Importance of the Study Protocol in Epidemiologic Research

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The overall quality of an epidemiologic research project depends on how well both the design and execution phases of the project have been accomplished. The written prestudy protocol, by serving as a bridge between these two project phases, plays a pivotal role in determining the success of the total research effort. The study protocol can contribute to improved observational research in four key areas. Arguments are presented for enhancing the scientific integrity of observational studies and for providing better study documentation, efficiency, and communications, all through careful prestudy planning.

One of the major challenges in conducting scientific research is to anticipate and to address in the study plan the criticisms likely to surface opposite the research conclusions, whatever those conclusions may be. As described by Ostle,¹ scientific criticisms most often arise from one of the following four arguments: the assumptions underlying the study were faulty, the study was poorly designed, the study was poorly executed, and the interpretation of the study was invalid. The first two arguments relate to conceptual issues, and the latter two relate to issues of study execution. Overall study quality depends on how well all these arguments have been addressed and relates to all aspects of the research project, not just to the data collection.

As scientific investigations, etiologic studies usually are initiated on the premise they will contribute to a better understanding of the causal relationships between specific environmental factors and health outcomes. The goal in designing and executing an etiologic study is ultimately the same as that of any other scientific study: to produce convincing arguments—arguments that counter the likely criticisms—in support of focused, and, one hopes, valid conclusions or explanations. In this context, the overall scientific quality of a study must be judged simultaneously in terms of the weak points in the arguments (these are the points usually recognized by critics) and the contribution of the conclusions or explanations to new knowledge.

There are weaknesses associated with studies that may be beyond the reach of the investigators. This is a frequent occurrence in observational studies involving human subjects and may be a particularly intractable problem where investigations are undertaken primarily to address nonscience issues. Although there may be good reasons for conducting studies under these circumstances, science is unlikely to be advanced by studies with such limitations. If we accept the well-conducted, randomized, double-blind clinical trial as the “gold standard” of scientific quality as did Feinstein recently,² then the quality of each epidemiologic study can be assessed in terms of how well it performs against that standard. The act of preparing a detailed research protocol and having that protocol reviewed by peers is perhaps the singly most important step in bringing epidemiologic studies into alignment with controlled clinical trials.

The Study Protocol

Experienced investigators have long acknowledged that prestudy planning and peer review is crucial to the scientific success of any research project. The written study protocol, as the most visible manifestation of that planning, is the anvil on which most research proposals come to be tempered. This report focuses on arguments to reinforce the positive relationship between the research protocol and the overall quality and acceptance of the resulting research study.

The written protocol can contribute to overall study quality through a variety of routes, several of which come immediately to mind: (1) by enhancing the scientific integrity of the research, (2) by prescribing and

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initiating the study documentation process, (3) by increasing the efficiency of the total work effort, and (4) by serving as a communication link. Although additional routes could be enumerated, these four will suffice to illustrate the importance of the relationship between the protocol and the scientific quality of a study. The first route, scientific integrity, concerns the research design, and thus, will be treated in greatest detail. The latter three routes of contribution primarily relate to issues of study execution.

Scientific Integrity

Among other descriptors, the American Heritage Dictionary, Second College Edition, defines protocol as "the plan for a medical or scientific experiment." An immediate problem facing the epidemiologist is that most human health research is observational, not experimental. Moreover, it is usually not possible to collect epidemiologic data in the double-blind mode of clinical trials and, certainly, homogeneity in the unit of observation, a characteristic of the "hard" sciences is, by and large, lacking in traditional epidemiologic investigations. Because the investigator has no control over the treatment regimen (the exposure conditions), one may ask why it is necessary to develop and adhere to a protocol while conducting an observational study. After a little reflection, it may be seen that preparing a research protocol is essential if the scientific credibility of the observational study is ever to approach that of the randomized clinical trial. The reasons for this are multiple, but a major underlying theme is integrity.

The apparent scientific integrity advantage of the clinical trial stems from the focused nature of the study design and the use of experimental procedures to control or account for sources of variability. Among variability accounting features of the clinical trial are (1) randomization in treatment assignment to assure the source population for the exposed and nonexposed groups is the same except for "a flip of the coin," (2) use of restriction to eliminate sources of variability extraneous to the main interest of the experiment, and (3) use of a double-blind study design, where feasible, to remove the effects of interactions between the observer and the observed mediated through either's knowledge of exposure or disease status. It may be argued that near equivalence can be achieved in observational research through careful selection of the study setting and through preparation of and adherence to an appropriate protocol.

