Greenleaf Health

Designing Data Integrity into Your Clinical Trial and Responding When Issues Arise

Cynthia Schnedar
Executive Vice President, Regulatory Compliance
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FDANEWS FDA Inspection Summit

OUR EXPERIENCE.
YOUR SUCCESS.

GREENLEAF HEALTH IS A FULL-SERVICE REGULATORY CONSULTING FIRM GUIDING COMPANIES THROUGH THE CHANGING FDA LANDSCAPE.

WHAT CAN TRIGGER AN FDA INSPECTION FOR GCPs?

- Submission of NDA/BLA
- Complaints/Referrals (for Cause)

TYPE OF FACTORS CONSIDERED IN SELECTING SITES TO INSPECT:

- Number of studies per site/Principal Investigator
- Enrollment
- Time since last inspection
- Protocol violations
- Serious adverse events

WHAT IS FDA LOOKING FOR IN GCP INSPECTION?

- Verify primary efficacy and safety data
- Source of subjects – Did subjects exist?
- Did subjects meet inclusion/exclusion criteria?
- Did IRB conduct review?
- Was informed consent obtained and documented?
- Was protocol followed?
- Was primary efficacy measure verified?
- Were there adverse events?
- What does safety data show? *EG EKG*
- Was there accountability – Blinding of data?

OFFICIAL ACTION INDICATED - OAI

- Regulatory violations uncovered during the inspection are repeated, deliberate, and/or involve submission of false information to FDA or sponsor in any required report
- Regulatory violations are significant/serious and/or numerous, and the scope, severity, or pattern of violations support a finding that:
    - Subjects have been or would be exposed to an unreasonable and significant risk of illness or injury
    - Subjects rights have been (or would be) seriously compromised
    - Data integrity or reliability has been compromised

COMMON CLINICAL INVESTIGATOR OBSERVATIONS*

- Failure to conduct an investigation in accordance with the signed investigator statement or agreement/investigational plan/applicable regulations
- Inadequate or inaccurate case histories
- Investigator's subject records inadequate
- Inadequate drug/device disposition records
- Failure to obtain informed consent in accordance with Part 50

*Clinical Investigator (CP 7348.811) observations identified in FDA Form 483 issued at close of inspections.

Bioresearch Monitoring (BIMO) Fiscal Year 2018 Metircs. Found at https://www.fda.gov/media/127110/download

COMMON S/M/CRO/SI OBSERVATIONS*

- Failure to ensure proper monitoring
- Failure to ensure the investigation is conducted in accordance with the general investigational plan and protocols(s)
- Failure to secure compliance or terminate an investigator's participation in the investigation
- Failure to ensure the FDA/IRB/investigators are informed of significant new information or significant new adverse effects

*Sponsors, Contract Research Organizations, Monitors (CP7348.810) and Sponsor Investigator inspection observations identified in FDA Form 483 issued at close of inspections.

Bioresearch Monitoring (BIMO) Fiscal Year 2018 Metircs. Found at https://www.fda.gov/media/127110/download

AGENCY'S TOOLKIT FOLLOWING GCP INSPECTIONS

- Form 483
- Untitled Letter
- Warning Letter
- Refuse to consider data
- Disqualification/Debarment
- Remove product from market
- Refer for criminal prosecution

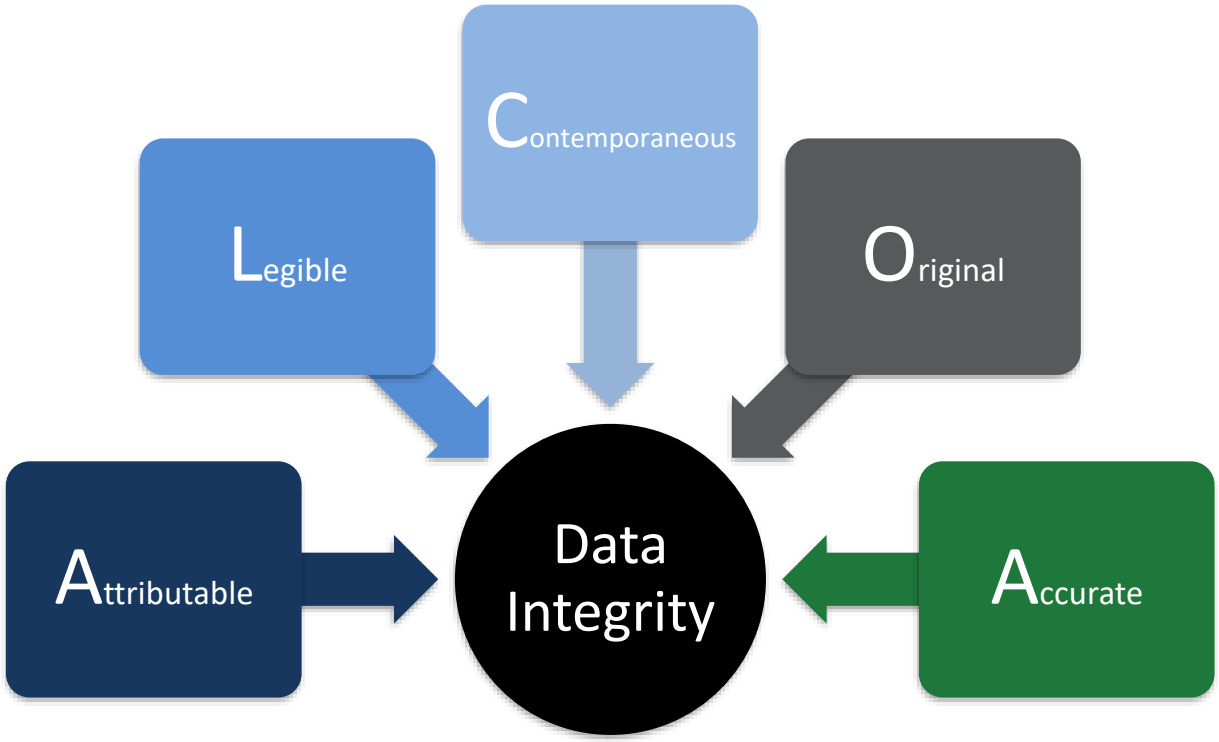
POST INSPECTION – IMPACT ON CLINICAL TRIAL

