Chapter 9
Formulating the Research Question

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Learning Objectives

- Understand how to turn a clinical question into a research question.
- Principles of choosing a sample.
- Approaches and potential pitfalls.
- Principles of defining the exposure of interest.
- Principles of defining the outcome.
- Selecting an appropriate study design.

9.1   Introduction

The clinical question arising at the time of most health-care decisions is: "will this help my patient?" Before embarking on an investigation to provide data that may be used to inform the clinical question, the question must be modified into a research query. The process of developing a research question involves defining several components of the study and also what type of study is most suited to utilize these components to yield valid and reliable results. These components include: in whom is this research question relevant? The population of subjects defined by the researcher is referred to as the sample. The drug, maneuver, event or characteristic that we are basing our alternative hypothesis on is called the exposure of interest. Finally, the outcome of interest must be defined. With these components in mind the researcher must decide which study design is best or most feasible for answering the question. If an observational study design is chosen, then the choice of a database is also crucial.

In this chapter, we will explore how researchers might work through converting a clinical question into a research question using the clinical scenario of indwelling

arterial catheters (IAC) use during mechanical ventilation (MV). Furthermore, we will discuss the strengths and weaknesses of common study designs including randomized controlled trials as well as observational studies.

9.2 The Clinical Scenario: Impact of Indwelling Arterial Catheters

Patients who require MV because they are unable to maintain adequate breathing on their own (e.g. from severe pneumonia or asthma attack) are often the sickest patients in the hospital, with mortality rates exceeding 30 % [1–3]. Multiple options are available to monitor the adequacy of respiratory support for critically ill patients requiring MV, ranging from non-invasive trans-cutaneous measures to invasive, indwelling monitoring systems. IACs are invasive monitoring devices that allow continuous real time blood pressure monitoring and facilitate access to arterial blood sampling to assess arterial blood pH, oxygen and carbon dioxide levels, among others [4–6]. While closer monitoring of patients requiring MV with IACs may appear at face value to be beneficial, IACs may result in severe adverse events, including loss of blood flow to the hand and infection [7, 8]. Currently, data is lacking whether benefits may outweigh risks of more intensive monitoring using IACs. Examining factors associated with the decision to use IACs, and outcomes in patients provided IACs as compared to non-invasive monitors alone, may provide information useful to clinicians facing the decision as to whether to place an IAC.

9.3 Turning Clinical Questions into Research Questions

The first step in the process of transforming a clinical question into research is to carefully define the **study sample (or patient cohort)**, the **exposure** of interest, and the **outcome** of interest. These 3 components—sample, exposure, and outcome—are essential parts of every research question. Slight variations in each component can dramatically affect the conclusions that can be drawn from any research study, and whether the research will appropriately address the overarching clinical question.

9.3.1 Study Sample

In the case of IAC use, one might imagine many potential study samples of interest: for example, one might include all ICU patients, all patients receiving MV, all patients receiving intravenous medications that strongly affect blood pressure, adults only, children only, etc. Alternatively, one could define samples based on specific diseases or syndrome, such as shock (where IACs may be used to closely

monitor blood pressure) or severe asthma (where IAC may be used to monitor oxygen or carbon dioxide levels).

The choice of study sample will affect both the internal and the external validity (generalizability) of the study. A study focusing only on a pediatric population may not apply to the adult population. Similarly, a study focused on patients receiving MV may not be applicable to non-ventilated patients. Furthermore, a study including patients with different reasons for using an IAC, with different outcomes related to the reason for IAC use, may lack internal validity due to bias called 'confounding'. Confounding is a type of study bias in which an exposure variable is associated with both the exposure and the outcome.

For instance, if the benefits of IACs on mortality are studied in all patients receiving MV, researchers must take into account the fact that IAC placement may actually be indicative of greater severity of illness. For example, imagine a study with a sample of MV patients in which those with septic shock received an IAC to facilitate vasoactive medications and provide close blood pressuring monitoring while patients with asthma did not receive an IAC as other methods were used to monitor their ventilation (such as end-tidal CO_2 monitoring). Patients with septic shock tend to have a much higher severity of illness compared to patients with asthma regardless of whether an IAC is placed. In such a study, researchers may conclude that IACs are associated with higher mortality only because IACs were used in sicker patients with a higher risk of dying. The variable "diagnosis" is therefore a confounding factor, associated with both the exposure (decision to insert an IAC) and the outcome (death). Careful sample selection is one method of attempting to address issues of confounding related to severity of illness. Restricting study samples to exclude groups that may strongly confound results (i.e. no patients on vasoactive medications) is one strategy to reduce bias. However, the selection of homogeneous study samples to increase internal validity should be balanced with the desire to generalize study findings to broader patient populations. These principles are discussed more extensively in the Chap. 10—"Cohort Selection".

