By Way of Introduction …

Daniel I. Sessler, M.D.

Selecting an appropriate topic is arguably the most difficult part of clinical research. It is easy to identify important questions that cannot be addressed with available resources; it is similarly easy to identify trivial questions that do not meaningfully improve our understanding. The challenge for investigators is to identify important questions they can address with available patients and resources. Even experienced investigators find the process challenging and often consider dozens of potential topics before identifying one that is suitable. It usually requires much study to determine whether a particular question is truly novel and important, and can be suitably addressed with available resources. Skilled investigators are willing to drop suboptimal topics even after investing considerable effort.

"It is common to assume that the importance of a study is determined by the results. It is not. … [I]ts importance is determined by the question."

Do not fall in love with the first topic you consider. Instead, consider many potential studies and select the strongest. Also, take a broad view: Do not ask yourself what can be done with your patients. Instead, seek to identify the most important questions in perioperative medicine—and then figure out how to address one. Do not focus on confirming a theory. Instead, address an important question and then gracefully accept whatever the results might be—no matter how unexpected.

While there are many approaches to identifying suitable clinical research topics, two seem especially helpful. Research takes place at the border between known and unknown—which means that investigators need to know where that border is. Reading published articles helps identify the current state of knowledge and what remains to be determined. Furthermore, nearly every article raises more questions than it answers. What about a different population? Might a different dose or treatment intensity matter? How about a different treatment duration? Is there a stronger methodologic approach? Pay attention to the limitations section. When well written, limitations present a roadmap to needed studies—often explicitly. A second way to identify research topics is to observe clinical practice. When skilled clinicians handle similar situations differently, it is because the best approach remains unknown. One approach probably is superior; a good study will identify which is best, thus providing useful guidance to clinicians.

It is common to assume that the importance of a study is determined by the results. It is not. Assuming a study was competently conducted, its importance is determined by the question. Most trials reported in major multispecialty journals have neutral results, and were nonetheless published because they address important questions. The introduction of a manuscript is the investigators' opportunity to present the question to readers and convince them that it truly matters. It is also the most difficult part of a research report to write, and possibly the most important, because it is the introduction that convinces readers to explore the rest of the report. Introductions typically include three key elements, usually presented in separate paragraphs. Overall, introductions are funnel-shaped, starting broadly and ending with considerable specificity.

The initial section of the introduction presents the scope and importance of the problem being addressed. For example, "Forty percent of U.S. adults suffer sleep disturbances, and nearly all postoperative patients sleep poorly consequent to residual anesthesia, pain, and analgesics. Inadequate postoperative sleep activates the sympathetic nervous system, promotes hemodynamic instability, and often requires pharmacologic treatment. It is also likely that sleep disturbances promote postoperative delirium, which in turn is associated with prolonged hospitalization."The goal of this section is to convince readers that the topic you will address is important—and that the rest of the report is worth reading.

Accepted for publication July 23, 2025.

Daniel I. Sessler, M.D.: Center for Outcomes Research, Department of Anesthesiology, UTHealth, Houston, Texas.

 ANESTHESIOLOGY 2025; 143:1153–5. DOI: 10.1097/ALN.0000000000005688

<zdoi;10.1097/ALN.0000000000005688>

The second part of the introduction presents the controversy or argument. Typically, writers use this section to identify what is known or at least reasonably well established, and contrast it with what has yet to be established. For example, "Melatonin is a critical hormone that spikes in the evening which initiates and maintains normal sleep. It is therefore unsurprising that supplemental melatonin facilitates sleep onset and improves sleep quality. The perioperative period is more complicated because many factors conspire to deny normal sleep. Melatonin nonetheless seems likely to improve postoperative sleep, just as it improves normal sleep. However, only a limited number of small trials in selected populations report the effect of melatonin on postoperative sleep." By the end of this section, readers should understand the research question in general terms.

The final section of the introduction presents the hypotheses. (Some studies, such as population prevalence evaluations, do not require hypotheses, but they are exceptions.) This is where authors specify exactly what will be tested and the criteria for success. The reason introductions end with hypotheses is that readers cannot evaluate the adequacy of the methods without understanding the research question. The primary hypothesis should be presented first, followed by secondary and then exploratory hypotheses. The study will be judged largely by the primary hypothesis and whether the relevant methodology was adequate, including sufficient power.