Consider first the issue of study focus. The clinical trial typically focuses from the start on one issue, that being a weighing of specific beneficial effects of a proposed new treatment against the effects of a standard treatment. This principal focus is established before any data collection has begun. The equivalent focus in the observational setting occurs (1) where the principal issue has been identified, well-researched, and succinctly stated in advance of data collection and in absence of foreknowledge as to what the formal data-collection process will produce and (2) where the observational setting permits collecting new scientific data pertinent to resolving the issue. This is not to disparage data-gathering efforts such as case reporting, surveillance activities, or cluster investigations that cannot achieve such a high degree of focus, but rather to suggest that these latter efforts should not be expected to yield convincing scientific arguments as to the validity of an etiologic hypothesis.

A conservative approach toward safety notwithstanding, there can be a powerful temptation when observing complex phenomena, such as the interplay of factors affecting human health, to lose sight of the many ways in which a set of observations can be rationalized after the fact. This is true regardless of whether a "shotgun" approach had been used in collecting or analyzing the data or the analyses had been proposed after pursuing part or all of the data set. Under all these circumstances, attention is likely to be drawn to unusual patterns in the data. In the enthusiasm of the moment, the observed association is recognized as the one that should have been hypothesized at the onset. This type of posterior reasoning process can easily undermine the integrity of the research. Vandenbroucke has discussed this issue in the context of conducting secondary analyses of data drawn from studies with extensive data-collection components. Inevitably, the chances of achieving an interesting result are increased simply by the number of possible analysis combinations.

A converse situation arises when plausible relationships are discounted simply on the basis that multiple analyses had been performed, when in fact, many of these were of a mindless nature. In all these situations, the integrity of the research is dependent on the intellectual honesty and reasoning prowess of the investigators. Yet that honesty and prowess can be difficult to evaluate given a lack of evidence for focus before data collection. This is especially true when the initial views and intentions of the investigators were not specified in advance. The protocol that provides the necessary background information and states clearly how the research objectives will be met becomes a major tool for assuring the integrity and raising the scientific quality of the observational study to almost the level of a well-conducted clinical trial.

Now let us consider the means of controlling sources of variation within observational compared with experimental settings. In an experimental setting, variability reducing tools include randomization to control "on average" for the effects of unmeasured factors that might otherwise confound a study, restriction to eliminate sources of variability not considered germane to the research objectives, and double-blinding to minimize biasing effects due to interactions between the observers and the observed.

Each of these devices typically is less available or absent in the observational setting. However, by understanding what is accomplished by each device, a comparable analogue can be found for the observational study and defended in the study protocol. The analogue to randomization is selecting a control group that resembles the exposed group(s) in unmeasured factors that could confound estimates of the disease-exposure
effect parameter. This must be accomplished as part of the conceptual process before actual data collection and should be justified in the written protocol. The rationale will be subjective because one is attempting to control for unmeasured factors. Thus, it is the process by which individuals come to belong to the study or to the control group that is important. As knowledge regarding the theory of confounding has expanded, so has our ability to determine when confounding may have important study design implications. It is incumbent on researchers to identify the observational setting that assures a satisfactory control group and to present convincing arguments that the equivalent of randomization has been achieved by their study design.

Restriction, another important device for controlling variability in scientific investigations, is a hallmark for experimental studies. Unfortunately, restriction generally is less available as a means of reducing complexity in the "natural experiment." The net result is that the analysis of attributable actions is less certain. Although there may be some opportunity to select a study setting that offers natural analogues to restriction, it is more likely that those analogues will be achieved through data analysis options.

Restriction may be used to exclude individuals from either an observational or an experimental study. Such exclusions are generally justified on the basis of the added difficulties in interpreting the study findings with these individuals included. In observational studies this use of restriction is feasible to the extent that sample size limitations do not preclude drawing meaningful conclusions from the remaining data. Alternatively, individual study participants may be stratified into homogeneous groups before data analysis. Analyses can then be performed both within and among strata.