9.3.2   Exposure

The exposure in our research question appears to be fairly clear: placement of an IAC. However, careful attention should be paid as to how each exposure or variable of interest is defined. Misclassifying exposures may bias results. How should IAC be measured? For example, investigators may use methods ranging from direct review of the medical chart to use of administrative claims data (i.e. International Classification of Diseases—ICD-codes) to identify IAC use. Each method of ascertaining the exposure of interest may have pros (improved accuracy of medical chart review) and cons (many person-hours to perform manual chart review).

Defining the time window during which an exposure of interest is measured may also have substantial implications that must be considered when interpreting the research results. For the purposes of our IAC study, the presence of an IAC was

defined as having an IAC placed after the initiation of MV. The time-dependent nature of the exposure is critical for answering the clinical question; some IACs placed prior to MV are for monitoring of low-risk surgical patients in the operating room. Including all patients with IACs regardless of timing may bias the results towards a benefit for IACs by including many otherwise healthy patients who had an IAC placed for surgical monitoring. Alternatively, if the exposure group is defined as patients who had an IAC at least 48 h after initiation of MV, the study is at risk for a type of confounding called "immortal time bias": only patients who were alive could have had an IAC placed, whereas patients dying prior to 48 h (supposedly sicker) could not have had an IAC.

Equally important to defining the group of patients who received or experienced an exposure is to define the "unexposed" or control group. While not all research requires a control group (e.g. epidemiologic studies), a control group is needed to assess the effectiveness of healthcare interventions. In the case of the IAC study, the control group is fairly straightforward: patients receiving MV who did not have an IAC placed. However, there are important nuances when defining control groups. In our study example, an alternate control group could be all ICU patients who did not receive an IAC. However, the inclusion of patients not receiving MV results in a control group with a lower severity of illness and expected mortality than patients receiving MV, which would bias in favor of not using IACs. Careful definition of the control group is needed to properly interpret any conclusions from research; defining an appropriate control group is as important as defining the exposure.

9.3.3 Outcome

Finally, the investigator needs to determine the outcome of interest. Several different types of outcomes can be considered, including intermediate or mechanistic outcomes (informs etiological pathways, but may not immediately impact patients), patient-centered outcomes (informs outcomes important to patients, but may lack mechanistic insights: e.g. comfort scales, quality of life indices, or mortality), or healthcare-system centered outcomes (e.g. resource utilization, or costs). In our example of IAC use, several outcomes could be considered including intermediate outcomes (e.g. number of arterial blood draws, ventilator setting changes, or vasoactive medication changes), patient-centered outcomes (e.g. 28-day or 90-day mortality, adverse event rates), or healthcare utilization (e.g. hospitalization costs, added clinician workload). As shown in our example, outcome(s) may build upon each other to yield a constellation of findings that provides a more complete picture to address the clinical question of interest.

After clearly defining the study sample, exposure of interest, and outcome of interest, a research question can be formulated. A research question using our example may be formulated as follows:

"*In the population of interest (**study cohort**), is the exposure to the **variable of interest** associated with a different **outcome** than in the **control group**?*", which becomes, in our example:

"*Among mechanically ventilated, adult ICU patients who are not receiving vasoactive medications (i.e., the study sample) is placement of an IAC after initiation of MV (as compared with not receiving an IAC) (i.e. the exposure and control patients) associated with improved 28-day mortality rates (primary outcome, patient-centered) and the number of blood gas measurements per day (supporting secondary outcome, intermediate/mechanistic)?*"

