The assessment of a new or existing treatment typically answers 1 of 3 central research-related questions: (1) “Can it work?” (efficacy); (2) “Does it work?” (effectiveness); or (3) “Is it worth it?” (efficiency or cost-effectiveness). There are a number of study designs that, on a situational basis, are appropriate to apply in conducting research. These study designs are generally classified as experimental, quasiexperimental, or observational, with observational studies being further divided into descriptive and analytic categories. This second of a 2-part statistical tutorial reviews these 3 salient research questions and describes a subset of the most common types of observational study designs. Attention is focused on the strengths and weaknesses of each study design to assist in choosing which is appropriate for a given study objective and hypothesis as well as the particular study setting and available resources and data. Specific studies and papers are highlighted as examples of a well-chosen, clearly stated, and properly executed study design type. (Anesth Analg 2017;125:00–00)

“...take the one less traveled by,
Two roads diverged in a wood, and I—
I took the one less traveled by,
And that has made all the difference.”

Robert Frost (1916): The Road Not Taken, from Mountain Interval

The first of this 2-part statistical tutorial focused on experimental and quasi-experimental research study designs. This second part of the statistical tutorial (a) revisits 3 central research-related questions and (b) discusses the strengths and weaknesses of a subset of the most common types of observational study design—in an effort to assist in choosing which design is appropriate (“right”) for a given study objective and hypothesis, as well as the particular study setting and available resources and data. Specific studies and papers are highlighted here (Table) as examples of a well-chosen, clearly stated, and properly executed study design type.

Efficacy, Effectiveness, Efficiency

In 1972, the pioneering and luminary British clinical epidemiologist, Archie Cochrane, first defined 3 salient concepts related to testing health care interventions. The testing of a new or existing treatment or other intervention typically answers 1 of 3 central, research-related questions (Figure 1). The assessment of a new or existing treatment typically answers 1 of 3 central research-related questions: (1) “Can it work?” (efficacy); (2) “Does it work?” (effectiveness); or (3) “Is it worth it?” (efficiency or cost-effectiveness). There are a number of study designs that, on a situational basis, are appropriate to apply in conducting research. These study designs are generally classified as experimental, quasiexperimental, or observational, with observational studies being further divided into descriptive and analytic categories. This second of a 2-part statistical tutorial reviews these 3 salient research questions and describes a subset of the most common types of observational study designs. Attention is focused on the strengths and weaknesses of each study design to assist in choosing which is appropriate for a given study objective and hypothesis as well as the particular study setting and available resources and data. Specific studies and papers are highlighted as examples of a well-chosen, clearly stated, and properly executed study design type.

The efficacy, or whether a treatment achieves its intended clinical benefits—“Can it work?”—is demonstrated under ideal or optimal circumstances, in a highly controlled setting, with carefully selected patients, typically by way of an “explanatory” randomized controlled trial. The effectiveness, or whether these benefits are observed under more ordinary or “real-world” conditions—“Does it work?”—is often assessed with an “exploratory” analytic cohort study or a “pragmatic” randomized controlled trial. The efficiency or cost-effectiveness of the intervention (the health status improvement realized for a given amount of resources expended)—“Is it worth it?”—is determined via a formal health care economic evaluation (cost-benefit analysis, cost-effectiveness analysis, or cost-utility analysis).

RESEARCH STUDY DESIGN CLASSIFICATION

There is an array of study designs that, on a situational basis, are appropriate to apply in conducting research. These study designs are classified as experimental, quasi-experimental, or observational, with observational studies being further divided into descriptive and analytic categories (Figure 2).

The first of this 2-part statistical tutorial discussed experimental study designs (eg, randomized controlled trial) and quasi-experimental study designs (eg, interrupted time series). In this tutorial, attention is focused on observational study designs.

