

## INFORMATION SHEET

# Drug Study Designs

*Guidance for Institutional Review Boards and Clinical Investigators*

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Final

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Office of Good Clinical Practice

Center for Drug Evaluation and Research

Center for Biologics Evaluation and Research

Before a new drug or biologic can be marketed, its sponsor must show, through adequate and well-controlled clinical studies, that it is effective. A well-controlled study permits a comparison of subjects treated with the new agent with a suitable control population, so that the effect of the new agent can be determined and distinguished from other influences, such as spontaneous change, "placebo" effects, concomitant therapy, or observer expectations. FDA regulations [21 CFR 314.126] cite five different kinds of controls that can be useful in particular circumstances:

1. placebo concurrent control
2. dose-comparison concurrent control
3. no-treatment concurrent control
4. active-treatment concurrent control, and
5. historical control

No general preference is expressed for any one type, but the study design chosen must be adequate to the task. Thus, in discussing historical controls, the regulation notes that, because it is relatively difficult to be sure that historical control groups are comparable to the treated subjects with respect to variables that could effect outcome, use of historical control studies has been reserved for special circumstances, notably cases where the disease treated has high and predictable mortality (a large difference from this usual course would be easy to detect) and those in which the effect is self-evident (e.g., a general anesthetic).

Placebo control, no-treatment control (suitable where objective measurements are felt to make blinding unnecessary), and dose-comparison control studies are all study designs in which a difference is intended to be shown between the test article and some control. The alternative

study design generally proposed to these kinds of studies is an active-treatment concurrent control in which a finding of no difference between the test article and the recognized effective agent (active-control) would be considered evidence of effectiveness of the new agent. There are circumstances in which this is a fully valid design. Active-controls are usually used in antibiotic trials, for example, because it is easy to tell the difference between antibiotics that have the expected effect on specific infections and those that do not. In many cases, however, the active-control design may be simply incapable of allowing any conclusion as to whether or not the test article is having an effect.

There are three principal difficulties in interpreting active-control trials. First, active-control trials are often too small to show that a clinically meaningful difference between the two treatments, if present, could have been detected with reasonable assurance; i.e., the trials have a high "beta-error." In part, this can be overcome by increasing sample size, but two other problems remain even if studies are large. One problem is that there are numerous ways of conducting a study that can obscure differences between treatments, such as poor diagnostic criteria, poor methods of measurement, poor compliance, medication errors, or poor training of observers. As a general statement, carelessness of all kinds will tend to obscure differences between treatments. Where the objective of a study is to show a difference, investigators have powerful stimuli toward assuring study excellence. Active-control studies, however, which are intended to show no significant difference between treatments, do not provide the same incentives toward study excellence, and it is difficult to detect or assess the kinds of poor study quality that can arise. The other problem is that a finding of no difference between a test article and an effective treatment may not be meaningful. Even where all the incentives toward study excellence are present, i.e., in placebo-controlled trials, effective drugs are not necessarily demonstrably effective (i.e., superior to placebo) every time they are studied. In the absence of a placebo group, a finding of no difference in an active-control study therefore can mean that both agents are effective, that neither agent was effective in that study, or that the study was simply unable to tell effective from ineffective agents. In other words, to draw the conclusion that the test article was effective, one has to know with assurance that the active-control would have shown superior results to a placebo, had a placebo group been included in the study.

For certain drug classes, such as analgesics, antidepressants or anti-anxiety drugs, failure to show superiority to placebo in a given study is common. This is also often seen with antihypertensives, anti-angina drugs, anti-heart failure treatments, antihistamines, and drugs for asthma prophylaxis. In these situations, active-control trials showing no difference between the new drug and control are of little value as primary evidence of effectiveness and the active-control design (the study design most often proposed as an alternative to use of a placebo) is not credible.

In many situations, deciding whether an active-control design is likely to be a useful basis for providing data for marketing approval is a matter of judgment influenced by available evidence. If, for example, examination of prior studies of a proposed active-control reveals that the test article can very regularly (almost always) be distinguished from placebo in a particular setting (subject population, dose, and other defined parameters), an active-control design may be reasonable if it reproduces the setting in which the active-control has been regularly effective.

It is often possible to design a successful placebo-controlled trial that does not cause investigator discomfort nor raise ethical issues. Treatment periods can be kept short; early "escape" mechanisms can be built into the study so that subjects will not undergo prolonged placebo-treatment if they are not doing well. In some cases randomized placebo-controlled therapy withdrawal studies have been used to minimize exposure to placebo or unsuccessful therapy; in such studies apparent responders to a treatment in an open study are randomly assigned to continued treatment or to placebo. Subjects who fail (e.g., blood pressure rises, angina worsens) can be removed promptly, with such failure representing a study endpoint.

IRBs may face difficult issues in deciding on the acceptability of placebo-controlled and active-control trials. Placebo-controlled trials, regardless of any advantages in interpretation of results, are obviously not ethically acceptable where existing treatment is life-prolonging. A placebo-controlled study that exposes subjects to a documented serious risk is not acceptable, but it is critical to review the evidence that harm would result from denial of active treatment, because alternative study designs, especially active-control studies, may not be informative, exposing subjects to risk but without being able to collect useful information.

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