9.4 Matching Study Design to the Research Question

Once the research question has been defined, the next step is to choose the optimal study design given the question and resources available. In biomedical research, the gold-standard for study design remains the double-blinded, randomized, placebo-controlled trial (RCT) [9, 10]. In a RCT, patients with a given condition (e.g. all adults receiving MV) would be randomized to receive a drug or intervention of interest (e.g. IAC) or randomized to receive the control (e.g. no IAC), with careful measurement of pre-determined outcomes (e.g. 28-day mortality). In ideal conditions, the randomization process eliminates all measured and unmeasured confounding and allows for causal inferences to be drawn, which cannot generally be achieved without randomization. As shown above, confounding is a threat to valid inferences from study results. Alternatively, in our example of septic shock verses asthma, severity of illness associated with the underlying condition may represent another confounder. Randomization solely based on the exposure of interest attempts to suppress issues of confounding. In our examples, proper randomization in a large sample would theoretically create equal age distributions and equal numbers of patients with septic shock and asthma in both the exposure and the control group.

However, RCTs have several limitations. Although the theoretical underpinnings of RCTs are fairly simple, the complex logistics of patient enrollment and retention, informed consent, randomization, follow up, and blinding may result in RCTs deviating from the 'ideal conditions' necessary for unbiased, causal inference. Additionally, RCTs carry the highest potential for patient harm and require intensive monitoring because the study dictates what type of treatment a patient receives (rather than the doctor) and may deviate from routine care. Given the logistic complexity, RCTs are often time- and cost-intensive, frequently taking many years and millions of dollars to complete. Even when logistically feasible, RCTs often 'weed out' multiple groups of patients in order to minimize potential harms and maximize detection of associations between interventions and outcomes of interest. As a result, RCTs can consist of homogeneous patients meeting narrow criteria, which may reduce the external validity of the studies' findings. Despite much effort

and cost, an RCT may miss relevance to the clinical question as to whether the intervention of interest is helpful for your particular patient or not. Finally, some clinical questions may not ethically be answered with RCTs. For instance, the link between smoking and lung cancer has never been shown in a RCT, as it is unethical to randomize patients to start smoking in a smoking intervention group, or randomize patients to a control group in a trial to investigate the efficacy of parachutes [11]!

Observational research differs from RCTs. Observational studies are non-experimental; researchers record routine medical practice patterns and derive conclusions based on correlations and associations without active interventions [9, 12]. Observational studies can be retrospective (based on data that has already been collected), prospective (data is actively collected over time), or ambi-directional (a mix). Unlike RCTs, researchers in observational studies have no role in deciding what types of treatments or interventions patients receive. Observational studies tend to be logistically less complicated than RCTs as there is no active intervention, no randomization, no data monitoring boards, and data is often collected retrospectively. As such, observational studies carry less risk of harm to patients (other than loss of confidentiality of data that has been collected) than RCTs, and tend to be less time- and cost-intensive. Retrospective databases like MIMIC-II [13] or the National Inpatient Sample [14] can also provide much larger study samples (tens of thousands in some instances) than could be enrolled in an RCT, thus providing larger statistical power. Additionally, broader study samples are often included in observational studies, leading to greater generalizability of the results to a wider range of patients (external validity). Finally, certain clinical questions that would be unethical to study in an RCT can be investigated with observational studies. For example, the link between lung cancer and tobacco use has been demonstrated with multiple large prospective epidemiological studies [15, 16] and the life-saving effects of parachutes have been demonstrated mostly through the powers of observation.

Although logistically simpler than RCTs, the theoretical underpinnings of observational studies are generally more complex than RCTs. Obtaining causal estimates of the effect of a specific exposure on a specific outcome depends on the philosophical concept of the 'counterfactual' [17]. The counterfactual is the situation in which, all being equal, the same research subject at the same time would receive the exposure of interest and (the counterfactual) not receive the exposure of interest, with the same outcome measured in the exposed and unexposed research subject. Because we cannot create cloned research subjects in the real-world, we rely on creating groups of patients similar to the group that receives an intervention of interest. In the case of an ideal RCT with a large enough number of subjects, the randomization process used to select the intervention and control groups creates two alternate 'universes' of patients that will be similar except as related to the exposure of interest. Because observational studies cannot intervene on study subjects, observational studies create natural experiments in which the counterfactual group is defined by the investigator and by clinical processes occurring in the real-world. Importantly, real-world clinical processes often occur for a reason,

and these reasons can cause deviation from counterfactual ideals in which exposed and unexposed study subjects differ in important ways. In short, observational studies may be more prone to bias (problems with internal validity) than RCTs due to difficulty obtaining the counterfactual control group.