Restrictions also may be used to narrow the exposures and health outcomes under consideration. A particular advantage of the experimental study is that levels of the exposure measure can be restricted purposefully so as to maximize information at a critical dose level and avoid the necessity of subjecting the exposure measure to arbitrary categorizations or transformations during data analysis. Vandenbroucke has pointed out problems related to arbitrary and after-the-fact categorization of exposure measures in observational studies. Each unique transformation or categorization will yield some impact on the calculated effect measure. Consequently, the strength of any arguments that rely on analyses for which a transformation was chosen simply because it yielded the greatest association should be discounted accordingly. The appropriate analogue in the observational setting is to take the time to specify in the study protocol a well-reasoned a priori categorization of the exposure measure. The price of being indecisive and opting to analyze data under numerous exposure categorizations could well be a weakening of the arguments in support of the study conclusions.

The objective of the double-blind study design is to guard against distortions in the observations that may result from researcher or participant knowledge of exposure or disease status. In the clinical trial, this is accomplished through third-party administration of the treatment and through nondisclosure of treatment assignment to the study subject and the health status evaluator. In the observational study analogue, there may be numerous ways of blinding the researcher to exposure status when subjectively evaluating a health outcome, however, it may or may not be possible to obtain data directly from study participants with any assurance that foreknowledge of exposure or disease status has not influenced the response with respect to the other outcome. Certainly, those data collection procedures are to be preferred that rely on objective measurements of both exposure and health outcome status. This issue of independence in the reporting of exposure and disease status is an important one that should specifically be addressed during the preparation of the study protocol.

Documentation

As previously indicated, the written protocol can be a major asset when it comes to study documentation. This is true, of course, to the extent that the conduct of the study is congruent with the requirements set forth in the protocol. For this to be assured, the requirements should be unambiguous, achievable, justifiable, verifiable, and written. By reflecting consensus agreements on the requirements and clearly stating those requirements, the protocol supports the principles of total quality.

When requirements are recognized as being applicable to multiple studies within a research unit, it can be advantageous to write these requirements as standard operating procedures (SOPs). The SOP then becomes an efficient vehicle for maximizing data quality while minimizing the effort involved in preparing future protocols. As it is becoming increasingly common to update existing epidemiologic studies (there are large cost-saving advantages in such enterprises) proper documentation of the prior study can be an invaluable aid in performing the update, particularly where there has been a change in principal investigators.

Efficiency

On balance, the efficiency gains realized through addressing quality and documentation issues at the protocol stage will more than offset any loss in efficiency due to time spent preparing the protocol. Prevention of problems is the key to achieving quality. On the preventive side of the ledger, efficiency may result from such avoidances as having to repeat a series of statistical analyses because of errors detected in the data set at analysis time or, worse yet, having to repeat a study after a determination that it is inadequate for the intended use.

Efficiency also may be realized by setting requirements that are appropriate to the overall study objectives rather than striving to achieve perfection in all data collection. The act of preparing a protocol usually facilitates taking a coordinated approach to the overall
project. This helps eliminate nonessential activities. An additional benefit that comes from the coordination of research activities is avoidance of delays in the project because tasks were not properly sequenced. One of the more important efficiency gains occurs when the final report of the study is to be written. It will often turn out that less time is spent searching for misplaced information and that much of the protocol language can be directly transferred to the final study report.

Communication Link

As a communication link, the written protocol connects the investigators to their funding source, to other members of the research team, to peer reviewers, and finally to those who would use the research findings to support policy decisions. It is surely a naive sponsor that is so accepting as to fund a project in the absence of a well-conceived research plan. However, there may also be a danger to the investigators for failure to specify what the project sponsors can expect in return for funding the research. Unless there is agreement on the specific nature of the research via a detailed study protocol, the investigators may find themselves subject to demands from the funding source after the project has been initiated.

In the execution phase of a research project, the protocol also provides a link for uniting team members “in the quality chain.” Although no substitute for day-to-day oversight of the progress of the research, reviewing the protocol with project workers can help demonstrate to them the importance of their role in the overall project and help resolve issues that arise during the conduct of the study.

Conclusions

In consideration of the importance of a peer-reviewed prestudy protocol in enhancing the integrity of the research, in prescribing and initiating the documentation process, in increasing work efficiency, and in serving as a communication link, it is difficult to imagine how a quality study could be conducted without a proper research protocol. Admittedly, preparing a written protocol and having it properly reviewed takes time and energy. The advantages of having that protocol will be evident to almost anyone charged with external review of the project. In the end, however, the principal beneficiaries of having prepared a study protocol are the researchers themselves. It is their opportunity to reflect on what they have written that contributes most to forcing clarity in the conceptualization of the research project and, hence, to assuring its success.

References