RESEARCH STUDY DESIGN TYPES

Because of their inclusion of more diverse patient populations, with common comorbidities and an often longer follow-up period, the findings from some types of observational study designs can expand upon the results of a randomized controlled trial. An observational study can complement the efficacy findings from an often smaller-scale randomized controlled trial because of the former’s assessing the effectiveness of a treatment or intervention in routine, day-to-day clinical practice.
Certain observational studies can thus have greater external validity (generalizability) than a randomized controlled trial. This is especially true for observational studies using large-scale health care databases containing so-called Big Data.

DESCRIPTIVE OBSERVATIONAL STUDY DESIGNS

Case Report and Case Series
A case report (case study) typically describes a single patient’s very unique clinical characteristics or clinical course. A case series conventionally includes more than 3 patients (n > 3) with similar clinical features and/or outcomes.

In the United States, IRBs generally permit up to 3 patients (n ≤ 3) to be included in a case report without it being considered research and thus needing a formal application and informed written consent. However, a written authorization for the release of protected health information is still required. Applicable regulations vary outside the United States. Anesthesia & Analgesia clearly describes its corresponding editorial policy in its current “Instructions for Authors.”

Given appropriate research ethics compliance, an uncontrolled case series (clinical series)—without a concurrent control or comparison group—can also describe the details, application, and associated outcomes of a novel treatment or intervention in a consecutive series of patients.

Incidence Versus Prevalence
Incidence is the occurrence rate of a new event during a specific time period (eg, serum troponin-positive postoperative myocardial injury after noncardiac surgery), whereas point prevalence is the proportion or percentage of individuals with an existing condition at a specific point in time (eg, preoperative coronary artery disease in noncardiac surgery patients diagnosed with cardiac catheterization or dobutamine stress echocardiogram).

Descriptive Cross-Sectional Study
A descriptive cross-sectional study is also referred to as a prevalence study. As its name implies, it takes a cross-sectional sample to generate a descriptive “snapshot” of a population at a specific point in time. The following table provides examples of a well-chosen, clearly stated, and properly executed study design type.

<table>
<thead>
<tr>
<th>Study</th>
<th>Title of Published Paper</th>
<th>Applied Study Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culley et al</td>
<td>Preoperative Cognitive Stratification of Older Elective Surgical Patients: A Cross-Sectional Study</td>
<td>Descriptive cross-sectional study</td>
</tr>
<tr>
<td>Brown et al</td>
<td>Postoperative Pain Management in Children of Hispanic Origin: A Descriptive Cohort Study</td>
<td>Descriptive cross-sectional study</td>
</tr>
<tr>
<td>de Oliveira et al</td>
<td>The Prevalence of Burnout and Depression and Their Association With Adherence to Safety Practice Standards: A Survey of United States Anesthesiology Trainees</td>
<td>Analytic cross-sectional study</td>
</tr>
<tr>
<td>Van Cleve et al</td>
<td>Associations Between Age and Dosing of Volatile Anesthetics in 2 Academic Hospitals</td>
<td>Analytic cross-sectional study</td>
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<tr>
<td>Zgleszewski et al</td>
<td>Anesthesiologist- and System-Related Risk Factors for Risk-Adjusted Pediatric Anesthesia-Related Cardiac Arrest</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Hsieh et al</td>
<td>The Association Between Mild Intraoperative Hypotension and Stroke in General Surgery Patients</td>
<td>Case-control study</td>
</tr>
<tr>
<td>Blijker et al</td>
<td>Intraoperative Hypotension and Perioperative Ischemic Stroke After General Surgery: A Nested Case-Control Study</td>
<td>Nested case-control study</td>
</tr>
<tr>
<td>Sprung et al</td>
<td>Anesthesia and Incident Dementia: A Population-Based, Nested, Case-Control Study</td>
<td>Nested case-control study</td>
</tr>
<tr>
<td>Henke et al</td>
<td>A Case-Cohort Study of Postoperative Myocardial Infarction: Impact of Anemia and Cardioprotective Medications</td>
<td>Case-cohort study</td>
</tr>
<tr>
<td>Bohnert et al</td>
<td>Association Between Opioid Prescribing Patterns and Opioid Overdose-Related Deaths Rates and Risk Factors for Prolonged Opioid Use After Major Surgery Population-Based Cohort Study</td>
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<tr>
<td>Clarke et al</td>
<td>Low-Risk Diet and Lifestyle Habits in the Primary Prevention of Myocardial Infarction in Men: A Population-Based Prospective Cohort Study</td>
<td>Cohort study</td>
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<tr>
<td>Akesson et al</td>
<td>Hypercholesterolemia After Noncardiac Surgery is Independently Associated with Increased Morbidity and Mortality: A Propensity-Matched Cohort Study</td>
<td>Cohort study</td>
</tr>
<tr>
<td>McCluskey et al</td>
<td>Comparative Safety of Anesthetic Type for Hip Fracture Surgery in Adults: Retrospective Cohort Study</td>
<td>Cohort study</td>
</tr>
</tbody>
</table>