Several types of biases have been identified in observational studies. Selection bias occurs when the process of selecting exposed and unexposed patients introduces a bias into the study. For example, the time between starting MV and receiving IAC may introduce a type of "survivor treatment selection bias" since patients who received IAC could not have died prior to receiving IACs. Information bias stems from mismeasurement or misclassification of certain variables. For retrospective studies, the data has already been collected and sometimes it is difficult to evaluate for errors in the data. Another major bias in observational studies is confounding. As stated, confounding occurs when a third variable is correlated with both the exposure and outcome. If the third variable is not taken into consideration, a spurious relationship between the exposure and outcome may be inferred. For example, smoking is an important confounder in several observational studies as it is associated with several other behaviors such as coffee and alcohol consumption. A study investigating the relationship between coffee consumption and incidence of lung cancer may conclude that individuals who drink more coffee have higher rates of lung cancer. However, as smoking is associated with both coffee consumption and lung cancer, it is confounder in the relationship between coffee consumption and lung cancer if unmeasured and unaccounted for in analysis. Several methods have been developed to attempt to address confounding in observational research such as adjusting for the confounder in regression equations if it is known and measured, matching cohorts by known confounders, and using instrumental variables—methods that will be explained in-depth in future chapters. Alternatively, one can restrict the study sample (e.g. excluding patients with shock from a study evaluating the utility of IACs). For these reasons, while powerful, an individual observational study can, at best, demonstrate associations and correlations and cannot prove causation. Over time, a cumulative sum of multiple high quality observational studies coupled with other mechanistic evidence can lead to causal conclusions, such as in the causal link currently accepted between smoking and lung cancer established by observational human studies and experimental trials in animals.

9.5   Types of Observational Research

There are multiple different types of questions that can be answered with observational research (Table 9.1). Epidemiological studies are one major type of observational research that focuses on the burden of disease in predefined populations. These types of studies often attempt to define incidence, prevalence, and risk factors for disease. Additionally, epidemiological studies also can investigate changes to healthcare or diseases over time. Epidemiological studies are the cornerstone of public health and can heavily influence policy decisions, resource

Table 9.1 Major types of observational research, and their purpose

Type of observational research	Purpose
Epidemiological	Define incidence, prevalence, and risk factors for disease
Predictive modeling	Predict future outcomes
Comparative effectiveness	Identify intervention associated with superior outcomes
Pharmacovigilance	Detect rare drug adverse events occurring in the long-term

allocation, and patient care. In the case of lung cancer, predefined groups of patients without lung cancer were monitored for years until some patients developed lung cancer. Researchers then compared numerous risk factors, like smoking, between those who did and did not develop lung cancer which led to the conclusion that smoking increased the risk of lung cancer [15, 16].

There are other types of epidemiological studies that are based on similar principles of observational research but differ in the types of questions posed. Predictive modeling studies develop models that are able to accurately predict future outcomes in specific groups of patients. In predictive studies, researchers define an outcome of interest (e.g. hospital mortality) and use data collected on patients such as labs, vital signs, and disease states to determine which factors contributed to the outcome. Researchers then validate the models developed from one group of patients in a separate group of patients. Predictive modeling studies developed many common prediction scores used in clinical practice such as the Framingham Cardiovascular Risk Score [18], APACHE IV [19], SAPS II [20], and SOFA [21].

Comparative effectiveness research is another form of observational research which involves the comparison of existing healthcare interventions in order to determine effective methods to deliver healthcare. Unlike descriptive epidemiologic studies, comparative effectiveness research compares outcomes between similar patients who received different treatments in order to assess which intervention may be associated with superior outcomes in real-world conditions. This could involve comparing drug A to drug B or could involve comparing one intervention to a control group who did not receive that intervention. Given that there are often underlying reasons why one patient received treatment A versus B or an intervention versus no intervention, comparative effectiveness studies must meticulously account for potential confounding factors. In the case of IACs, the research question comparing patients who had an IAC placed to those who did not have an IAC placed would represent a comparative effectiveness study.

Pharmacovigilance studies are yet another form of observational research. As many drug and device trials end after 1 or 2 years, observational methods are used to evaluate if there are patterns of rarer adverse events occurring in the long-term. Phase IV clinical studies are one form of pharmacovigilance studies in which long-term information related to efficacy and harm are gathered after the drug has been approved.

