VIEWPOINT

Why Stating Hypotheses in Grant Applications Is Unnecessary

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"Our hypothesis is that statins do not increase the risk of cancer." Such explicit statement of investigators' beliefs is often found in applications for research funding, which follows common advice on how to write grant applications by colleagues,[1-3] academic institutions, and funding agencies. The statement of the hypothesis is viewed as "the backbone of your grant."[1] Hence, many investigators, aware that hypothesis-driven research is highly regarded by funders and reviewers, declare their hypothesis in their grant applications. This hypothesis-centric approach, however, is problematic, as the following example of causal inference from observational data illustrates.

Suppose that the idea that using statins for more than 10 years causes cancer is spreading through social networks and causing much alarm because a large number of people use statins to prevent cardiovascular disease. We therefore decide to study the impact of statins on cancer. To do so, we apply for funding to support the analysis of a clinical database of millions of people. Because we believe that statins do not cause cancer, we write this piece's opening sentence ("Our hypothesis is that statins do not increase the risk of cancer") in our grant application. We then proceed to describe the design and analysis of our study. If our study gets funded, we analyze the data and obtain the following estimate: the 10-year risk of cancer is 1.01 times greater for long-term statin use compared with no statin use, and the 95% CI for this risk ratio goes from 0.99 to 1.03.

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Now imagine a universe identical to this one except for 1 thing: we believe that statins do cause cancer. In the parallel universe we also apply for funding, but we write "Our hypothesis is that statins increase the risk of cancer" in our grant application. We then proceed as we did in this universe to describe the same study design and data analysis, get funding, and obtain the same result: the 10-year risk ratio of cancer is 1.01 (95% CI, 0.99-1.03) for statin use compared with no use.

So here we are: 2 identical sets of results arising from 2 identical studies described in 2 grant applications that differ only in the statement of the researchers' hypothesis. In one grant application, researchers state their hypothesis is that statins do not cause cancer, whereas in the other application, researchers state their hypothesis is that statins do cause cancer. Assuming the researchers follow their stated protocol, their initial hypotheses, beliefs, guesses, or conjectures should be irrelevant to their results and inferences.

But, someone may ask, how can we evaluate whether the study appropriately tests a hypothesis if the hypothesis is not explicitly stated at the outset? In our view, the answer is that an uncontroversial analysis goal is not statistical hypothesis testing (which has been assailed for decades[4]) but rather is estimating the targeted effect or association as precisely and unbiasedly as possible with our data. Suppose for a moment we had some infallible procedure to determine whether any particular causal hypothesis is true or false based on our data only. When applied to the hypothesis "Long-term use of statins does not affect the risk of cancer," our procedure declares the hypothesis false. Unknown to us, the true causal risk ratio is 1.00001 and thus different from 1. Can we consider our job done and write an article that concludes "Long-term statin use affects the risk of cancer"? No. Our readers should immediately ask, "How much does statin use affect the risk of cancer?"

That is, we do not gain much information by knowing that long-term statin use causes lung cancer if we do not know the magnitude of the effect. (Also, let us not forget, we do not have an infallible method to determine whether a scientific hypothesis is true or false.) Before banning or restricting statin therapy, which has a large beneficial effect on cardiovascular disease, we need to know whether it increases cancer risk by, say, 10% or 0.001% in the target population.

In practice, we can identify a range of effect sizes that are very compatible with our data, as quantified by, say, the 95% compatibility ("confidence") interval.[5] In our study of long-term statin use vs no use, this interval goes from 0.99 to 1.03. Therefore, we would conclude that anything between a 1% decrease and a 3% increase in the risk of cancer is highly compatible with our data. This conclusion assumes that we succeeded in adjusting for all systematic biases (eg, confounding) and, therefore, that we need only worry about precision. Also, the earlier discussion presupposes the use of frequentist statistical analyses that are based exclusively on the data at hand. In bayesian analyses, each group of investigators must state their prior beliefs in the form of a prior probability distribution for the effect, and the resulting effect estimates will differ across groups that use different prior distributions.

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Rather than the superfluous guesses such as "Our hypothesis is that statins do not increase the risk of cancer," grant applications should describe the question researchers are asking, why they are asking it, and how they propose to answer it. One could further argue that framing the goal around a hypothesis might bias the research toward supporting the hypothesis. Therefore, funders should require a statement of the *quantitative* causal question and a detailed explanation of why answering that question is important, *whatever the quantitative answer might be*. When funding of a randomized trial is requested, the causal question is precisely articulated by the trial's protocol. Similarly, when funding for an observational study is requested, one helpful device to precisely articulate the causal question is to specify the protocol of the hypothetical randomized trial—the target trial—that would answer it.[6] A grant application that characterizes the causal question would specify the eligibility criteria, treatment strategies, outcomes, start and end of follow-up, and effect measures to be estimated. It would also specify the analysis methods for the target trial. Then funders should require a detailed description of the procedures and assumptions (eg, proposed confounders) to emulate the target trial and its analysis.

As an example, our grant application would explain that the alarm generated by the notion that long-term statin use causes cancer needs to be addressed with a precise quantification of the magnitude of the effect of statins on cancer, especially because possible harms must be weighed against the well-known benefits of statins. Thus, the application would specify the protocol of a target trial of statins that can be reasonably emulated using the available observational data, and the emulation procedures and assumptions. The statistical methods section could replace power calculations based on testing 1 hypothesis with precision calculations to indicate the expected yield of information to estimate the effect of statins on cancer risk.[5]

This reorganization of the proposal is a way to operationalize long-standing calls for shifting research away from testing for effects to estimating effects.[4,5,7] This shift would decrease the use of statistical tests of null hypotheses as the sole basis of decision making, which is, as has long been argued,[7-10] misguided. Decisions need to consider many factors (systematic bias, harms and benefits, cost, available courses of action, etc), as well as the precision of results, which may be visualized by a compatibility interval as we did earlier. Because interval estimates show a range of values (alternative hypotheses) that are highly compatible with the data, descriptions of results should focus on the interval end points rather than on whether the null value is included in the interval. A more detailed way to visualize precision is to graph *P* values across a relevant range of effect sizes.[7] In our example, the investigators would then present not only a *P* value for the hypothesis of no effect (ie, risk ratio of 1) but also for a range of alternatives of clinical relevance, including risk ratios representing small but important effect sizes. *P* values for those alternatives can be obtained as immediate by-products of the methods that produce the effect estimates.[7]

In summary, funding applications need to be evaluated by their relevance and methodological quality rather than by qualitative assertions about reality before the study is conducted. Tell funders your quantitative question, why it is important, and how you plan to answer it. If the question is sufficiently important, your methodology is sound, and you follow your protocol, they should not care about what you guess the qualitative answer will be.

ARTICLE INFORMATION

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