Data Integrity in Clinical Trials

DIA/ISPE Workshop

06-07 NOV 2014

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Agenda

- Data Integrity Definitions
- Health Authority Expectations / GCP Considerations
- ALCOA+/POLDAT Approach to Data Integrity Analysis
- My Case Studies
- Your Case Studies

Data Integrity Definition (Simple)

- **Data Integrity** is trustworthiness of your data.
- **Am I comfortable when a <Sponsor> drug is prescribed for a member of my family**

Data Integrity Definition (Complete)

- The following data quality attributes support data integrity:
  - **Attributable:** Information is captured that identifies the source of the data. Audit Trails and Electronic Signatures are examples of attributability.
  - **Legible:** Information is human-readable. Reports, tables, and listings should be legible.
  - **Contemporaneous:** Information is recorded at the time of data generation or event observation.
  - **Original:** Source of data is available. The process of source data verification compares handwritten data (such as clinician's notes) to data entered in electronic forms (such as electronic case report forms).
  - **Accurate:** Data can be verified as correct via repeatable calculation, algorithm or analysis.

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Health Authority Expectations

- "Data Integrity Policy" within a sponsor's QMS (Definition/Failure Mode/Process/Training)
- Holistic Data Integrity Review w/Risk-Based remediation
- All systems will be "Validated for Intended Use"
  - Business Process + Computing Environment + Data Chain-of Custody
- Well-Managed Data Lifecycle and System Lifecycle
- Evidence of strong design control (Code Reviews, Detailed Architecture Diagrams)
- 'Evergreen' / Up-to-Date System Documentation

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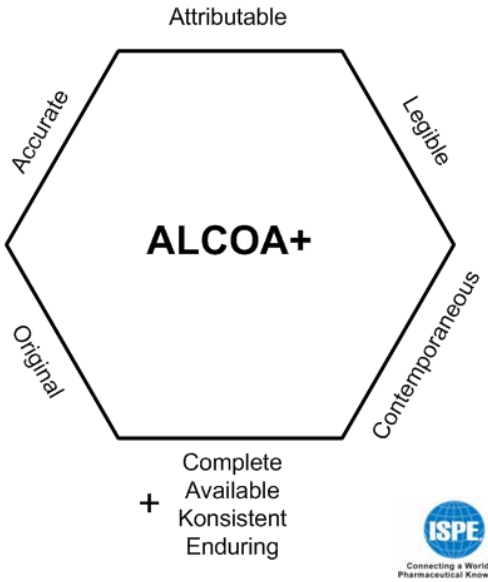
Part 11 Add-On Initiative

- 5 Key Focus Areas:
  1. Do you have, or are you deleting e-Source data?
  2. Do you review e-Source data? SOPs? Training Records?
  3. Does review include examination of meaningful metadata?
  4. Is there segregation of duties/roles? QA, System Admins?
  5. Is COTS System validated for intended use, or repeat of vendor validation package?
- "Proof-In-The-Pudding" demonstrations of system operation are expected, esp. during GLP and GXP inspections
- Help Desk records are examined as suspected 'trigger' points for back-end data changes

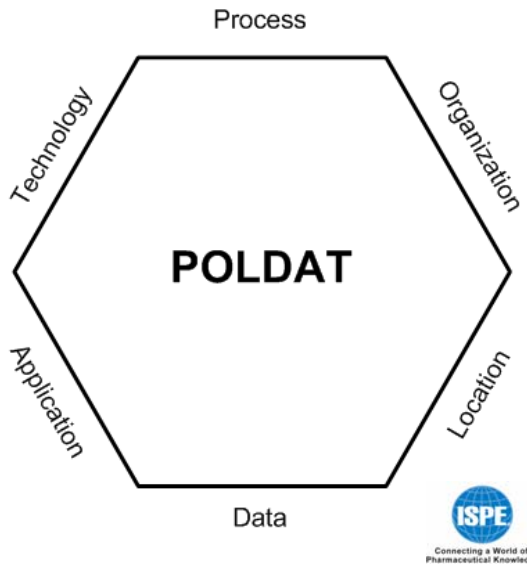
GCP vs. GLP/GMP Data Integrity Considerations

