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# Research: Guidelines on Conducting Research in Pharmacy (2011)

Canadian Society of Hospital Pharmacists
Société canadienne des pharmaciens d'hôpitaux

# Research: Guidelines on Conducting Research in Pharmacy

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# Research: Guidelines on Conducting Research in Pharmacy

## INTRODUCTION

This is the second edition of the guidelines on research in pharmacy practice of the Canadian Society of Hospital Pharmacists (CSHP). These guidelines were developed as a tool to assist pharmacy staff in developing and carrying out research in organized health care settings. They offer a concise overview of the steps in conducting research, which will be helpful to novice and experienced researchers alike. The approach to research presented here is general, and the information can be applied to innumerable kinds of research projects (e.g., single-centre or multicentre studies, drug usage reviews, case reports, literature reviews). The references provided in the Literature Cited section expand upon the information presented. Users of this document are also referred to the CSHP statement on research.

These guidelines were written by CSHP staff in collaboration with Society volunteers. The guidelines reflect consensus-based best practice, supported by literature sources where available.

## 1. SCOPE

These guidelines are intended as a tool to assist pharmacy staff, working individually or in groups (within a single institution or across multiple institutions), in developing and carrying out research in organized health care settings.

The guidelines outline the general steps in undertaking a research project; however, they do not provide detailed technical information on selecting the most suitable study design for the research question, determining sample size, analyzing the results, or undertaking knowledge translation and transfer. These guidelines should be used as a complement to, not a substitute for, the policies and procedures of the organization under whose auspices the research is undertaken.

## 2. GLOSSARY OF TERMS, ABBREVIATIONS, AND SYMBOLS

The following definitions apply for terms used in these guidelines. They may have different meanings in other contexts.

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| **A priori** | Latin for "in advance"; used to describe a research hypothesis, set of conditions, or method of analysis that is firmly decided before a study is initiated. |
| **Applied research** | Research that is conducted to answer a specific question, with the intention of a direct or immediate application to practice (e.g., determining the effect of prescribing by pharmacists in an intensive care unit) (compare "Basic research"). |
| **Basic research** | Research that is conducted purely for the purpose of answering a question, without the intention of a direct or immediate application to practice; results are typically not generalizable to the general population (e.g., determining a drug's mechanism of action) (compare "Applied research"). |
| **Biomedical research** | "Research with the goal of understanding normal and abnormal human functioning, at the molecular, cellular, organ system and whole body levels, including development of tools and techniques to be applied for this purpose; developing new therapies or devices that improve health or the quality of life of individuals, up to the point where they are tested on human subjects. Studies on human subjects that do not have a diagnostic or therapeutic orientation."[1] |
| **Case-control study** | A type of observational study in which an outcome is identified, with participants being classified according to those with and those without the outcome, and participants are then compared to determine how many originally possessed the exposure under study and whether the proportion of those exposed differs between people with the outcome and those without the outcome. |
| **Clinical equipoise** | "The existence of a genuine uncertainty on the part of the relevant expert community about what therapy or therapies are most effective for a given condition."[2] |
| **Clinical research** | "Research with the goal of improving the diagnosis, and treatment (including rehabilitation and palliation), of disease and injury; and improving the health and quality of life of individuals as they pass through normal life stages. Research on, or for the treatment of, patients."[1] |
| **Clinical significance** | "The clinical significance of a treatment refers to its ability to meet standards of efficacy set by consumers, clinicians, and researchers."[3]<br><br>"Clinical significance goes beyond statistical significance to identify whether the statistically significant difference is large enough to have implications for patient care."[4] |
| **Clinical trial** | See "Experimental study". |

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| **Cohort study** | A type of observational study in which a group is identified as having or not having the exposure under study and is then followed through time (concurrently or nonconcurrently) to determine the outcome under natural or test conditions. |
| **Confidence interval** | A statistical indicator of precision, consisting of a range of values for a specified variable calculated such that the range has a known probability of including the true value of the variable (e.g., a 95% confidence interval is the range within which the true value of the variable will fall in 95% of replications).[5,6] |
| **Confounding variable** | A variable other than the variable that is being tested that might influence the outcome of the study and thus confuse the study results, leading to an erroneous conclusion. A confounding variable is related to the exposure of interest and is independently associated with the outcome of interest, without lying on the causal pathway between exposure and outcome. |
| **Continuous data** | Data for which there are an unlimited number of equally spaced categories, making possible a continuum of values. |
| **Control group** | A group that is used for comparison with the study group. |
| **Cross-sectional study** | A type of observational study in which a population is evaluated at one point in time or over a specified time interval. Can be used only to evaluate association (not causation). |
| **Data and safety monitoring board (DSMB)** | "An independent advisory committee who review accumulated safety and efficacy data in a clinical trial and advise the principal investigator and/or the trial steering committee on the future management of the trial."[1] |
| **Dependent variable** | A variable that changes in response to the intervention or the independent variable. Dependent variables are used to assess outcomes in a research study (compare "Independent variable"). |
| **Descriptive research** | Observations not driven by a specific hypothesis. May consist of a case report, a case series, or a description of a population (including evaluation of drug utilization). Also known as a descriptive study. |
| **Descriptive statistics** | Statistics that are used to summarize and describe the data collected (compare "Inferential statistics"). |
| **Directional hypothesis** | A hypothesis that anticipates the type of relationship between variables; expressed in general terms as "when this, also that". |
| **Exclusion criteria** | Criteria used to define who is ineligible to participate in a study (compare "Inclusion criteria"). |
| **Experimental study** | A study in which participants are assigned to a study group or a control group before the study conditions are imposed. Also known as a clinical trial (compare "Observational study"). |
| **External validity** | The extent to which the study results can be generalized to certain populations, settings, treatment variables, and measurement variables.[7] Also known as generalizability (compare "Internal validity"). |
| **Feasibility** | Characteristic of a study indicating whether the variables that have been defined in the study objectives can be measured. |

