FDA Perspective on Data Quality

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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

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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.

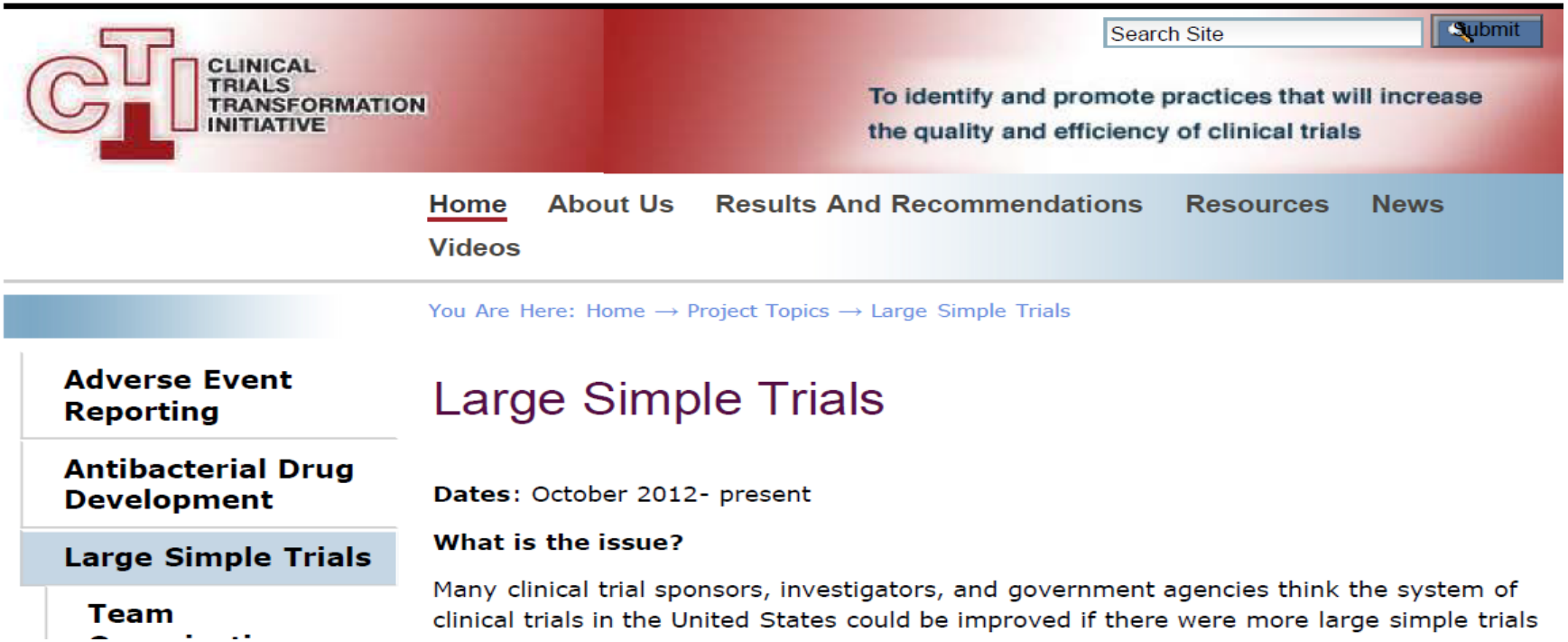
Methods A data set comprising 96 346 clinical studies from ClinicalTrials.gov was downloaded on September 27, 2010, and entered into a relational database to analyze aggregate data. Interventional trials were identified and analyses were focused on 3 clinical specialties—cardiovascular, mental health,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

CLINICAL TRIALS ARE THE CENtral means by which preventive, diagnostic, and therapeutic

- 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

(JAMA, May 2, 2012 Vol 307, No. 17)

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



- 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