FDA develops a Clinical Inspection Summary for Review Division which includes assessment and recommendations concerning:

- Subject safety and welfare protections
- Data quality, reliability and/or acceptability of study data
- Adequacy of study conduct by inspected entities
- Record keeping and documentation

ASSESSING DATA INTEGRITY – ALCOA PLUS

- ALCOA –Attributable, Legible, Contemporaneous, Original, and Accurate
- Plus Reliability, Interpretability, and Traceability
- Must address risks that come with both paper and electronic records
- Data integrity issues can have extreme consequences on clinical trial



CLINICAL INSPECTION SUMMARY WILL CLOSELY EVALUATE:

- Descriptions of protocol violations, with a discussion of whether they are isolated or a pattern, and what the impact is on interpretability

- Descriptions of subject safety concerns or inadequate safety reporting that should be considered by Review Division

"ACTIVE RECOMMENDATIONS" IN CLINICAL INSPECTION SUMMARIES CAN INCLUDE:

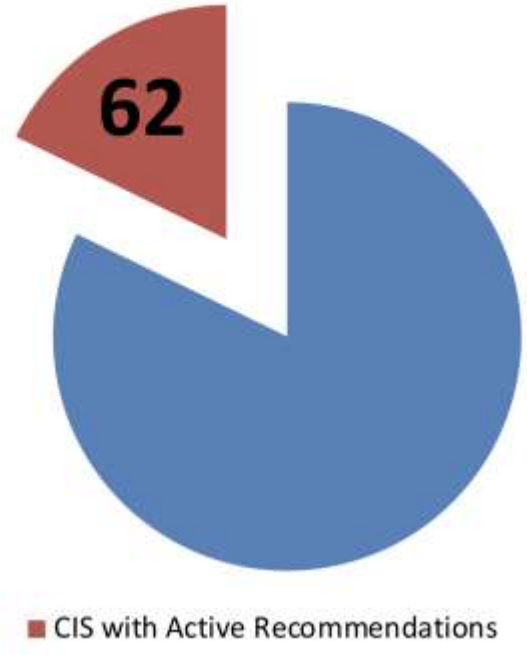
- Conduct a sensitivity analysis due to data reliability concerns
- Conduct additional inspections to verify outstanding issues
- Consider excluding data generated from all or individual inspected sites
- Address safety/efficacy concerns
- Conduct a third-party audit
- Conduct additional studies
- Conduct additional analysis

ACTIVE RECOMMENDATION IN CLINICAL INSPECTION SUMMARY IS NOT THE SAME AS OAI CLASSIFICATION

Inspections with NAI or VAI classifications can still result in active recommendation in the Clinical Inspection Summary

FDA Uses Active Recommendations in Clinical Inspection Summaries to Address Data Reliability Concerns Result Does Not Ensure a Positive Clinical Inspection Summary

OSI Active Recommendations to OND (FY15-17)



62 of 334 CIS with OSI Active Recommendation to OND

= 19%

Found at https://healthpolicy.duke.edu/sites/default/files/atoms/files/rbm_master_slide_deck_final.pdf

REPORTING ADVERSE EVENTS

See 21 CFR 312.32

FDA Guidance for Industry and Investigators, Safety Reporting Requirements for INDs and BA/BE Studies

REPORTING SUSPENSIONS OR TERMINATIONS:

21 CFR 312.56(b) - requiring sponsors to notify FDA when terminating investigator's participation in a study

21 CFR 56.113 - requiring institutional review board to notify FDA when suspending or terminating approval of research

If the trial is prematurely terminated or suspended, the sponsor "should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension