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| **Health services research** | "Research with the goal of improving the efficiency and effectiveness of health professionals and the health care system, through changes to practice and policy. Health services research is a multidisciplinary field of scientific investigation that studies how social factors, financing systems, organizational structures and processes, health technologies, and personal behaviours affect access to health care, the quality and cost of health care, and, ultimately, [the public's] health and well-being."[1]<br><br>This type of research includes topics related to pharmacy practice such as safe medication practises, seamless care, pharmacoeconomics, pharmacoepidemiology, and quality management. |
| **Hypothesis** | An unproved theory, question, idea, or supposition put forward to provide a basis for further investigation or argument. |
| **Hypothesis-driven research** | Research that requires a priori establishment of a hypothesis, collection of data, and analysis of the data with inferential or descriptive statistics. Hypothesis-driven research can be further subdivided into basic ("bench-top") and applied research (defined above). |
| **Inclusion criteria** | Criteria used to define who is eligible to participate in a study (compare "Exclusion criteria"). |
| **Independent variable** | The intervention variable that is proposed to alter the dependent (outcome) variable (compare "Dependent variable"). |
| **Inferential statistics** | Statistics that are used to draw inferences or conclusions from data (compare "Descriptive statistics"). |
| **Institutional review boards (IRBs)** | Bodies "set up by research institutions to ensure the protection of rights and welfare of human research subjects participating in research conducted under their auspices. IRBs make an independent determination to approve, require modifications in, or disapprove research protocols based on whether human subjects are adequately protected, as required by federal regulations and local institutional policy."[8] |
| **Intent-to-treat** | "Analyzing participant outcomes according to the group to which they were randomized, even if they did not receive the planned intervention [or remain in the study until its end]. This principle preserves the power of randomization, thus ensuring that important known and unknown factors that influence outcomes are likely to be equally distributed across comparison groups."[9] |
| **Internal validity** | The extent to which a study measures what it set out to measure. Answers the question of whether the experimental treatments that were applied made a difference in the research (compare "External validity").[7] |
| **Interobserver variation** | The variation in results or outcomes arising as a result of differences in perceptions or in collection and interpretation of data by different observers in the study (compare "Intraobserver variation"). |
| **Intraobserver variation** | The variation in results or outcomes arising as a result of differences in perceptions or in collection or interpretation of data by the same individual |

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| | (i.e., an individual data collector) at different times in the study (compare "Interobserver variation"). |
| **Knowledge translation** | "A dynamic and iterative process that includes synthesis, dissemination, exchange and ethically-sound application of knowledge to improve the health of [the public], provide more effective health services and products, and strengthen the health care system. This process takes place within a complex system of interactions between researchers and knowledge users which may vary in intensity, complexity and level of engagement depending on the nature of the research and the findings as well as the needs of the particular knowledge user."[10] |
| **Literature review** | Analytical or non-analytical summation of published knowledge about a specific subject. Literature reviews do not involve the collection of original data or observations, but they may involve novel analysis of aggregated data. |
| **Meta-analysis** | The process of combining results of previous research studies on a specified topic to generate a statistical summary of overall effect size. |
| **Minimal important difference** | "The smallest difference in score in the outcome of interest that informed patients or informed proxies perceive as important, either beneficial or harmful, and that would lead the patient or clinician to consider a change in the management."[11] |
| **Narrative review** | A literature review addressing a clinical question of interest, without a systematic approach to evaluating the literature of interest. Narrative reviews are more prone to bias than are systematic reviews. Because they simply report on previously published findings, without imposing a critical, predesigned framework of appraisal or statistical analysis, narrative reviews are not generally considered a form of research. |
| **Nominal data** | Data that can be classified into a discrete number of categories that cannot be ranked or numbered (e.g., patients who lived or died, interventions deemed appropriate or inappropriate) (compare "Ordinal data"). |
| **Null hypothesis** | See "Null statement". |
| **Null statement** | A statement of no significant relationship between or among the variables of interest (e.g., "The efficacy of Drug A does not differ from the efficacy of Drug B"). Also known as "null hypothesis". |
| **Observational analytic study** | A study in which the exposure of interest occurs spontaneously, not as the result of action by an investigator (compare "Experimental study"). Can be categorised into these types of studies: "Case-control study", "Cohort study, and Cross-sectional study. |
| **Ordinal data** | Data that can be classified into ordered categories, although the interval between categories may not be uniform (e.g., a visual analogue scale for pain). |
| **Outcome** | "Outcomes are events, variables, or experiences that are measured because it is believed that they may be influenced by the intervention."[12] |
| **Outcome measure(s)** | Measurements of the results achieved. (See Primary outcome and Secondary outcome). |

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| **PICO framework** | Framework for design of a research question so that it provides specific information about the patient (or problem), intervention, comparison interventions, and outcome.[13] |
| **Point estimate** | "The results of a study which represent the best estimates of the treatment" (e.g., relative risk or odds ratio).[9] |
| **Power** | Statistical term describing a study's ability to detect a statistically significant difference or association if one truly exists. |
| **Primary outcome** | "The main outcome(s) used to determine the effects of the intervention(s). Most trials should have only one primary outcome."[12] (Compare "Secondary outcome measure".) |
| **Prospective study** | A study that identifies a group of participants at the outset and then follows the group forward in time to look for the outcome of interest (compare "Retrospective study"). |
| **Randomization** | Method of selection of study participants whereby each individual or entity in the target study population has an equal opportunity of being included in any arm of the study. Also known as "random assignment". |
| **Research** | "An undertaking intended to extend knowledge through a disciplined inquiry or systematic investigation."[2]<br><br>Healthcare-related research is typically categorized into the following areas of study,[1] all of which are applicable to pharmacy practice: biomedical research; clinical research; health services research; and social, cultural, environmental, and population health research (see individual definitions).<br><br>The term "research" can be used to describe many endeavours in pharmacy practice, including systematic reviews, descriptive studies, and hypothesis-driven research (see individual definitions). |
| **Research integrity** | "The coherent and consistent application of values and principles essential to encouraging and achieving excellence in the search for, and dissemination of knowledge. These values include honesty, fairness, trust, accountability, and openness."[14] |
| **Retrospective study** | A study that uses previously recorded information about events that occurred in the past to assemble data about patients, follow-up, and outcomes (compare "Prospective study"). |
| **Sample** | A component group within a larger group or population (i.e. "Target population"). The sample is used in conducting research, and conclusions are drawn from the results as if the research had been performed using the larger group. |
| **Secondary outcome** | An outcome that is of secondary interest or that is measured at time points of secondary interest. It may involve the same event, variable, or experience as those of primary interest; it may also be measured at time points other than that of the primary outcome.[12] (Compare "Primary outcome.") |
| **Selection bias** | An error due to systematic differences in characteristics between those who take part in a study and those who do not.[15] |