Figure 1. Three questions that can be asked in assessing a new or existing treatment or other intervention. This is especially true for observational studies using large-scale health care databases containing so-called Big Data.
population. Information from a descriptive cross-sectional study can be used to generate a hypothesis, as well as a sample size determination and power analysis, for a subsequent study with a stronger, analytic cause-and-effect design.

**ANALYTIC OBSERVATIONAL STUDY DESIGNS**

**Association Versus Causation**

In interpreting any research data, but especially those from an analytic observational study, a key distinction should be made between association and causation. A research study identifies a statistical relationship or association between 2 variables (an exposure or intervention and the disease or other outcome). There are then 5 possible categories of statistical association in clinical research:

- Causal associations that are real and due to direct cause and effect
- Causal associations that are real but due to effect and cause ("cart before the horse"—the outcome caused the effect)
- Spurious associations due to chance (random error)
- Spurious associations due to bias (systematic error)
- Indirect associations that are real but due to confounding

True causation thus requires a real and direct cause-effect relationship or association between the study variables, which supports making a valid causal inference. However, as originally stated by Sir Bradford Hill in his classic and seminal 1965 paper entitled “The Environment and Disease: Association or Causation?” and more recently reiterated by others, (a) statistical significance per se should not be mistaken for evidence of a substantial association, (b) an observed association does not prove definitive causation, and (c) statistical precision should not be mistaken for scientific validity. Otherwise, a study’s findings can further contribute to what Grimes and Schulz have labeled as the “false alarms and pseudo-epidemics” that can stem from observational research.

**Analytic Cross-Sectional Study**

In an analytic cross-sectional study, data on the prevalence of both (a) an exposure, demographic, or clinical characteristic and (b) the disease or other health outcome are simultaneously obtained for the purpose of comparing the proportions of subjects with the disease or other health outcome in the study groups. This specific bias exists when, even if seemingly plausible to do so, it cannot be assuredly determined that the exposure preceded the disease, since both are ascertained at the same time. Because both exposure and outcome are ascertained at the same time, no assuredly valid conclusions can be made about their temporal relationship or a causal relationship (causation).

While no valid conclusions can be made about causation with an analytic cross-sectional study, one can determine if there is evidence of a significant association between an exposure, demographic, or clinical characteristic and the disease or other health outcome. Information from an analytic cross-sectional study can also be used to generate a hypothesis for a subsequent study with a stronger, analytic cause-and-effect design.

**Case-Control Study**

A case-control study assesses the relationship or association between a single outcome (diagnosed disease) and one or more possible previous contributing factors (exposures). A case-control study is retrospective, starting with the explicitly observed and well-defined outcome (disease) and looks backward in time at possible contributing factors (exposures).

