knowledge database Supports basic, advanced, and cited reference searches	Full-text	Yes	No

^aPublished manuscripts of original research.

^bFull-text links may be added by libraries, subscription holders, or vendors.

^cFDA = Food and Drug Administration.

^dNIH = National Institutes of Health.

support the considerable resources required to maintain the collaboration's mission, full access to the library is a fee-for-service endeavor; however, abstract searches and browse features are freely available. The Cochrane Database of Systematic Reviews (CDSR), likely the most prominent of the library components, contains several systematic reviews of health care interventions.

Abstracts of systematic reviews that have been assessed for overall quality can be found in the Database of Abstracts of Reviews of Effects (DARE). The entries are essentially summaries and critical evaluations of original review articles that have been published in medical literature. This database bridges the gap between review articles published in journals and the completion of a Cochrane systematic review on the same topic. The reader may also find specific shortcomings of the current literature, as identified by the authors of the analyses in CDSR and DARE.

Practitioners engaging in economic evaluations might seek entries in the National Health Service Economic Evaluation Database (NHS EED). This resource contains critical appraisals of health care economic literature (e.g., cost-minimization, cost-effectiveness studies), which also includes flaws of previous research efforts.

Cochrane resources are generally considered to be the world's preeminent source of unbiased, rigorously structured, evidence-based reviews of biomedical literature. Many practitioners may not realize the depth of the content in other areas, including features that essentially represent comprehensive literature searches. A bibliography of references that includes clinical trial methods can be found in the Cochrane Methodology Register (CMR) and the Cochrane Central Register of Controlled Trials (CENTRAL). The scope of content includes journals, meeting proceedings, and books. Information eli-

gible for entry is identified through MEDLINE, EMBASE, and hand searches. While full-text information is not provided, citations allow the user to find the original publications as a mega search engine would.

Other databases. Databases that fall outside the traditional realm of use in practice settings should also be explored. Aimed at all scholarly disciplines, Google Scholar is an emerging database for pharmacist practitioners and investigators.^{10,11} This bibliographic reference lacks a structured vocabulary, which makes narrowing a search somewhat difficult. Records are retrieved by a weighting system, which is heavily influenced by the citation frequency of each entry; therefore, older literature tends to appear at the top of the search retrieval list. However, the citation tracker enables users to follow the string of authors that have cited an original work in subsequent publications. Google Scholar also seeks to include references outside the scope of MEDLINE, particularly papers, theses, and prepublication abstracts. However, the full extent to which this fairly new database covers data sources is unclear, so the user may be left wondering if a search was truly comprehensive.

Much like Google Scholar, Web of Science is a bibliographic database of original research (beyond health care) with a citation tracking feature.¹² Queries of individual author publications can be conducted, in addition to traditional subject searches.

Geared toward life sciences as a whole, Biological Abstracts contains bibliographic records of peer-reviewed articles, meeting proceedings, and other publications that may support basic science or translational research efforts.¹³ Similarly, Chemical Abstracts (available via SciFinder) provides content in chemistry, life sciences, and biomedicine, including journal articles, meeting proceedings, patents, dissertations, and web preprints.¹⁴ Pharmacists seeking

information about instruction or training may find the Educational Resources Information Center to be valuable.¹⁵ This digital library of content is sponsored by the U.S. Department of Education. It is not limited to pharmacy or health care in general but facilitates insight into approaches used by a number of disciplines. Like most secondary references, its content has expanded to include more full-text availability.

In addition to conducting a literature search, routinely perusing the literature can make one a more effective and efficient clinician and scholar. Tracking association or organization listservers is a common approach to examining the literature. Scanning journal content through electronic tables of content services is also common. Current Contents is designed to yield a searchable listing of the contents of most health care journals.¹⁶ Users can tailor their subscription to focus on journals by content. This feature is essential because over 7000 references are routinely indexed, which makes an unlimited subscription impractical. The reference's electronic alert service functions much like an automatic notification of publications within the user's predefined scope of interest, which increases the potential efficiency.