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| **"Shall"** | A mandatory requirement. |
| **"Should"** | A recommendation, something that is advised but not mandatory. |
| **Social, cultural, environmental and population health research** | "Research with the goal of improving the health of the … population, or of defined sub-populations, through a better understanding of the ways in which social, cultural, environmental, occupational and economic factors determine health status."[1] |
| **Statistical significance** | A measure of "how likely [it is] that any apparent differences in outcome between treatment and control groups are real and not due to chance."[16] |
| **Systematic review** | A literature review which provides a comprehensive, critical assessment of the available published data on a specific subject to address a research question. It includes the use of inclusion and exclusion criteria for evidence to be considered, a detailed, comprehensive search strategy for identifying literature, and a priori rules for combining research results. It may or may not include meta-analysis to produce an overall point estimate. |
| **Target population** | The population about which we wish to draw conclusions.[17] (See "Sample".) |
| **Type I error** | The error that occurs when data from a sample indicates that there is a statistically significant difference or association, even though a true difference or association is not present in the population. |
| **Type II error** | The error that occurs when data from a sample indicates that there is no statistically significant difference or association, even though a difference or association exists in the population. |
| **Uncertainty principle** | In clinical research, a construct based on the notion that there should be genuine uncertainty at the beginning of a randomized clinical trial regarding which arm of the trial may prove to be superior, after taking into account the risks and benefits of the treatments under study.[18,19] Such uncertainty may exist at the level of the community, the individual clinician, or the patient.[19] |
| **Variable** | Any characteristic that can be classified or measured. (See Confounding variable, Dependent variable, and Independent variable.) |
| **Well-built clinical question** | A question that seeks specific knowledge about the diagnosis or clinical management of a patient or problem. Such questions typically use the "PICO framework".[13] |

# 3. RESEARCH TEAM

The principal investigator(s) should create a team with sufficient experience and knowledge to be responsible for all aspects of the research plan. The roles and responsibilities of each member of the team should be defined early in the project. If the original team does not possess expertise in a particular area, additional individuals should be consulted as needed. For example, consultation with a statistician may be helpful in preparing a data analysis plan.

Anyone conducting research shall follow the Fundamental Principles of Research Integrity as set out by the Council of Canadian Academies.[14]

## 3.1. Responsibilities of the Principal Investigator

The principal investigator has ultimate responsibility for the research. This includes the following aspects of the research project:

a) the assembling the group of people who will undertake the research, ideally a multidisciplinary group representing diverse perspectives, with the required skills and expertise to complete the work, including a member who is knowledgeable about and experienced in study design and biostatistics.[20]
b) overseeing the work of personnel involved in the project;[21]
c) hiring personnel involved in the project,[21] as needed;
d) serving as the point of contact for all communication,[20] or appointing a delegate;
e) ensuring the research activity is not started until the protocol is approved by the appropriate IRB and other stakeholders;
f) overseeing all project management tasks;[20,21]
g) directing all research activities, according to the project timeline and following the research activities approved by the IRB;[20]
h) involving the IRB and other researchers and stakeholders as needed;[20]
i) taking steps to prevent problems from arising and managing emergent problems as they arise;[20]
j) ensuring appropriate documentation to provide a clear record of the activities undertaken, including any critical decisions, as well as the rationale behind those decisions and their outcomes;[20]
k) managing all financial aspects of the project, including managing any grants;[21]
l) ensuring that the financial records account for all expenses associated with the project;
m) ensuring that costs of the research project are funded;
n) determining how the data will be collected and analyzed;
o) retaining all records arising from the research for the required period of time (which will be determined by the type of records, the type of study, and the jurisdiction in which the research is conducted);
p) ensuring that the research is conducted ethically; and
q) developing and implementing an effective knowledge translation plan that will reach all major stakeholders, for dissemination of study results.

## 3.2. Involvement of Key Stakeholders

The research team or its representative (e.g., principal investigator) should collaborate with key stakeholders, including administrators and other decision-makers in the institution where the research will take place, and obtain their support for the project's objectives and research plan.[21,22,23] The project's goals shall align with those of the institution.[22] Benefits to the stakeholders should outweigh the costs and potential risks, and the principal investigator should be prepared to acquire and present baseline data to demonstrate this net benefit.[23]

## 3.3 Support for New Investigators

Any new investigator (i.e., novice researcher) should have a mentor or supervisor who is interested in the project and can help to guide the research.[20]

## 3.4 Requirement of Training In Research Ethics

Each member of the research team shall have a working knowledge in the following topics related to research ethics:

a) ethical principles and philosophical presupposition (e.g., clinical equipoise, uncertainty principle);
b) misconduct and fraud (types, implications, preventive measures);[24]
c) criteria for authorship;
d) conflicts of interest;[24]
e) data management;[24]
f) ethical guidelines for research;
g) good clinical practice;
h) institutional review boards (IRBs) (ethics committees);[24]
i) legislation governing research;[24] and
j) reporting results.