E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry. Found at: https://www.fda.gov/media/93884/download

REPORTING "SIGNIFICANT ISSUES"

"Significant issues identified through monitoring and the actions to be taken should be documented and communicated to the appropriate parties, which may include, but are not limited to the following: (1) sponsor management, (2) sponsor teams, (3) CI sites, (4) institutional review board(s), (5) other relevant parties (for example, DMCs and relevant contract research organizations), and (6) FDA, when appropriate"

A Risk-Based Approach to Monitoring of Clinical Investigations Questions and Answers Guidance for Industry DRAFT GUIDANCE. Found at: https://www.fda.gov/media/121479/download (highlight added)

WITHDRAWAL OF PROPOSED RULE

FDA proposed rule in 2010 - would have required sponsors to report information indicating that any person has, or may have engaged in the falsification of data in the course of conducting a study

FDA withdrew proposed rule in 2018, and commented:

“Based on our review of recent data, we conclude that we are receiving adequate notice of falsification of data, and we do not believe that adopting the proposed requirements would provide us with substantial additional information.”

Found at: https://www.govinfo.gov/content/pkg/FR-2018-09-28/pdf/2018-21133.pdf

FDA Is Encouraging Early Engagement When Data Integrity Issues Arise in Trial

"We were pleased we could work together with the sponsor to salvage the data. Our goal is to work together and get a drug approved but with reliable data."

"We really wished the sponsor had disclosed this early on and we could have addressed this early on."

"We are here to work with you."

Dr. Phillip D. Kronstein, FDA and MHRA Good Clinical Practice Workshop: Data Integrity in Global Clinical Trials, Are We There Yet? October 23-24, 2018

Found at https://www.fda.gov/drugs/cder-small-business-industry-assistance-sbia/regulatory-education-industry-redi-fda-mhra-good-clinical-practice-workshop-data-integrity-global

The New York Times

Novartis Hid Manipulated Data While Seeking Approval for $2.1 Million Treatment

The failure to report the issue has not put patients at risk, the F.D.A. said, but the drugmaker could face criminal and civil penalties.

A branch of the Swiss drugmaker Novartis. Arnd Wiegmann/Reuters

By Katie Thomas

Aug. 6, 2019

"The drug maker Novartis concealed manipulated data from the Food and Drug Administration while applying for approval of an extremely expensive gene therapy treatment and then delayed reporting the issue, the agency said on Tuesday.

Officials said the inaccurate data, which involved testing in mice of two different strengths of the treatment, did not affect the safety or efficacy of the therapy, Zolgensma, used to treat a rare, often fatal genetic disease called spinal muscular atrophy."

Found at https://www.nytimes.com/2019/08/06/health/novartis-fda-gene-therapy.html

What Have We Learned So Far From Novartis and AveXis?

- Importance of maintaining trust in relationship with FDA
- Timing is critical when application is pending
- Need for mechanism to flag issues and drive upwards through company
- Importance of due diligence when acquiring/integrating new companies
- Need for accuracy and consistency in public communications

FDA is Emphasizing the Risks in the Rush to Discovery

"Every day there's new research that offers great promise. But with some of this rapid desire for progress comes a risk: the potential for taking a shortcut with the FDA, by collecting not GOOD but BAD data, and then submitting this BAD data to [FDA] in support of a medical product."

Dr. Norman E. "Ned" Sharpless, Remarks to the Research!America 2019 National Health Research Forum, September 5, 2019

Found at https://www.fda.gov/news-events/speeches-fda-officials/remarks-dr-sharpless-researchamerica-2019-national-health-research-forum-09052019

FDA is Emphasizing that Companies Need to Recognize Safety Risks – Particularly with Gene Therapy

"We just happened to be lucky in this case" while noting that any case in which data are mishandled could harm patients and also set the whole field of gene therapy back again.

Interview with Dr. Peter Marks, STAT Plus, August 21, 2019

Found at https://www.statnews.com/2019/08/21/fda-on-novartis-data-manipulation-controversy-we-happened-to-be-lucky/

FDA Is Pointing Out that Sloppy Data Can Present the Same Risks to Patients as Fraudulent Data

"From one point of view, it does not matter that much whether we are dealing with incompetence or malfeasance because either case can lead to a regulatory decision that harms patients."

Dr. Sharpless, Research!America 2019 remarks

FDA Is Messaging That It Will Pursue Companies Who Submit Fraudulent Data

"At the FDA, we don't have the resources to check every aspect of every bit of research. We have to trust sponsors at some level. But we will be vigilant concerning the accuracy of the research we review. And when we do identify data fraud, we will use the full range of our authorities to address this; including civil and criminal penalties."

Dr. Sharpless, Research!America 2019 remarks

FDA Is Stressing the Importance of Commitment to Quality Management Principles in Research

"I would argue that good data is the product of good research culture, and building this culture is the work of the scientific community."

Dr. Sharpless, Research!America 2019 remarks

THANK YOU

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