A common mistake is to specify too many secondary hypotheses. Having many augments the risk of a spurious finding or, if corrected for multiple comparisons, makes false-neutral findings likely. Too often secondary hypotheses are included with insufficient consideration. There should rarely be more than one to three secondary hypotheses, and each should be plausible, important, well powered, and not simply a minor variant of the primary hypothesis.

Studies should be designed to optimize the primary outcome, but too often the primary outcome is compromised for secondary outcomes, often in subtle ways. For example, sleep disturbances probably promote delirium. It therefore might seem reasonable to add delirium prevention as a secondary outcome in our hypothetical trial of melatonin to enhance postoperative sleep. However, it would be a poor idea for several reasons. One is that postoperative delirium is rare in patients younger than 65 yr. In contrast, sleep disturbances occur at all ages. If delirium is included as a secondary analysis, either enrollment must be restricted to older patients (clearly compromising the primary outcome) or younger patients can be included (which will dilute the delirium signal). An additional problem is that sleep scores are essentially a continuous outcome, so perhaps 100 patients per group will provide adequate statistical power for sleep quality. In contrast, delirium is a sparse dichotomous outcome that will require at least an order of magnitude more patients. Attractive as it might seem, combining these outcomes in a single trial would therefore be problematic.

In contrast to secondary hypotheses, there is no limit on exploratory hypotheses, but any resulting finding will be considered, well, exploratory. But still, like secondary hypotheses, exploratory hypotheses should be plausible and important. However, they need not be adequately powered if explicitly serving as a pilot for a future trial. In our example, delirium could be considered an exploratory outcome, serving as a pilot for a future (very much larger) trial with delirium as the primary outcome.

Most investigators start with a vague idea such as, "I'm interested in the relationship between melatonin and delirium." While a reasonable starting point, fuzzy thinking does not lead to well-designed research. The challenge for investigators, then, is to convert a vague idea into a formal hypothesis. A hypothesis is a present-tense statement of fact. Of course, a hypothesis isn't (yet) a fact, but the accepted process is to state an assertion and then try to disprove it. That sequence used to be formalized in the form of null and alternate hypotheses. For clarity, investigators now generally skip directly to the alternate hypothesis, but the convention of stating hypotheses as facts (to be disproved) remains.

There are five elements to a complete hypothesis: population, exposure, outcome, time frame, and expected direction of change. Increasingly, investigators also define what outcome magnitude will be considered clinically meaningful. "Evaluate the relationship between melatonin and delirium" is not a hypothesis. Formulated properly, the corresponding hypothesis might be as follows: "Nightly administration of melatonin 3 mg improves sleep quality by an average of at least 10 T-score points on the NIH PROMIS scale during the initial 3 nights after major noncardiac surgery." This short declarative sentence explicitly includes all required elements: *population* ([patients] recovering from noncardiac surgery), *exposure* (nightly melatonin 3 mg), *outcome* (sleep quality assessed using the NIH PROMIS scale), *time frame* (initial 3 [postoperative] nights), *expected direction of change* (improves), and *clinically meaningful difference* (by an average of at least 10 T-score points).

In summary, selecting an appropriate research topic is challenging. It requires considerable effort to objectively evaluate the quality and practicality of various potential topics. Even experienced investigators consider dozens of ideas before selecting one to attempt. And the more experienced investigators are, the more willing they are to discard suboptimal projects—even after considerable effort. The introduction is arguably the most important part of a research report because it explains why your question is important—and why readers should be interested. Well-written introductions explain the topic's global importance, identify a controversy, and end with hypotheses that anchor the article. All methods and interpretation of results follow from the hypotheses. Selecting a strong primary hypothesis and expressing it properly is thus key to a study's success—and to a subsequently clear research report.

Competing Interests

Dr. Sessler serves on advisory boards and has equity interests in Calorint (Philadelphia, Pennsylvania), TransQtronics (Philadelphia, Pennsylvania), the Health Data Analytics Institute (Boston, Massachusetts), Medasense (Tel Aviv, Israel), and Perceptive Medical (Newport Beach, California). He consults for Dynacardia (Cambridge, Massachusetts), Diagnopitics (Groningen, The Netherlands), and Forge Laboratories (Lubbock, Texas). He occasionally consults for temperature-related companies, with all fees donated to charity. He is a senior international fellow at the Population Health Research Institute, McMaster University (Hamilton, Canada). None is relevant to this submission.

Correspondence

Address correspondence to Dr. Sessler: daniel.sessler@UTH.TMC.edu