Initial training in research ethics should be supplemented by lifelong formal learning sessions and the institution's organizational culture.[24]

# 4. THE RESEARCH QUESTION

Before the study protocol is developed, the principal investigator(s) should formulate a starting research question. The question should inform the methods and the data analysis and should promote knowledge translation.[25]

Since research remains incomplete until the results have been disseminated, researchers should begin their work with the end publication in mind. They should endeavour to understand and apply the reporting guidelines that are relevant to the type of study undertaken (e.g., randomized controlled trial, observational study).

As described below, a number of steps are required to formulate a suitable research question from an initial idea.

## 4.1 Defining the Problem

Every research project shall be based on a well-defined problem. An idea for a research project usually emerges from a perceived problem for which there is no clear solution. Defining the problem enables formulation of a suitable research question for resolving the problem.

The following situations are examples of sources of research ideas:

a) practice situations and case studies;[22]
b) discussions with colleagues;
c) unclear benefit associated with treatment;
d) unclear harm associated with treatment;
e) lack of understanding as to why or how something has occurred;
f) observation of an unexpected occurrence or phenomenon;[22]
g) lack of evidence to support recent advances in an area of practice;
h) comparison among practice alternatives;
i) unresolved drug information questions;
j) lack of a clear answer (to a specific question) from the existing literature; and
k) review of policies, procedures, and programs.[22]

Building on background knowledge, the researcher should search the literature to determine if the problem has already been addressed. In keeping with the Declaration of Helsinki,[26] it is unethical to ask people to participate in research if the problem has already been adequately addressed.[27]

## 4.2 Developing a Research Question

The researcher should use the PICO framework to develop a comprehensive research question. A properly defined research question is the starting point for a thorough literature review and should have the following attributes.

a) It is specific and unambiguous,[20] and narrows down what the researcher wants to know.
b) It reflects a realistic research idea.[20]
c) It can be answered using ethical methods.[25]
d) It specifies the patient or population of study, the intervention or exposure of interest, the comparison or alternative intervention or exposure, and the outcome or values to be evaluated.[9]
e) It should be informed by the researcher's background and foreground knowledge, which may include but is not limited to his or her clinical experiences, knowledge, expert opinion.
f) It is carefully developed and sets the stage for an efficient and effective search of the literature to identify and retrieve the best evidence. An effective literature search uses the components of a) patient intervention and b) outcome for the questions, and it provides the resources to support evidence-based practice.

The research question should address one or several aspects of the problem, but care should be taken to avoid tackling too many questions in one study. A useful rule of thumb is to develop one main question (the primary objective) along with a couple of smaller questions (secondary objectives) to summarize what the research team seeks to know about the problem.

## 4.3 Reviewing Existing Evidence

Existing evidence related to the research question shall be reviewed to help inform the research plan.

This review should serve the following functions:

a) help the researcher to become more familiar with the research topic;
b) identify study methods that have been used in previous work addressing the research topic;
c) summarize current information about the topic;
d) identify gaps in existing information about the topic; and
e) identify possible collaborators.[28]

### 4.3.1 Conducting a Comprehensive Literature Search

The researcher should conduct a thorough review of the literature by examining primary, secondary and tertiary resources, and then identify and review original research manuscripts, poster abstracts, and presentations. A health research librarian should be consulted for information on how to properly search the medical literature.

Depending on the research topic, the following sources could be explored:

a) health sciences libraries;
b) local drug information centre;
c) databases such as MEDLINE (or Index Medicus), Embase, SCOPUS, Current Contents, Science Citation Index, DIALOGUE to search International Pharmaceutical Abstracts, and CINAHL (Cumulative Index to Nursing and Allied Health Literature);
d) other online sources or search engines (e.g., Google Scholar) accessible via the Internet; and
f) local libraries.

Journals and other resources outside the researcher's immediate practice area but relevant to the topic should also be reviewed.[28]

Acknowledging that different sources of information will have varying features, the search for evidence should be designed taking the following into consideration:[28]

a) the degree of information to be sought (e.g., published research, abstracts, case studies);

b) the applicability of the information relevant to the area of investigation;
c) the ability to access the full text of articles and documents; and
d) the frequency at which relevant literature is updated.

If the researcher is unable to identify major journals in the field, he or she should review the most recent 6 months of publications from at least 3 of the journals with the largest number of citations relevant to the research question.

The references cited in articles pertinent to the research topic should be reviewed to identify any sources relevant to the research topic that have been missed.

The researcher should consider the following additional sources of evidence:

a) experts in the field;
b) attendance at conferences dealing with topics relating to the research question; and
c) the drug company whose product may be evaluated in the research.

### 4.3.2 Critically Appraising the Evidence

All evidence shall be critically appraised to assess the current state of knowledge.

The researcher should analyze the studies for enrolment and dropout rates, statistical power, and frequency of outcomes.[26] The researcher should also identify gaps in knowledge or incorrectly drawn conclusions, which may serve as a rationale for further investigation.[28] The attributes of successful and unsuccessful research plans should be noted to inform development of a feasible research plan and to help design a study that will control for bias, confounding variables, and effect modifiers.[28]

**Note:** For additional information on how to critically appraise the medical literature, refer to Users' Guides to the Medical Literature: A Manual for Evidence-Based Clinical Practice.[9]

## 4.4 Refining the Research Question

If the literature search confirms that current information is insufficient to address the clinical question or situation, the researcher should refine the research question to address the knowledge gap.

## 4.5 Formulating the Hypothesis

By definition, hypothesis-driven research requires the formulation of a hypothesis. The hypothesis should express the research question in a testable form and should predict the nature of the answer.

The hypothesis can be written in a number of formats (e.g., null statement, directional hypothesis). The way in which the hypothesis is stated will influence the choice of statistical analysis. By predicting the outcome, the hypothesis creates a bridge between the theoretical aspects of the research question and the research process through which the research will attempt to answer the question.

