AHA Scientific Statement

The Clinician as Investigator
Participating in Clinical Trials in the Practice Setting

Appendix 1: Fundamentals of Study Design

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Study Types

Before the present era of the randomized clinical trial (RCT), most published research was observational in nature. Now, however, there are many types of studies, differing in design and complexity but all aimed at answering a scientific question. The most basic type of study is the case report, which presents an observational report of the course of a single subject; there may or may not have been an intervention. The case report is the building block of the case series, accumulated data from several case reports. On a larger scale, the case registry collects data on similar patients without specifying an intervention. Although this sort of study does not evaluate a new therapy in a randomized fashion, it does serve to develop a body of data on a new technique (such as intracoronary stenting), disease (such as primary pulmonary hypertension), or treatment strategy (as for unstable angina) that may help formulate hypotheses and guide the development of new RCTs. Case registries can provide material for epidemiological studies and health services research. A registry also permits the evaluation of treatment strategies over time and may be particularly useful in an institution’s own quality-improvement program. Because of inherent biases, a registry cannot be used to effectively compare two therapies. A case series or registry is the easiest type of study for an individual investigator to set up alone or in collaboration with local colleagues. Registries require subjects to give informed consent only if there is any way an individual can be identified; this informed consent also addresses HIPAA (Health Insurance Portability and Accountability Act) concerns. Regardless of whether informed consent is required, the local Institutional Review Board must review the project.

Almost as basic is a nonrandomized clinical trial, also known as a single-arm study, in which study participants are simply assigned a known therapy and monitored. The “control” for this type of study is either historical data or a concurrent single-arm study. Nonrandomized clinical trials may be advantageous because they do not deny the experimental treatment to any subjects and thus may be considered more ethical. In addition, enrolling sites may find recruitment easier than in randomized trials, because prospective subjects face no uncertainty about the therapy they may receive. The data may be used to assess the efficacy of a drug or device, but given the problematic nature of comparisons with either a concurrent single-arm study or historical controls, the findings cannot reliably be used to compare one therapy with another.

RCTs are the backbone of today’s “evidence-based medicine.” In these studies, an investigational therapy or intervention is assigned at random to a participant, either an alternative standard therapy or placebo assigned to other participants as controls. The randomization process avoids bias in selecting treatments, which can confound the trial (e.g., if clinicians selected treatment in β-blocker heart failure trials, patients with worse heart failure might not have received the active drug, with less likelihood of finding benefit from the use of β-blockers in this setting). In trials in which treatments are randomized, baseline characteristics of the study arms are usually comparable, and when the results between (or among) the groups are compared, differences in outcome cannot be confused by bias in selecting treatments or by baseline differences between the groups. In practice, randomization takes place after a subject has been determined to be eligible and has given informed consent. In large,
multicenter trials, the enrolling physician generally contacts a central trial coordinating center by telephone, fax, or e-mail, and the center responds with a number that corresponds to an enrollment kit and study drug for that specific patient. Although more subject to error and tampering, in some trials, randomization may also be accomplished by a system of sequenced, sealed envelopes that contain the treatment assignment.

**Trial Size**
The number of patients to be studied is a prime consideration in the design of clinical trials. Although larger trials generally provide more reliable data, there are often economic obstacles to mounting large-scale trials, and some circumstances, such as rare disease states, individually tailored therapies, or studies involving members of small, isolated communities, make recruiting large numbers of subjects impractical or impossible. Calculating the appropriate number of subjects needed to answer the scientific question while keeping economic and clinical realities in mind is an important part of trial design. This topic is discussed more fully in Appendix 2 (available online only at http://www.circulationaha.org [Circulation. 2004;109:e305–e307]).

**Large, Simple Trials**
A type of randomized trial that is gaining favor in some therapeutic areas is the large, simple trial. These trials eschew detailed data collection and extensive screening processes in favor of rapid enrollment and the ability to detect modest differences in hard clinical end points between treatments. This reduction in complexity and per-subject cost allows rapid enrollment of very large numbers of subjects—often tens of thousands—with the idea that subgroups of participants will respond similarly so that less detailed baseline characterization is necessary. Another important aspect for the clinician to consider is that a large, simple trial typically does not make specifications about patient care; all decisions (other than the randomized treatment) are left to the physician’s discretion. This arguably provides a better real-world picture of what would happen if the experimental treatment were adopted.