Clinical trial registries. Many online references provide insight into ongoing, proposed, or recently concluded, funded clinical trials. Reviewing these databases can help avoid duplication of ongoing research endeavors, uncover methods used in current trials, and identify potential collaborators for future research efforts. Computer Retrieval of Information on Scientific Projects is among the most prominent of these searchable registries.¹⁷ This database is maintained by the National Institutes of Health and tracks federally-funded health care investigations conducted at research institutions. A number of data fields (e.g., granting agency, topic, investigator name, institution)

can be used to create a succinct, structured query of federal research awards dating back to 1972. A less structured listing of ongoing clinical research is ClinicalTrials.gov.¹⁸ Created in response to the Food and Drug Administration Modernization Act of November 1997, the database provides updated overviews of trials, including patient enrollment criteria, general study methods, and investigator contact information. Current Controlled Trials is a global clearinghouse of clinical investigations that accumulates data from 13 trial registries worldwide, including ClinicalTrials.gov.¹⁹ Organizations or information sources focusing on specific therapeutic areas often contain clinical trial details and should be considered as sources of information. For example, pharmacists seeking information on disease-specific investigations may turn to AIDSinfo,²⁰ a searchable registry of relevant clinical trials, or the clinical trial content of the National Cancer Institute Comprehensive Cancer Information website.²¹ Several pharmaceutical manufacturers provide links to ongoing clinical trials on their own websites. A number of other countries (e.g., Australia, Japan) also have national registries of current research efforts.

Confirming the need for investigation

Gaps in the medical literature can be clear opportunities for future research efforts, but a paucity of information is not the only indicator of the need for further investigation. Bagshaw et al.²² identified the pitfalls in the assessment of acetylcysteine in the prevention of contrast-induced nephropathy. Despite the publication of more than 30 trials and meta-analyses, the exact efficacy of the antioxidant in preventing nephropathy remains unclear. The reason for this is likely related to the design of the efficacy trials as well as subsequent attempts to resolve the clinical ques-

tion via meta-analysis, which is not often used for interpreting divergent results. Clinical trials generally exhibit statistical or clinical heterogeneity, and a meta-analysis cannot successfully overcome such discordant factors.²³ However, recognizing the sources of clinical heterogeneity gives way to further investigation. For example, there may be differing patient populations, eligibility criteria, intervention protocols, co-interventions, follow-up periods, caregiver levels of experience or training, or primary outcomes that have yet to be assessed.²⁴

Identifying a need for information is inherent in the process of beginning a research endeavor. Conducting a thorough literature review should also include a scan of information outside the practice area. The potential for similar investigations being conducted outside the realm of pharmacy should be considered. For instance, residency structures and assessment methods described in the medical literature may serve as inspiration for pharmacy residency program directors who seek innovative training techniques. Pharmacists who desire to explore novel approaches to and measure the impact of staff education may look to the descriptions of their colleagues' efforts in the nursing literature.

Learning from the mistakes of others

Once literature has been retrieved, it should be analyzed for applicable content. Early research efforts are often susceptible to methodological flaws, small sample sizes, or poor reporting approaches. Reviewing the research literature can uncover these and other suboptimal study approaches. It is incumbent on an investigator to learn from the efforts of others. The appendix provides a checklist of items to consider when reviewing the research literature. Strive to identify bias and confounding variables, which may be used to

guide the study design (e.g., matching, randomization technique), implement techniques to carve out and select the patient population, and develop study instruments (e.g., scales to measure patient response, medication adherence assessments, survey questionnaires). Variables that can influence study results, whether present by chance or systematically, should be anticipated and minimized. Bias can enter into a research endeavor at any point—the literature review phase, designing an intervention, or submitting a manuscript for publication.²⁵ The ability to identify bias and its potential impact on existing work, as well as one's own work, is vital. The ability to employ methods to adjust the study design accordingly is also important.²⁶ Individuals not associated with the conduct of the study (e.g., epidemiologists) may be of great assistance in this process. In addition, the ability to identify confounders builds upon the investigator's knowledge of the therapeutic area, clinical judgment, and observation of findings in previous scholarly efforts. Confounders are characteristics that may affect the study outcome. In patient-focused research, these may include sex, age, health status, concomitant diseases and medications, medical history, economic status, and disease severity. Once identified, confounders should be minimized by stratification, matching patients with similar characteristics, or other methods.