It is good practice to limit the number of hypotheses to no more than 3 and to provide the rationale for selecting each hypothesis.[22] Similarly, it is recommended that the assumptions associated with each hypothesis be explicitly acknowledged, since this information can help to inform a sound research plan.[22]

## 4.6 Defining Outcome Measures

Appropriate outcome measures should be identified and defined before the study begins. The outcome measures shall be precise, complete, and appropriate to the study aims and study type.

Care should be taken to avoid specifying several *primary* outcomes. The existence of multiple primary outcomes can result in problems of interpretation associated with the multiplicity of analyses.[27] Multiple primary outcomes also complicate

calculation of the appropriate sample size. To avoid using multiple primary outcomes the investigator may specify secondary outcomes to be evaluated in the study. (These secondary outcomes assist only in generating hypotheses for future research since the necessary sample size calculation is based on the primary outcome only.)

The outcome measures should be relevant to patients, healthcare providers, administrators, and other stakeholders and should refer to both positive and negative outcomes.[23] Variables to be measured as part of the research project should be selected with consideration of associated costs and the need for the sensitivity or specificity of that particular measure.[33]

The outcome measures chosen shall be measureable throughout the study period and shall be directly related to the study's primary and secondary research questions. Consideration should be given to selecting measures that reflect economic, clinical, and humanistic outcomes of the intervention.

Common outcomes of interest in clinical studies include, but are not limited to, the following:[34]

a) survival;
b) incidence of disease;
c) complication or specific adverse event of the disease or treatment;
d) effect on particular symptoms;
e) laboratory measurement;
f) other clinical findings; or
g) cost and ease of administering the intervention.

Outcomes of interest in health services research include, but are not limited to, the following:

a) clinical markers of disease;
b) satisfaction (e.g., of the patient, of staff);
c) adherence (e.g., to prescribed therapy, to published guidelines);
d) health status;
e) quality of life;
f) hospitalization (e.g., admission rates, length of stay);
g) medication errors (e.g., rates and severity);
h) lifestyle (e.g., smoking, exercise, alcohol consumption);
i) productivity; and
j) cost-effectiveness and other economic outcomes.

For each primary and secondary outcome the researcher should determine the metric or method used to measure the outcome and the point(s) in time when the measurement will be used.[11]

## 5. STUDY DESIGN

The design of a study has a substantial effect on its internal and external validity. Therefore, every study should be designed using a systematic process to ensure that the questions posed are appropriately addressed and investigated.

The design of the study and the rationale for that design should be documented for future reporting purposes.

The research team should be aware of relevant legislation and administrative policies and procedures governing research activities, as they may affect options for study design.

The project management plan for the study should include mechanisms to track and manage the key steps of the project.[20] The plan should be accessible to all members of the research team and should be updated and discussed at regular project meetings.[20]

### 5.1 Identifying the Study Design

A wide variety of study designs are available, including descriptive (surveys and qualitative) studies and analytical (experimental and observational analytical) studies.[29] The choice of appropriate study design should be based on the study hypothesis. Some study designs have disadvantages that may make it difficult to achieve the aims of the particular study. The research team

should review the methods used in similar studies identified during the literature review and should confer with persons working in the practice area for guidance on choice of study design.[20]

## 5.2 Refining the Outcome Measures

The outcome measures should be reviewed and revised as needed, considering the type of study design and maintaining the integrity of the original hypothesis.

## 5.3 Selecting the Study Sample

The study sample shall be representative of the target population which is relevant to the research question. The method for deriving the study sample (i.e. sample size and recruitment criteria) from the population of interest should be carefully planned, clearly defined, and well documented.[9]

### 5.3.1 Establishing Inclusion and Exclusion Criteria

Appropriate inclusion and exclusion criteria should be established without compromising the feasibility of recruiting participants.[23]

Barriers to participation in a study should be anticipated, identified, and reduced whenever possible.[23]

If the researcher chooses an experimental (rather than observational) study design, he or she should endeavour to ensure that the treatment and control groups are as nearly identical as possible in all respects except exposure to the intervention under study. This is accomplished through effective randomization, e.g., by assignment to groups on the basis of a random numbers table or a computer-generated randomization program.

Selection bias should be minimized through a systematic recruitment process.[23]

### 5.3.2 Calculating the Sample Size and Power

There shall be an a priori calculation of sample size and power, based on study design and the expected effect on the primary outcome of interest, such that type I and type II errors are kept within acceptable limits. More specifically, the study should have sufficient statistical power to ensure that a meaningful, minimal important difference can be observed between groups, taking into consideration the differences between statistical significance and clinical significance. The measure of clinical significance varies depending on the outcome and population being studied.

## 5.4 Determining the Research Plan and Methods

The research plan (protocol) should be well organized and should be broken down into key measurable steps.[20] The plan should include appropriate and reasonable timeframes for accomplishing the various tasks.[20]

The methods used within the plan shall be appropriate to the study type and shall be described, in writing, in sufficient detail to permit another researcher or research team to reproduce the study.

The research plan should incorporate approaches to avoid pitfalls gleaned from the studies identified in the literature review.[28]

### 5.4.1 Detailing the Methods

The methods should provide answers to the questions Who? What? When? Where? and How?[30]

a) Who will participate in the study? Who will constitute each study group? Who will collect the data and carry out other activities related to the research project?

b) What constitutes the dependent variable (or the anticipated outcome)?
c) When will each component of the study commence? When will study procedures be carried out (e.g., "Blood will be taken at time X in relation to administration of the drug")?
d) Where will the study population be obtained or recruited? Where will the study procedures be conducted?
e) How will the study be carried out (e.g., describe the documentation of blinding procedures)?

The research team should anticipate potential drawbacks and limitations and adjust the methods to minimize the effects of any such limitations.[20,28] The team should review the methods used in previous studies, identify flaws in study design and implementation, and develop a plan to address these flaws.[20]

Interobserver and intraobserver variation shall be minimized or eliminated, where applicable. Any assumptions made in developing the methods should be specified. It is good practice for investigators to recognize and understand the biases that can affect the internal and external validity and interpretation of their research.[31] Investigators shall strive to control bias when designing their study and when analyzing its results.[31]

### 5.4.2 Developing a Training Plan to Support the Research

An a priori standardized training protocol should be developed for the research project to minimize observer bias.[32] The training should address the collection of data, provision of the intervention, and assessment of endpoint(s).

