Non-Inferiority Clinical Trials to Establish Effectiveness

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
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Contains Nonbinding Recommendations

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This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

I. INTRODUCTION

This document provides guidance to sponsors and applicants submitting investigational drug applications (INDs), new drug applications (NDAs), biologics licensing applications (BLAs), or supplemental applications on the appropriate use of non-inferiority (NI) study designs to provide evidence of the effectiveness of a drug or biologic, usually because a superiority study design (drug versus placebo, dose response, or superiority to an active drug) cannot be used.[2] The guidance gives advice on when NI studies intended to demonstrate effectiveness of an investigational drug can provide interpretable results, how to choose the NI margin, and how to test the NI hypothesis.

This guidance does not provide recommendations for the use of NI study designs to evaluate the safety of a drug.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in FDA guidance documents means suggested or recommended, but not required.

This guidance finalizes the draft guidance for industry, *Non-Inferiority Clinical Trials*, published in 2010. In addition, it supersedes the guidance for industry, *Antibacterial Drug Products: Use of Noninferiority Trials to Support Approval*, also published in 2010, which will be withdrawn.

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[1] This guidance has been prepared by the Office of Biostatistics and the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) and the Center for Biologics Evaluation and Research (CBER) at the Food and Drug Administration.

[2] For the purposes of this guidance, all references to *drugs* include both human drugs and therapeutic biologic products unless otherwise specified. While most concepts discussed will be broadly applicable, certain issues related to vaccines, such as the choice of the NI margin when the study endpoint is the level of antibodies, would call for consultation from CBER.

II. BACKGROUND

FDA's regulations on adequate and well-controlled studies (21 CFR 314.126) describe four kinds of concurrently controlled trials that provide evidence of effectiveness. Three of them — placebo, no treatment, and dose-response controlled trials — are superiority trials that seek to show that a test drug is superior to the control (placebo, no treatment, or a lower dose of the test drug). The fourth kind, comparison with an active treatment (active control), can also be a superiority trial, if the intent is to show that the new drug is more effective than the control. More commonly, however, the goal of such studies is to show that the difference between the new and active control treatment is small — small enough to allow the known effectiveness of the active control, based on its performance in past studies and the assumed effectiveness of the active control in the current study, to support the conclusion that the new test drug is also effective. How to design and interpret the results of such studies so that they can support a conclusion about effectiveness of the new drug is challenging.

Active controlled trials that are not intended to show superiority of the test drug but rather to show that the new treatment is not inferior to an unacceptable extent were once called clinical equivalence trials. The intent of an NI trial, however, is not to show that the new drug is equivalent, but rather that it is not materially worse than the control. Therefore, the interest is one-sided. The new drug could be better than the control, and therefore at a minimum non-inferior, but it would not be equivalent.

The critical difference between superiority and NI trials is that a properly designed and conducted superiority trial, if successful in showing a difference, is entirely interpretable without further assumptions (other than lack of bias) — that is, the result speaks for itself and requires no extra-study information. In contrast, the NI study is dependent on knowing something that is not measured in the study, namely, that the active control had its expected effect in the NI study. When this occurs, the trial is said to have assay sensitivity, defined as the ability to have shown a difference from placebo of a specified size. A "successful" NI trial, one that shows what appears to be an acceptably small difference between treatments, may or may not have had assay sensitivity and therefore may or may not support a conclusion that the test drug was effective. Thus, if the active control had no effect at all in the NI trial (i.e., did not have any of its expected effect), then even ruling out a very small difference between control and test drug is meaningless and provides no evidence that the test drug is effective. (See Section III.D. for further discussion on assay sensitivity.) In the absence of a placebo arm, knowing whether the trial had assay sensitivity relies heavily on external (not within-study) information, giving NI studies some of the characteristics of a historically controlled trial.

FDA regulations have recognized since 1985 the critical need to know, for an NI trial to be interpretable, that the active control had its expected effect in the trial. Thus, 21 CFR 314.126(a)(2)(iv), unchanged since 1985, says:

> If the intent of the trial is to show similarity of the test and control drugs, the report of the study should assess the ability of the study to have detected a difference between treatments. Similarity of test drug and active control can mean either that both drugs were effective or that neither was effective. The analysis of the study should explain why the

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