The acronym PICO (patients, intervention, comparison, and outcomes) is commonly used to describe the integral steps of constructing a study. With each of these steps, there are numerous factors that can be improved upon:

- Patients—Define the new population of interest or determine which populations have been analyzed previously.
- Intervention—Are there differing lengths of treatment, routes of administration, or dosages that should

be considered? Are there key timing elements that have not been evaluated or data points that have yet to be gathered or assessed?

- Comparison—Differing comparator groups may be necessary, or useful.
- Outcomes—Changing the study endpoints, measurements, clinically important differences, or indirect measures should be considered.

Common areas for improvement

A number of facets of study design may be susceptible to flaws. The adage that hindsight is 20/20 certainly holds true in this setting, as some aspects are often identified during study completion. Yet, anticipating potential design drawbacks gives the researcher an opportunity to make alterations to the study plan. Investigators that set out with an unrealistic study scope may struggle with study completion, identification of true differences among the number of study measurements, or enrollment of a sufficient number of patients.

Too often the literature includes reports that fail to draw meaningful conclusions because of an inadequate sample size. Previous studies should be analyzed for enrollment rates, dropout rates, and outcome frequency. Areas in which previous investigators fell short of their goals, such as predicting the percent of patients that would complete the study or the number of patients that could be enrolled during the study's conduct, should be noted and adjusted. Alterations may include broadening inclusion criteria, prolonging the length of the enrollment period, increasing sample size or number of study centers, or lengthening the follow-up period. Any changes should be dependent on study design, outcome prevalence, and anticipated effect size. An investigator should also consider that sample size calculations should reflect primary study aims, not those of a secondary nature, yet another reason to carefully refine and construct the study's primary goals.

Failure to predict a realistic research timeline may hamper an investigator's ability to recruit a sufficient number of subjects, review an adequate number of medical records, or extract the requisite number of data points. The research team should review projects of a similar scope to shape the development of the projected timeline. Prospective study designs may need to be converted to retrospective data collection, or crossover investigations may need to be reconfigured to parallel study groups. Excessive extrapolation of data from the study sample to the entire population is a common error, particularly if analyzed subjects were not fully representative of the reference population. Patients lost to follow-up should be compared to those remaining to determine any potentially important differences. A larger number of patients with greater disease severity who fail to complete the study may lead to false conclusions of the efficacy of an intervention. However, if data are analyzed using an intent-to-treat approach, this may limit the possibility of such an outcome. A review of patient dropouts and discontinuances, if detailed in the reference research manuscript, may assist in the identification of important patient factors that should be included in future research efforts. Analyzing the characteristics of patient dropouts and exclusions can also give insight into populations that have yet to be assessed. In addition, these factors may indicate patient populations that can be expected to drop out in similar future investigations. Modifying the research design to minimize this potential would be prudent.

Conclusion

A thorough review and analysis of the literature can aid one in avoiding duplication of completed or current research projects. A survey of the research landscape can also ensure the novelty of the research question, as

well as determine methods that may be adapted to meet the study design needs.

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Appendix—Design characteristics to consider when evaluating existing literature

- Study design (e.g., parallel versus crossover, cohort versus case control, observational)
- Data collection approach (e.g., retrospective, concurrent, prospective)
- Study duration, with duration of subsequent patient follow-up
- Number of study sites and settings
- Participant eligibility criteria
- Specific details of intervention (e.g., dosage, duration, frequency)
- Relative equivalency of comparator or controls
- Use of washout phase
- Method to generate participant allocation
- Methods to blind or mask participants and investigators
- Methods to assess patient adherence
- Endpoints selected
- Corresponding measurement for each study endpoint
- Definition of exposure
- Baseline disease incidence
- Expected effect size
- Subject retention methods
- Data management for patient dropouts (e.g. intent-to-treat, per-protocol assessment)
- Ability to recruit, enroll, or maintain anticipated sample size
- Relative adherence of subjects to study intervention
- Measures to assess adverse events
- Author-identified limitations, sources of bias