The researcher should train more people than will be required, in case one or more providers drop out of the study.[32] The training plan should also include an allowance for periodic retraining in case of poor adherence to the established research protocol.[32] The research plan should incorporate quality control processes (both ongoing and episodic), including plans to monitor adherence to the study protocol.[20, 32] Consideration should be given to developing approaches to quality control that are not resource-intensive (such as process-evaluation forms or checklists[23]).

### 5.4.3 Defining the End of the Study

Rules and procedures for early termination of the study and for defining the end of the data collection period should be determined in advance, before the proposal is submitted for approval and implementation.

## 5.5 Identifying Other Data to Be Collected

The following types of information should be gathered during the course of the study:

a) number of subjects screened versus enrolled;
b) evidence demonstrating the level of conformity with inclusion and exclusion criteria;
c) evidence that reflects the internal validity of the intervention, such as intervention completion rate, consistency of intervention delivery among providers, and drop-out rates;[23]
d) data measuring the effect of the intervention or exposure on all end points;
e) evidence demonstrating the comparability of study groups (if there is more than one group) with respect to characteristics other than the dependent variable; and
f) in the case of an experimental study design, evidence that demonstrates the effectiveness of blinding measures.

Only information necessary to answer the research question should be collected. Data that are of limited interest but minimal value to the planned analyses should not be collected, as such data-gathering increases costs and may actually reduce the response rate.[35] Any personal and health

information about subjects shall be collected in a manner consistent with privacy legislation.

## 5.6 Describing the Data Analysis

The methods for data analysis, including planned subgroup analyses, shall be explicitly established before initiation of the study.

There are many ways to analyze experimental data. The specific purpose (e.g., description, analysis of differences, analysis of associations) of the data analysis shall be determined before the methods of analysis are defined. Researchers should be familiar with the principles of statistical analysis for the planned study.[35]

The method of analysis shall be depend on the number and type of data (variables) collected (e.g., nominal, ordinal, continuous data), and if each variable being analyzed is dependent or independent.[36]

The possibility of confounding within the study should be assessed, and if possible, adjusted for within the statistical analysis.

Consultation with a statistician is highly recommended.

**Note:** *See the Literature Cited section and Appendix A to these Guidelines for additional sources of information on statistical methods.*

## 5.7 Planning Data Management

The data management plan should list the data elements to be collected; determine systems for entering, storing, and analyzing the data; and outline processes for ensuring the quality and security of the data.[20] Processes for collecting and storing the data shall adhere with established measures to protect the privacy of study participants and the confidentiality of their data.[20] All original data collected for research purposes shall be stored in a secure location for a minimum of 7 years, or longer as defined by relevant legislation.

## 5.8 Addressing Potential Pitfalls

Potential barriers and facilitators should be identified as early as possible in planning the research.

Researchers should be aware of the following pitfalls in conducting research:

a) failure to secure commitment to the study from front-line personnel;[18]
b) failure to apply the uncertainty principle;[18]
c) failure to understand the determinants of the confidence interval and failure to employ techniques to increase the confidence of the study results by underestimating the ability to recruit participants or overestimating the effectiveness of treatments;[37]
d) failure to obtain adequate funding;
e) failure to accurately estimate the time required to perform the study;
f) failure to account for losses to follow-up or drop-outs; and
g) poor adherence with data-collection procedures and poor quality of data.

# 6. INSTITUTIONAL SUPPORT AND ETHICS APPROVAL

The research team shall obtain approval for the research before the study is initiated.

The research team shall seek administrative approval from the institutional location where the study will be conducted (e.g., hospital ward, clinic, intensive care unit). Signed approval should be obtained from any departments that will be affected by the research (e.g., nursing, laboratory medicine) as established in the approved research plan.

If the research is to involve collaboration with other institutions or organizations, the research team shall

also obtain approval from those bodies before undertaking the study.

## 6.1 Research Proposal

The research proposal should summarize the current status of knowledge on the proposed topic, identifying any gaps in the literature. Research questions and aims or objectives related to the work to be done in the course of the research should inform the scope of the proposed research.[20]

### 6.1.1 Purpose of the Proposal

The proposal shall clearly state why the study is needed, including reasons why it should be conducted at this particular time and providing details of how the research will be performed.

The proposed project shall align with the organization's goals and be supported within the organization, and completion of the work within a reasonable timeframe should be feasible.[22]

### 6.1.2 Content of the Proposal

The proposal should address the following elements of the planned research:

a) background information supporting the need for the research;
b) all aspects of the well-built clinical question (according to the PICO framework);
c) study objectives;
d) study hypotheses;
e) methods by which the research will be conducted;
f) primary and secondary outcome measurement(s);
g) methods by which the data will be analyzed;
h) methods of knowledge translation and knowledge transfer;
i) potential significance of the research;
j) benefits expected to arise from the research;
k) feasibility of the proposed research; and
l) timeline for the proposed research.

The proposal shall describe the significance and relevance of the proposed research to pharmacy practice, as well as its significance to a particular setting or a specified patient population. The significance of the research may be indicated by its potential to generate new knowledge, to refine or validate current knowledge, or to influence practice and health outcomes. The proposal should include a complete description of each specific objective, including detail about how each outcome will be measured.[21]

The proposal should expand on any elements that will attest to the principal investigator's ability to carry out the proposed research (e.g., personal expertise, availability of facilities or equipment, expertise of co-investigators).

## 6.2 Ethics Approval

Before initiating any study involving animal or human subjects, the principal investigator(s) shall request ethics approval from the local animal care committee or IRB. The approval shall be received in writing before the study can begin.[2,38]

If the research is to be conducted in collaboration with one or more other organizations, the research team shall also obtain ethics approval from the animal care committee or IRB of the other organizations before the study begins.