9.6   Choosing the Right Database

A critical part of the research process is deciding what types of data are needed to answer the research question. Administrative/claims data, secondary use of clinical trial data, prospective epidemiologic studies, and electronic health record (EHR) systems (both from individual institutions and those pooled from multiple institutions) are several sources from which databases can be built. Administrative or claims databases, such as the National Inpatient Sample and State Inpatient Databases complied by the Healthcare Cost and Utilization Project or the Medicare database, contain information on patient and hospital demographics as well as billing and procedure codes. Several techniques have been developed to translate these billing and procedure codes to more clinically useful disease descriptions. Administrative databases tend to provide very large sample sizes and, in some cases, can be representative of an entire population. However, they lack granular patient-level data from the hospitalization such as vital signs, laboratory and microbiology data, timing data (such as duration of MV or days with an IAC) or pharmacology data, which are often important in dealing with possible confounders.

Another common source of data for observational research is large epidemiologic studies like the Framingham Heart Study as well as large multicenter RCTs such as the NIH ARDS Network. Data that has already been can be analyzed retrospectively with new research questions in mind. As the original data was collected for research purposes, these types of databases often have detailed, granular information not available in other clinical databases. However, researchers are often bound by the scope of data collection from the original research study which limits the questions that may be posed. Importantly, generalizability may be limited in data from trials.

The advent of Electronic Health Records (EHR) has resulted in the digitization of medical records from their prior paper format. The resulting digitized medical records present opportunities to overcome some of the shortcomings of administrative data, yielding granular data with laboratory results, medications, and timing of clinical events [13]. These "big databases" take advantage of the fact many EHRs collect data from a variety of sources such as patient monitors, laboratory systems, and pharmacy systems and coalesce them into one system for clinicians. This information can then be translated into de-identified databases for research purposes that contain detailed patient demographics, billing and procedure information, timing data, hospital outcomes data, as well as patient-level granular data and provider notes which can searched using natural language processing tools. "Big data" approaches may attenuate confounding by providing detailed information needed to assess severity of illness (such as lab results and vital signs). Furthermore, the granular nature of the data can provide insight as to the reason why one patient received an intervention and another did not which can partly address confounding by indication. Thus, the promise of "big data" is that it contains small, very detailed data. "Big data" databases, such as MIMIC-III, have the potential to expand the scope of what had previously been possible with observational research.

9.7   Putting It Together

Fewer than 10 % of clinical decisions are supported by high level evidence [22]. Clinical questions arise approximately in every other patient [23] and provide a large cache of research questions. When formulating a research question, investigators must carefully select the appropriate sample of subjects, exposure variable, outcome variable, and confounding variables. Once the research question is clear, study design becomes the next pivotal step. While RCTs are the gold standard for establishing causal inference under ideal conditions, they are not always practical, cost-effective, ethical or even possible for some types of questions. Observational research presents an alternative to performing RCTs, but is often limited in causal inference by unmeasured confounding.

Our clinical scenario gave rise to the question of whether IACs improved the outcomes of patients receiving MV. This translated into the research question: "Among mechanically ventilated ICU patients not receiving vasoactive medications (study sample) is use of an IAC after initiation of MV (exposure) associated with improved 28-day mortality (outcome)?" While an RCT could answer this question, it would be logistically complex, costly, and difficult. Using comparative effectiveness techniques, one can pose the question using a granular retrospective database comparing patients who received an IAC to measurably similar patients who did not have an IAC placed. However, careful attention must be paid to unmeasured confounding by indication as to why some patients received IAC and others did not. Factors such as severity of illness, etiology of respiratory failure, and presence of certain diseases that make IAC placement difficult (such as peripheral arterial disease) may be considered as possible confounders of the association between IAC and mortality. While an administrative database could be used, it could lack important information related to possible confounders. As such, EHR databases like MIMIC-III, with detailed granular patient-level data, may allow for measurement of a greater number of previously unmeasured confounding variables and allow for greater attenuation of bias in observational research.

Take Home Messages

- Most research questions arise from clinical scenarios in which the proper course of treatment is unclear or unknown.
- Defining a research question requires careful consideration of the optimal study sample, exposure, and outcome in order to answer a clinical question of interest.
- While observational research studies can overcome many of the limitations of randomized controlled trials, careful consideration of study design and database selection is needed to address bias and confounding.

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