



FDA Perspective on Data Quality

Rachel E. Sherman, MD, MPH
Associate Director for Medical Policy
Center for Drug Evaluation and Research

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Substantial Evidence

- Substantial evidence is defined in the FD&C Act as:
"evidence consisting of adequate and well controlled investigations, including clinical investigations, by [qualified experts who could fairly and responsibly conclude that the drug will have the effect it purports or is represented to have in the labeling]."
[505(d) of the FD&C Act]
- Recent commentary on Kefauver-Harris Amendments:
[Greene, J. Reform, 2012, Regulation, and Pharmaceuticals – The Kefauver-Harris Amendments at 50, NEJM, 367:1481-1483.]

Applicable Regulations

- Adequate and Well-Controlled Studies are defined in FDA regulations at 21 CFR 314.126
- Clinical Holds and Requests for Modification:
 - FDA has the authority under 21 CFR 312.42(b)(4) to put on hold any trial that is not adequate and well controlled
 - FDA has the authority under 312.42(b)(2)(ii) to put on hold any phase 2 or phase 3 study clearly deficient in design to meet its stated objectives
- IND Safety Reporting

Safety Reporting

- IND safety reports (21 CFR 312.32)
 - *Expedited* (7-day and 15-day) reports from the sponsor to FDA and all participating investigators
- Investigator reports (21 CFR 312.64(b))
 - Reports from investigators to the sponsor
- Safety reports for bioavailability or bioequivalence studies (21 CFR 320.31(d))
 - *Expedited* reports from the person conducting the study to FDA and all participating investigators

Recent FDA Guidance

- Determining the Extent of Safety Data Collection Needed in Late Stage Premarket and Postapproval Clinical Investigations
 - Intent is to help clinical trial sponsors determine the amount and types of safety data that should be collected during late-stage premarket and postapproval clinical investigations
 - Extends thinking that is present in ICH-E9
- Oversight of Clinical Investigations: A Risk-Based Approach to Monitoring
 - Makes clear sponsors can use a variety of approaches to fulfill their monitoring responsibilities
 - Focus monitoring activities on important and likely risks to critical data and processes
- Safety Reporting Requirements for INDs and BA/BE Studies

Safety Surveillance

- Sponsors should ensure that they have in place a systematic approach for safety surveillance
- Should include processes for reviewing, evaluating, and managing accumulating safety data from the entire clinical trial database at appropriate intervals
- May be carried out by independent committee with external representation or an internal safety team

Content of Aggregate Reports

- Narrative format which includes:
 - Description of the suspected adverse reaction and all relevant information (e.g., summary information of symptoms, concomitant medications, timing of events, duration of treatment)
 - Data from previously submitted individual case IND safety reports
 - Description of the characteristics and results of the analysis (e.g., how the conclusion was reached, any planned changes in monitoring or to study documents, any planned further analyses)
 - Individual cases that were analyzed (e.g., completed 3500A for each case)
 - Description of sponsor's approach for reporting subsequent occurrences of the same event

Alternative Reporting Arrangements

- Sponsors may request different reporting formats or frequencies for IND safety reporting and investigator reporting
 - An alternative reporting arrangement may be described in the protocol or by requesting a waiver
 - The arrangement must be agreed to by FDA in advance
- FDA may require a sponsor to submit IND safety reports in a different format or at a different frequency

Most trials use study designs incapable of meeting FDA standards for substantial evidence

Characteristics of Clinical Trials Registered in ClinicalTrials.gov, 2007-2010

Robert M. Califf, MD

Deborah A. Zarin, MD

Judith M. Kramer, MD, MS

Rachel E. Sherman, MD, MPH

Laura H. Aberle, BSPH

Asba Tasneem, PhD

CLINICAL TRIALS ARE THE CENTRAL means by which preventive, diagnostic, and therapeutic strategies are evaluated. But the

Context Recent reports highlight gaps between guidelines-based treatment recommendations and evidence from clinical trials that supports those recommendations. Strengthened reporting requirements for studies registered with ClinicalTrials.gov enable a comprehensive evaluation of the national trials portfolio.

Objective To examine fundamental characteristics of interventional clinical trials registered in the ClinicalTrials.gov database.

Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze aggregate data. Interventional trials were identified and analyses were focused on 3 clinical specialties—cardiovascular, mental health, and oncology—that together encompass the largest number of disability-adjusted life-years lost in the United States.

- Characteristics of 96,346 clinical studies were evaluated
- 96% had 1000 or fewer participants and 62% had 100 or fewer participants
- Median number of participants per trial was 58 for completed trials
- Only 34% of the interventional trials were double blinded
- 30% of the interventional trials were not randomized

Public-Private Partnership Project to Clarify Opportunities to Perform Simple Trials Capable of Providing Substantial Evidence



To identify and promote practices that will increase the quality and efficiency of clinical trials

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Adverse Event Reporting

Antibacterial Drug Development

Large Simple Trials

Team

Large Simple Trials

Dates: October 2012- present

What is the issue?

Many clinical trial sponsors, investigators, and government agencies think the system of clinical trials in the United States could be improved if there were more large simple trials

- CTTI project will identify real and perceived barriers that prevent sponsors from conducting large simple trial
- Will collect data from both sponsors and also regulators
- Will facilitate interaction between sponsors and regulators to clarify appropriate applications for this study design

Summary

- Agency emphasis on data quality, not quantity and not proscriptive trial design
 - Generalizability
 - Labeling
- Societal obligation to ensure that every trial counts