The principal investigator(s) should consider meeting with a representative of the IRB to learn about the processes in obtaining ethics approval, with a specific focus on their research project.[20] In particular, the investigator shall hold such a discussion with an IRB representative if there is any doubt about the type of project or if the investigator believes it qualifies for exemption from IRB review or expedited IRB review.[38] If the IRB representative confirms that the proposed research qualifies for exemption from IRB review, the investigator should procure written confirmation of the exemption.

A submission to the IRB should fulfill the following requirements:

a) be relevant to the specific objectives of the proposed research;[38]
b) provide a complete, detailed, and understandable plan and justification for the proposed research;[38]
c) be easily understandable and accessible to both scientist and nonscientist members of the IRB;[38]
d) include a description of how the research team will address any specific ethical concerns;[38] and
e) include full disclosure of conflicts of interest of members of the research team.[25]

The principal investigator(s) should expect to receive written notice from the IRB regardless of whether the IRB approves or disapproves the research or requests further information or changes before making a final decision.[38] If the IRB disapproves the research, the investigator(s) should follow up with the IRB to discuss the reasons for the decision.[38] If changes to the proposal or more information are needed, communication in this regard by the principal investigator(s) should be prompt and thorough to avoid any further delays.[38]

Note: See the Tri Council Policy Statement, Ethical Conduct for Research Involving Humans (2010).

## 6.3 Key Personnel in the Study Institution

The principal investigator(s) should present the results of the literature review, along with the research question and objectives of the study, to researchers and clinicians experienced in the field of study.[20] This step may help the principal investigator(s) to gain support for the project as well as advice regarding the proposed methods. Leaders in pharmacy, along with leaders in universities and residency programs, should consider developing organized forums to assist new researchers in obtaining feedback on each step of their research plans, to help ensure that all research plans are relevant and can be successfully executed.[20]

Individuals whose work might be affected by the study should be involved early in the development of the research proposal.

In the case of a prospective study, the principal investigator(s) shall educate all those who enroll participants and perform various aspects of the study protocol.[18,32]

The principal investigator(s) should encourage discussion during this educational process, resulting in the following benefits:[18]

a) improve clinical usefulness of the research question, if needed;
b) improve “buy-in” among front-line staff, which should lead to greater adherence with the study protocol;
c) facilitate understanding of the uncertainty principle within front-line personnel and its applicability to the study (to preserve patient choice and clinical judgement and to maintain study validity); and
d) when the discussion includes other scientists, improve application of the scientific basis for answering the question.

# 7. FINANCIAL SUPPORT

The research team should secure adequate financial resources to fully support the proposed research. The team should prepare a budget that adequately expresses the research plan in financial terms. The team should obtain support from the organization’s financial staff and with other experienced researchers in preparing the budget.[33]

## 7.1 Funding Sources

There are many granting agencies that financially support research activities.[21] The principal investigator(s) should seek funding from the granting

agencies whose interests align with those of the research team.[21] Investigators can apply for funding to more than one appropriate agency, but generally can only accept funding from one agency. If financial resources must be obtained from outside sources, the principal investigator(s) should contact possible funding organizations. Sources of research funds and all roles performed by the funding agency in relating to the research should be documented and acknowledged during subsequent knowledge translation and transfer.

**Note:** *Various national, provincial, or local organizations may fund research related to specific diseases. Other sources of research funds include research and education foundations associated with teaching hospitals or professional organizations, the pharmaceutical industry, and government agencies.*[21]

## 7.2 Preparing the Budget

The research team should prepare a financial budget for the costs of activities and supplies related to the study. Consideration should be given to conducting a pilot test of the study methods to help determine the costs of the study.[20]

The study budget should have the following characteristics:

a) enhances the overall strength of the proposal;
b) presents a reasonably accurate estimation of the costs of doing the research according to the proposed methods (specific price quotations are preferred);[33]
c) does not include any cost mark-up;
d) does not include funds to develop new processes, programs, or equipment, unless such development is the specific goal of the research proposal;
e) considers funding for all aspects of the research, including salaries (for the principal investigator(s), co-investigators, research associates, technicians, and other personnel)[33] consultants' fees, equipment and supplies, patient costs and honoraria, subcontracting fees,[33] and facility and administration costs;[33]
f) includes expenses for items such as photocopying, photography, telephone service, postage;
g) includes costs to train persons who will be implementing the study protocol;
h) includes costs of knowledge translation and transfer; and
i) reflects local practices (e.g., such as requirement for cost recovery).

Multiyear budgets may account for inflation, depending on the granting agency's guidelines.[33]

Some granting agencies will not pay certain of the costs listed above (e.g., travel costs). Therefore, the funding application should take into account any specific guidelines of the granting agency.[29] Financial support costs not covered by the granting agency should be sought from other sources.

## 7.3 Budget Justification

The budget proposal shall justify all requested items by means of a "budget justification narrative",[33] as directed by the granting agency. Justification for all items, including personnel costs, shall be supported by the proposed study methods. Investigators should be aware that inflating the budget may contribute to the proposal being declined.

Justification of personnel costs should be based on the amount of time that each person will spend on the project. These calculations shall be supported by the proposed methods.

Justification for personnel such as research associates, technicians, and consultants should include a list of special skills, knowledge, or expertise that these people will bring to the research.

## 7.4 Funding Application

Each research proposal should be customized to address the goals of the granting agency. The principal investigator(s) may contact the grant

officer from the granting agency to learn about the organization's process for administering grants.[17] The investigator may also ask experienced researchers not involved in the study to critically review the grant application.[20]

Before submitting an application, the research team should ensure that the proposal is complete and that the application has been thoroughly reviewed.[21] Failure to do so may contribute to delays in receiving funding or may lead to the application being turned down.

