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Ten strategies to formulate a strong research question

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A critical moment in science is the research question formulation. Albert Szent-Györgyi, Nobel Prize winner in medicine in 1937 due to his work on vitamin C and metabolism, described this formulation as "seeing what everyone else is seeing, but thinking of what no one else has thought." Indeed, this process implies creativity and an innovative point of view; however, to achieve a good research question requires a systematic approach and proper training. For most younger researchers, this formulation is still considering challenging and confusing. To assist during this process, we present a practical framework with ten strategies to formulate a strong research question, from the initial idea to the final question.

Strategy 1: The research question cannot be a "fishing expedition."

Designing a study must aim to answer a specific question. The goal is not to do a fishing expedition and drop the net into the sea; contrariwise, you should identify what you need and spearfishing it. In research, this could be translated as including multiple groups and outcomes (i.e., net) versus thoroughly selecting your independent and dependent variables (i.e., the spear). For the net case, the exaggerated inclusion of variables might result in a confusing design, and interpretations from that data might be more difficult to do. Furthermore, the inclusion of numerous groups and/or several outcomes might inflate the false positive rate (Wacholder, Chanock, Garcia-Closas, El Ghormli, & Rothman, 2004). Using the fishing analogy, an even worse problem arises when you go out into the open ocean, and without any map indicating where the fishes are, you start throwing the net. Then two things can happen: you come with an empty net, then you conclude: there is no fish in the sea (i.e., false-negative result). This conclusion is an obviously wrong conclusion because probably you are fishing in an area with no fishes. Or if, for a random chance, you get some passing fishes there, you conclude: this is a great place to fish, which may be wrong if you were just lucky to get some passing fishes there (i.e., false-positive result). These two examples correspond to the hypothesis testing errors that are possible to make in research, namely, the type I error that represents a positive finding when there is not any effect and the type II error that occurs when the study misses to find an effect when there is a real effect. Therefore, a scientist needs to truly study the ocean, the behavior of the fishes, to find out where they are, when is the best time to fish, and then go directly to where they are. If with all this work, they do not find fishes, this becomes an interesting conclusion. For instance, this area may have suffered contamination, and fishes died, so you can correctly

explore alternative hypotheses, discover information, and generate new knowledge.

Strategy 2: **You need to have a very specific research question and a very specific hypothesis.**
The research question must be precise and guided by a specific hypothesis. In general, ambiguous questions are more challenging to answer due to their complexity. Research questions are not an exception for that rule. In very complex research questions, the methodology and statistical analysis could turn very difficult. Thus, a cautious and straightforward definition of each component in the PICOT format (Population, Intervention, Comparison, Outcome, and Time) and the underlying hypothesis might help design a robust method to test what is being proposed.

Strategy 3: The research question must address a reasonable gap in the literature (not too large, not too small).
The approval process of a drug is an excellent example of how the scientific method should be conducted (Umscheid, Margolis, & Grossman, 2011). Initially, preclinical studies are performed in animals to ensure the drug is safe enough to be tested in humans. Phase 1 studies are the first ones to test the safety of the new drug in humans. If safety is demonstrated in this phase, then the drug must be tested in a larger sample focusing on its efficacy and safety (i.e., Phase 2). At last, if the results of the previous phase indicate that the study of this drug can move forward, then it is tested in a very large sample to ensure its efficacy in comparison with the standard treatment or placebo. This sequence of phases allows for these gaps to be filled in an orderly and coherent manner. For instance, we could not perform a Phase 3 clinical trial right after finishing a preclinical trial, because the gap of knowledge between those two would be too large. The same logic applies to build a house; namely, in phase 1, the house foundation is built, followed by framing the house in phase 2, and finishing with the house exterior and interior in the last phase. Following this analogy, as it is impossible to work on a house exterior and interiors without house framing, it is impossible to perform a phase 3 clinical trial without all the other previous steps. It is important to follow each step carefully because extrapolations may lead to very ambitious research questions, which increases the probability of failure and inconclusive results. Therefore, collectively addressing small gaps, allows the constant adding and fitting of little bricks (i.e., data, evidence, studies) to the wall of knowledge.

Strategy 4: Research questions need to be novel.
The development of science depends on innovation. Thus, researchers need to be exposed to multiple sources of information related and non-related to the topic of interest. They need to explore different points of view of their topic from distinct disciplines; this will increase the likelihood of creating new ideas and hypotheses. The NIH assess innovation in research questions in their novel theoretical concepts, methods, instruments, and interventions. Knowledge is developed by answering small gaps with new hypotheses and new data. Nonetheless, replications also have their role in science, given that they represent the way that science has, to self-correct through the acknowledgment of false-positive studies (Maxwell, Lau, & Howard, 2015). Considering the topic 3 (gap to be addressed) and innovation, the art of getting a robust research question is to find a balance between the innovation aspect and what we know about the topic.

Strategy 5: Research questions need to be feasible.
The researchers must consider obstacles to test their questions. For instance, the possible difficulties in recruitment, patient's compliance with the intervention, total amount of funding, and/or ethical issues with the control group may block the start and/or continuation of a clinical trial. These feasibility issues may explain the high number of clinical trials reported in ClinicalTrials.gov that are not completed and published afterward (Chen et al., 2016; Zwierzyna, Davies, Hingorani, & Hunter, 2018). Therefore, when formulating a research question, have in mind how you can answer it in the "real-world" and if it is feasible to do it. Failing to do this step may result in a loss of funds and time, and in some cases exposing the enrolled subjects to an unnecessary risk.