**Blinding**
Depending on the nature of the intervention, an RCT may or may not be blinded. A single-blinded study is one in which the investigator knows what the study allocation is, whereas the patient does not. A double-blinded trial is one in which neither the subject nor the investigator knows what treatment has been assigned. Clearly, some RCTs cannot be blinded at all; for example, in a trial comparing angioplasty with coronary artery bypass surgery, both the patient and the investigators will know the study assignment. In these situations, some bias may be avoided by keeping individuals involved in end-point adjudication blinded to treatment assignment. Sham procedures are sometimes advocated to achieve blinding, but this raises serious moral concerns, is very controversial, and should never be considered without strict ethical evaluation. Drug studies lend themselves to double blinding, although in some, such as those to evaluate markedly different anticoagulants, blinding to treatment assignment requires substantial trial infrastructure and effort. Some studies go to great lengths to protect double blinding, such as having routine blood draws shipped from study sites to a central laboratory to be analyzed and including sham “dosage changes” to subjects who are actually receiving placebo. Although double blinding adds expense and complexity to a trial, it eliminates biases that might be introduced by patient or investigator expectations, which improves the reliability of the results. The double-blind RCT has been considered the “gold standard” for study design.

**End Points**
The design of the study will also vary according to the type of end point being used in the study (in other words, what is actually being measured). The most valuable end points may be “hard” clinical events, such as death, stroke, or myocardial infarction. The results from studies that use these types of end points can be applied directly to clinical practice with confidence. Other studies may measure clinical findings such as blood pressure, degree of glucose control, ejection fraction, or patency of coronary arteries. Trials that use such surrogate end points can be much smaller than those that require clinical end points, and they often require a shorter time to complete. If a trial were able to show, for example, a comparable degree of blood pressure control between two medications (a surrogate end point) one would hope that mortality (a clinical end point) would also be comparable. This, unfortunately, is not always true, which highlights the importance of the trials that use clinical end points. However, smaller studies that establish mechanisms and efficacy are the necessary building blocks for larger trials with clinical end points, and well-designed registries have generated much useful data; all should therefore be considered valuable to the potential investigator.

Not all trials measure purely clinical end points, however. Many trials include an economic component that measures such factors as length of hospital stay, overall cost of treatment, or quality of life. Because the economic and social circumstances of real-world medical care often introduce factors not evident in a controlled trial setting, these types of analyses frequently provide a valuable look not just at which therapy is superior in the laboratory, but which therapy would be superior as medicine is actually practiced.

**Follow-Up**
The length and frequency of follow-up are important considerations in the design of a clinical trial. These aspects will depend on the disease state, the therapy, and the population being studied, but an investigator participating in a study should be aware of what will be required. Some studies simply call for subjects to return postcards or surveys or to complete a telephone interview; others require office visits and laboratory work over a period of years. Investigators should ensure that study personnel will be sufficient to handle the follow-up tasks that may be required.

**Monitoring**
The Code of Federal Regulations and Good Clinical Practice guidelines for clinical research specify that trial sponsors are
responsible for ensuring that a clinical investigation is being conducted according to protocol. This process generally involves on-site visits by a sponsor-designated monitor and may include site audits and inspections. The types of monitoring being done are usually outlined in a monitoring plan provided with the study protocol.

Conclusions
The world of clinical trials has produced a remarkable variety of study designs, each intended to maximize the utility of the data generated. Medical journals frequently publish articles highlighting innovations in trial design, and certain journals such as Clinical Trials and Controlled Clinical Trials are dedicated entirely to this area. A more in-depth review of study design is available to the interested reader.10

References

KEY WORDS: AHA Scientific Statements trials evidence-based medicine
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doi: 10.1161/01.CIR.0000128807.57602.61

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2004 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/109/21/e302

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