#### 7.4.1 Assembling the Proposal to a Granting Agency

When assembling a proposal, the research team should consult the granting agency's guidelines. Each agency has its own requirements, but most agencies request the following information:

a) title page, containing the title of the proposed research, details about the principal investigator(s) (name, position title, mailing address, telephone number, fax number, email address, and signature), details about the collaborating investigators (names, position titles, and signatures), and the name and address of the facility where the research will be conducted, along with the signature of the president or authorized signing official of that facility;
b) brief summary of the research proposal;
c) description of preliminary work completed to date;
d) introduction, reviewing research that has already been conducted in the topic area (with appropriate references) and providing the rationale for the research proposal;
e) research hypothesis and objectives;
f) description of methods, with adequate discussion of experimental design, study population, sample selection, and procedures for data collection (including interventions to be performed);
g) procedures for data analysis;
h) confirmation of ethics approval;
i) justification of sample size (if applicable);
j) strengths and weakness of the proposal;
k) description of the significance of the research;
l) knowledge translation plan, including submission to open-access journals if required by the granting agency;
m) references;
n) appendices (if applicable);
o) budget, which should describe and justify the requested funds for each item, including personnel, supplies, and equipment; and
p) curriculum vitae of the principal and collaborating investigators.

Submission of pilot data may be required or useful to strengthen the proposal for the purposes of granting.

### 7.5 Project Accounting

Appropriate accounting for all receipts and disbursements shall be maintained throughout the life of the study, or longer as determined by applicable legislation and related policies.

## 8. CONDUCT OF THE STUDY

The study shall be conducted in accordance with the approved and documented methods and the research plan. Any deviations from the established research plan shall be documented, and any changes to the research protocol shall be documented, justified, and approved by the IRB.

The necessary resources (e.g., personnel, supplies, equipment, space) should be obtained before conducting the study.

### 8.1 Enrolling Participants

When enrolling participants, every effort should be made to adhere to the study's predefined exclusion

criteria. If the recruitment protocol has been modified, reasons for the change and any possible implications shall be documented and approved by the IRB.

Human participants shall provide informed consent to participate in the study, according to local policies or procedures for consent. Consent should be obtained at the earliest possible time and must be in place before a participant is formally enrolled. A participant or his or her agent may withdraw consent at any time, without any effect on the participant's current or future care.

Informed consent involves a thorough discussion of study methods and risks to allow the potential subject to make an informed voluntary decision.[38] The discussion between the potential subject and the study personnel should be open and honest, and occur in a manner that protects privacy and ensures confidentiality of information collected.[38] If the study design requires waived or altered consent procedures, this approach shall be adequately justified.[38] Any such revisions shall be approved by the IRB.

Enrolment in the study should continue until the desired number of patients (the predetermined sample size) has been reached.

## 8.2 Documenting Project Data

Complete records of the study shall be maintained. Records of all participants, including those who did not complete the study, shall be maintained.

Such records will include the following information:

a) methods of enrolling participants;
b) details of participants enrolled in the study;
c) methods of applying treatments (if applicable);
d) details of treatments applied;
e) methods of collecting data;
f) data collected during the course of the study;
g) methods of analyzing and interpreting the results; and
h) data analysis and interpretation.

The data files of all participants who are disqualified from the final study analysis shall be retained, and the reason for disqualification shall be recorded in each case. Reasons for disqualification may include errors made during data collection, inappropriate randomization, and inadvertent unblinding of treatment. If participants in a randomized controlled trial with a prespecified intent-to-treat analysis plan must be disqualified, every effort should be made to follow up with those participants to determine study outcomes of interest.

## 8.3 Data and Safety Monitoring Board

If the researcher is conducting a clinical trial, the IRB or ethics committee may require an establishment of a data and safety monitoring board (DSMB). The DSMB shall be established prior to the initiation of the study to review accumulated study safety and efficacy data at prespecified intervals. Members of the DSMB shall be independent of the researchers involved in the study, and shall advise the study researchers of the future management of the trial. The DSMB will use prespecified reasons for early study termination to guide their decisions for future management of the study.

## 8.4 Study Termination

The study should continue until the predetermined stop date or when prematurely terminating the study is justified.

### 8.4.1 Documenting Reasons for Premature Termination

For a variety of reasons, a study may be terminated early. The reasons for early termination include the following:

a) interim analysis revealing an unacceptable risk to patients who have not yet been enrolled;

b) interim analysis revealing a prespecified benefit threshold to the treatment group making it unethical to continue and not allow all participants to receive the treatment;
c) lack of funding; and
d) inadequate number of patients enrolled, despite best efforts at recruitment.

The reason(s) for early termination shall be documented and reported in the study results.

#### 8.4.2 Interpreting the Results of the Analysis

The results of the analysis should be interpreted and form the basis of decisions about the significance (e.g., scientific, clinical, and statistical) of the study results and other conclusions (e.g., about cause and effect) drawn from the study. Researchers should also identify and report how the results of their study contribute to the available literature, the strengths and limitations associated with their study (for example, bias that could not be controlled in the study design or statistical analysis), and the practice implications of the study results.

#### 8.4.3 Informing Stakeholder Organizations

Once a study has been concluded, the research team should inform, in writing, the IRB that granted ethics approval, the granting agencies that provided financial support, and departments or institutions involved in the study.

## 9. KNOWLEDGE DISSEMINATION

Upon completion of the study, the research team shall use appropriate means to disseminate the study results to the persons or groups (such as practitioners or policy makers) who will benefit from the information. A variety of channels should be considered, such as presenting results at conferences, publishing results in a peer-reviewed journal, presenting results during information sessions with patients, participating in media engagements, and holding meetings with key stakeholders and policy makers.[39]

### 9.1 Choice of Reporting Format

The choice of reporting format should take into consideration the following factors:[27]

a) journal style;
b) direction given by the journal's editorial board; and
c) traditions of the research field related to the study.

Author preferences may also be considered where possible.

### 9.2 Disclosure of Funding Sources

The authors of any publication related to the research study should disclose all sources of funding.[2]

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