

Let Medicine Lead the Way Beyond the Registration of Clinical Trials: Registering Hypotheses

NORMAN A. DESBIENS, MD

ABSTRACT: There has been much recent interest in improving the quality and reporting of clinical research. Major journals now require clinical trialists to register studies a priori and follow specific reporting guidelines. While best developed for randomized, controlled trials, guidelines for other study types are being developed. A hypothesis is presently available for 4 of 5 publications reporting randomized, controlled trials, much less common for other study designs and scarce in the general scientific literature. The declaration of a hypothesis or its absence should be a standard feature of all scientific

reporting. The recording of the hypothesis in a registry before data collection would assure readers that the hypothesis was a priori. Medicine has been in the vanguard in requiring methodological rigor in the reporting of science and should again push the envelope by developing a hypothesis registry. If successful, the gauntlet would be thrown down for the rest of science. **KEY INDEXING TERMS:** Research, Research methodology; Hypotheses; Scientific method; Registries. [Am J Med Sci 2008;335(2):137–140.]

The recent requirement by journals that clinical trialists register their studies a priori has been generally welcomed by interested parties.¹ It has been recognized that the profit motive can influence the conduct and reporting of trials by researchers, pharmaceutical companies, and device manufacturers.² Academic physicians may be subject to explicit or implicit influences on the proper conduct of clinical trials—so-called intrinsic conflicts of interest.³ Target sample size, 1 of the 20 items in the minimum trial registration dataset recommended by the International Clinical Trials Registry Platform, should allow interested parties to estimate the effect size being sought.⁴ But what about studies that use other designs?

Improved Reporting of Medical Science

There is evidence that recently enacted journal submission requirements have already improved the quality of reporting of clinical trials, and perhaps the quality of the science behind the trials.

From the University of Tennessee, College of Medicine–Chattanooga Unit.

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Correspondence: Dr. Norman A. Desbiens, Department of Medicine, University of Tennessee College of Medicine–Chattanooga Unit, Box 94, 975 E. Third Street, Chattanooga, TN 37403 (E-mail: nadesbiens@gmail.com).

Most medical journals with a high citation index now require that manuscripts reporting the results of randomized, controlled trials (RCTs) contain a sample size or power calculation.⁵ Reporting standards for other study types, while being developed, are still not prevalent.

The Centrality of Hypotheses in Science

The history of the hypothesis as a key component of the scientific method can be traced to Aristotle's proposal of a scientific method based on alteration between inductive and deductive steps based on a mental model that today would be referred to as a hypothesis. Medieval schoolmen, especially Robert Grosseteste, further refined this methodology.⁶ More recently, Karl Popper⁷ has re-emphasized the importance of hypotheses being testable and falsifiable.

Despite the centrality of hypotheses in the scientific method, a recent study of prominent medical journals suggests that nearly half of research papers do not explicitly state hypotheses or that they are not inferable from the text.⁸ In contradistinction, RCTs report explicit or inferable hypotheses 4 of 5 times. Compared with other study types, RCTs have about 19 times greater odds of stating hypotheses or sample size calculations. The reporting of hypotheses is even scarcer in the general scientific literature, where only 1 in 10 articles in *Science* and *Nature* explicitly states a hypothesis.^{9,10}

Hypotheses Should Be Clearly Stated

The declaration of a hypothesis should be a standard feature of all scientific reporting. Even better, a hypothesis should be registered at the time a study is conceptualized. Of Hill's 7 postulates for causality, only the lack of temporal ambiguity is unassailable: a cause must precede an effect.¹¹ Similarly, a dated hypothesis stated a plausible amount of time before a publication would strengthen the temporal inference.

Arguments Favoring the Registering of Hypotheses

Why is the a priori statement or registration of a hypothesis crucial to the proper conduct of science? First, it keeps the researcher honest. One of the great temptations in medical research, abetted by computerization, is checking for associations among variables and then designing the study. This method is sure to lead to many associations that are later found to be irreproducible.¹² While such an exercise might be helpful in generating hypotheses, researchers often have strong biases to produce scholarly work that tests hypotheses. In the past, this proclivity, which may improve faculty promotion and scholarly repute, was abetted by publication bias.¹³ Even unconscious and unintentional self-serving biases may lead scientists to present their work as if it were hypothesis-driven.¹⁴ One of the great benefits of rigid scientific methodology is that it minimizes the chance that unconscious bias will impede truth.

Second, the registration of hypotheses will give peer reviewers and readers more confidence. When asked to do so by reviewers, authors often state hypotheses in revisions. However, the reviewer is then left to wonder if this was indeed their intention, or whether it was an a posteriori hypothesis, or indeed whether the author is trying to please the reviewer in order to increase the chances of publication. Though the dated registration of a prior hypothesis does not guarantee that data had not been analyzed before the registration and that the hypothesis was really a posteriori,¹⁵ reporting in the manuscript when data were collected and analyzed (similar to the submission and resubmission date trail reported by some journals) would further strengthen the claim that the hypothesis was a priori.

A third benefit of preregistration of a hypothesis is that it prevents the overfitting of multivariable models. Rather than determining the number of cases they need to address a hypothesis based on the degrees of freedom of the variables in the model, researchers may have accessed data collected for other reasons and then looked at many variables that might be associated with a given outcome in a multivariable model. Unless there are an adequate number of cases for the degrees of freedom subsumed by the model, it will be overfitted and the

findings may not be reproducible in an independent dataset.¹⁶ In addition, the confidence intervals around an adjusted association will almost certainly be too narrow and biased.¹²

What Possible Objections?

Given these obvious benefits, why might researchers object to registering their hypotheses? One possibility could be disagreement about foundational issues in science. Some may perceive that the first step in science is observation from nature, and that deductive reasoning from these observations leads to hypotheses that are testable.¹⁷ For example, the International Committee on Harmonization¹⁸ states that "Like all clinical trials, these exploratory studies should have clear and precise objectives. However, in contrast to confirmatory trials, their objectives may not always lead to simple tests of predefined hypotheses. In addition, exploratory trials may sometimes require a more flexible approach to design so that changes can be made in response to accumulating results. Their analysis may entail data exploration." However, Gauch⁶ has strongly argued that even observation must be based on hypotheses that drive the investigation. These types of disagreements need not stymie the development of a hypothesis registry. Either not reporting the hypothesis in the registry or reporting "none" in an appropriate field would indicate that the findings of a given study were exploratory or serendipitous and would require further corroboration in independent studies. Even in observational studies, registration keeps one honest in the reporting of the chronology of research and mitigates hindsight and other biases. For example, a number of articles in *Nature* and *Science* do not mention a hypothesis initially, but later discuss that findings are consistent with a hypothesis.⁹ With proper methodology, reliance on potentially biased memory or impression is unnecessary.

Scientists may feel that the demand for prespecification of a hypothesis is a methodological straight-jacket that stifles creativity. This argument harks back to that of practitioners who posit that evidenced-based medicine subtracts from individual judgments about patients and diminishes the art of medicine.¹⁹ Scientific methods do impose rigor on the approach to the solution of a scientific problem, but it is necessary. There is still plenty of room for creativity in choosing an area to study, formulating a testable hypothesis, deciding on sampling scheme and subject recruitment, and introducing and discussing findings.

Some scientists might feel that boldly stating and dating a hypothesis will prevent the serendipity in medical science that they value. The lore of medical science is replete with the importance of kismet. But surely hypothesis-driven work will not prevent serendipity. There are many examples of hypothesis-

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