Cases are subjects with the outcome or diagnosed disease of interest, whereas controls are subjects without this outcome or diagnosed disease of interest. It is imperative that the controls be independently drawn from the...
same source population as the cases, so that the controls are essentially equivalent to the cases—except for having the primary outcome of interest. A 1:1 to 1:4 ratio of cases to controls is sampled.12,33,34,36,37

Case-control studies utilize existing data and are thus typically less time consuming and less costly to perform than prospective observational studies. Its study design is well suited for outcomes that are rare or have a protracted onset.12,33,34,36

However, a case-controlled study is prone to selection bias with nonequivalent chosen controls (the participants without the outcome or disease) as well as recall bias with differential recollection about exposures among cases (the participants with the outcome or disease).12,33–36

**Nested Case-Control Study**
A nested case-control study is a case-control study in which both the cases and controls are selected from members of an existing longitudinal cohort.12,33 Thus, unlike in a conventional case-control study, all participants in a nested case-control study are selected from a well-defined cohort (source population), for which data on all members can be readily and consistently obtained.12,33 This more greatly assures satisfying the major assumption of a case-control study that its cases and controls represent random samples from the same source population.38

A key design element is that the controls are a sample of the cohort of individuals who are at risk for the disease at time each case of the disease occurs.33 Furthermore, in a nested case-control study, the cases and controls are matched by age, sex, race, calendar period, length of follow-up, and other pertinent characteristics.39,40

**Case-Cohort Study**
The case-cohort study design is similar to the nested case-control study design, in that the cases and controls are sampled from the same source population (cohort).33,40,41 However, in a case-cohort study, all the cases in the defined cohort are collected on all participants.12,42,43

A key design element is that the controls are a sample of the cohort of individuals who are at risk for the disease at time each case of the disease occurs.33 Furthermore, in a nested case-control study, the cases and controls are matched by age, sex, race, calendar period, length of follow-up, and other pertinent characteristics typically is not performed between the sample of the cases and the controls.33,40

**Cohort Study**
A cohort study assesses the relationship or association between a single possible contributing factor (exposure or intervention) and one or more outcomes (diagnosed diseases) of interest.12,42–44 All cohort studies start with the single possible contributing factor (exposure) and look forward in time to observe for the well-defined outcomes (diseases).12,35,42–44

However, while all cohort studies look forward in time from the exposure to outcomes, not all cohort studies are performed in real time.13,42 Depending on whether some or all of the needed data have been collected prior to the start of the study, the data in a cohort study can validly be collected prospectively, retrospectively, or ambispectively. Stated alternatively, cohort studies can be concurrent, nonconcurrent, or ambidirectional.13,42

It is imperative that all participants in a cohort study are free of the outcome or disease prior to the exposure (intervention) and at the outset of the longitudinal data collection. Passive assignment to an exposure (intervention) group occurs in a naturalistic fashion—or by participants’ self-selection. Outcomes data are then chronologically collected on all participants.12,42,43

It bears noting that a randomized controlled trial is essentially a type of prospective cohort study in which the active assignment of some participants to an exposure (intervention) group occurs intentionally yet randomly.1,11 A nonrandomized controlled trial is more experimental and clinical, whereas a prospective cohort study is more naturalistic and environmental.1,45,46

Prospective cohort studies are considered the gold standard of observational research.57 Compared to a case-control study, a prospective cohort study is less prone to recall bias, but it is subject to differential attrition bias, whereby subjects in one group exit the study at an unequal rate. A prospective cohort study is also typically more time consuming and costly than other observational study designs, especially for rare outcomes (diseases) and those with a protracted onset or natural history.12,35,42,43

**CONCLUSIONS**
In designing a research study, investigators should first determine which of 3 central, research-related questions a new or existing treatment or other intervention seeks to addresses: efficacy, effectiveness, or efficiency (cost-effectiveness; Figure 1).1,3,4 This insight in turn provides direction as to which among the array of available study design types (Figure 2)1,4,11–13 to apply on a situational basis in conducting the planned research.

No one study design is universally applicable or superior to another. Instead, investigators should identify the one that is most appropriate for the questions, circumstances, resources, and data at hand. Specific studies and papers are highlighted here (Table) as examples of a well-chosen, clearly stated, and properly executed study design type.

**DISCLOSURES**
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Contribution: The author wrote and revised the manuscript.

This manuscript was handled by: Jean-Francois Pittet, MD.

**REFERENCES**