Strategy 6: Research questions need to be significant.
Significance in clinical trials is defined by addressing important problems, improving scientific knowledge and/or clinical practice, and potentially enhancing interventions. These are the three main factors to the National Institute of Health (NIH) to assess significance in their reviews for funding. The current pandemic of Covid-19 is a good example of how science is constantly adapting to the high impact situations affecting society (Zheng, 2020). Nevertheless, it is critical to emphasize the importance of research in rare genetic diseases or in basic science studies. The researcher needs to go

through this exercise to find out the significance of his work. This exercise may even help to change the question to be a more significant one. But also consider the early work in quantum mechanics by Max Planck, Albert Einstein, Erwin Schrödinger, Werner Heisenberg, among others, that explored the physical properties of our world at an atomic level. They were probably unaware that their work could result in a technologic revolution allowing us to use so many different devices that surround us and keep us connected continuously (De Wolf, 2017). Even though significance can be tricky to measure, your work's potential academic or clinical implications should be considered a priori during your research question formulation.

Strategy 7: Focus on the primary outcome.

The choice of the main outcome should be supported by the aim and feasibility of the study. The design of the study is based on the main outcome and not on secondary questions. The main outcome might help to answer secondary questions. Therefore, secondary outcomes are useful to raise hypotheses to be tested in future studies but should never be used to change the study design. We recommend having robust and objective outcomes (e.g., mortality, hospitalization days, clinical complication, validated blood marker, bio signals, etc.). However, it is important to validate and justify your primary outcomes, their reliability and measurement tools, based on the literature or with your own pilot studies. Furthermore, although the use of combined outcomes (combining two events or markers) may be useful to increase a study power, they also decrease the interpretability of the findings. Researchers need to weigh the pros and cons before choosing a composite outcome. In addition, defining well your primary outcome is relevant to correctly select your statistical analysis and gives you the basis to the sample size calculation, required for a good powered study.

Strategy 8: Choosing the outcome – surrogate vs. clinical variables.

The outcomes may assume different types of data (e.g., categorical, continuous), and collection methods (e.g., self-report questionnaires, biological measures). These features must be contemplated following the study's goal and feasibility. Take into consideration the example of the different phase studies in drug approval. In phase 1 studies, the goals are mostly testing the effect of a drug in a physiological outcome (i.e., surrogate marker), while phase 3 studies aim the clinical improvement (i.e., clinical variable). A surrogate outcome is especially useful in early phases of investigation as it may allow small studies to be powered and allow additional mechanistic insights. Therefore, the outcome should be driven by your research question.

Strategy 9: Your study should be designed as such that a negative result would also be interesting.

Studies with positive and negative results compose the wall of knowledge discussed in Strategy 3. In clinical research, it is important not only to show the efficacy of new treatment but also to acknowledge the ones that might not be. The Covid-19 pandemic has shown the importance of negative results, demonstrating, in some cases, the potential harm of some interventions, such as hydroxychloroquine (Pacheco-Barrios & Fregni, 2020). Therefore, it is important to consider the interpretation and significance of negative results in your research question and to think about alternative hypotheses. Nevertheless, negative-outcome studies have decreased in literature in the latest years (Fanelli, 2012), despite showing most of the higher quality standards regarding its methodology compared with studies with positive results (Chiavetta, Martins, Henriques, & Fregni, 2014). The decrease in negative results in literature could affect this wall of knowledge, as is not only built with positive data results.

Strategy 10: Dedicate a reasonable amount of time exploring the literature on your question.

The choice of research question demands a lot of ponderation about each component (i.e., PICOT) and how they are related. One of the ways to help you understand the state of the art more efficiently is to start looking the most updated systematic reviews and meta-analyses. These articles provide a sum up of the literature about research topics, which helps to have a notion about the "big picture" of the current knowledge. But when there is a need to make decisions about the different components of research question (i.e., PICOT), it is advised to take a deeper look into the included studies in the systematic review and to search for new related studies. In order to organize your ideas, we highly recommend to create a summary and comparative tables to understand their hypothesis (i.e., from the last paragraphs of the introduction), how they proposed to answer the research question (i.e., from methods section), and what was the answer to the question (i.e., from the results and discussion sections).

All the strategies above provide a glimpse into how difficult the formulation of a research question can be. On the other hand, if all these aspects are thoughtfully considered, the research question will likely produce essential answers. Moreover, not only the outcomes, the interventions, and the practical implications of research should be considered, but also the ethical questions must be always pondered in light of the current knowledge. Clinical research must ensure equipoise principle while providing high-quality evidence that answers the research question. Hence, a good amount of time should be taken into reading about the topic and into going deep in the literature, because the research question is the key that will drive all the next steps of the study.

We believe that putting in to practice these strategies will help young researchers systematically improve the quality of their research questions and guide the creation of a valid research methodology. Furthermore, this will help to build the wall of knowledge with transparent, innovative, and significant future studies.

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Conflict of Interest

Dr. Fregni is the editor-in-chief of the Principles and Practice of Clinical Research journal. Therefore, he excused himself from the peer-review process and followed the journal guidelines for peer-reviewing when an editor co-authors a manuscript. He did not influence the editorial process and final publication decision.

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