- GCP systems 'flag' data changes in the UI, while many GLP/GMP systems require more active audit trail review
- GLP/GMP systems are more likely to allow local/admin access for end users, creating a technical opportunity for fraud
- GCP systems are more likely to use relational databases over 'flat files', which are easier to delete and manipulate
- GCP data (humans) are inherently more variable than GLP and GMP data (ingredients)

ALCOA+ Hexagon
Data Integrity Attributes and Enablers



POLDAT Hexagon
Domains of Change @ Data Integrity

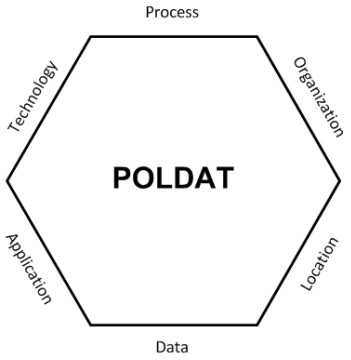


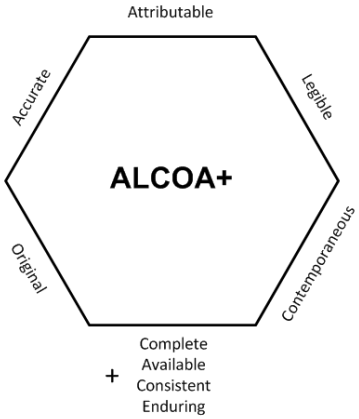
Data Integrity Analysis: <System>

Business Requirement(s):

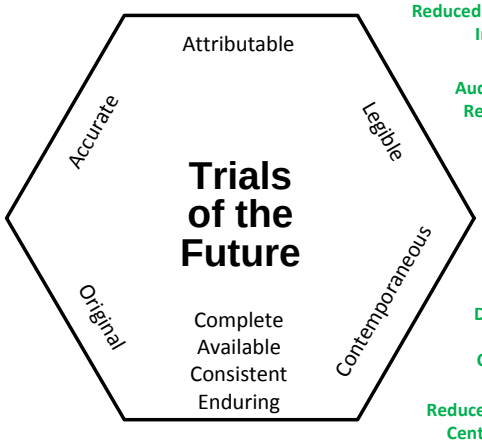
Summary:

Notes:





ALCOA+ Analysis (Trials of the Future)



Reduced Human Transcription + Reduced Human Transcription Errors = Increased Data Quality

Audit Trails / Relational Databases + Reduction of Handwritten Notes = Increased Data Attribution, Legibility

Reduced flat files/paper files + Increased relational databases = Increased Data Endurance and Consistency

Direct Data Entry Increases Data Availability, Allows for Contemporaneous Data Review

Reduced Source Data Verification + Centralized Data Monitoring = Increased Data Availability

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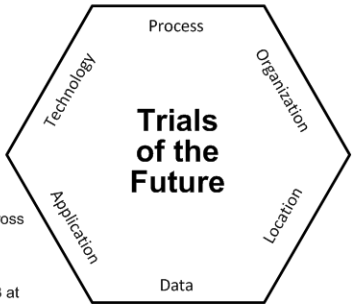
POLDAT Analysis (Trials of the Future)

Audit / Assessment Process

PSPs/SOPs:
-Data Review (4)
-Data Management (8)
-Vendor Management (16)
Project Documentation:
-Data Handling Plans

Program / Project Management

New Platforms:
-Direct Data Capture
-EHR2ECRF
-Web Services @ Data Transfers
Paperless Study:
-Is this realistic?



Clinical Development/ Operations/QA:
-Different approaches and interpretations across Franchises
Development Informatics:
-'Program' approach needs to be developed

Innovation Implies Risk (Technology)

Technology Innovation Reflects Process Changes

System Validation:
-Multiple IT Systems across multiple Vendors
-Data Transfers
Project Timelines:
-Complete, validated DB at RIS

eSource Regulations:
-Different interpretations of eSource between FDA and EMA

Collection Standards:
-NOVDD vs. NCDS
-EHR/EMR

Validation Effort Scaled to Risk

Communication/Marketing

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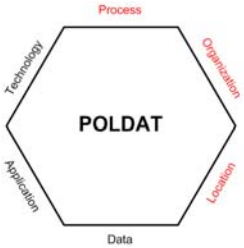
Clinical Business Cases (Data Integrity)

Concerns are often brought to e-Compliance groups for non-CSV issues. These "business cases" do not lend themselves to technical solutions or workarounds.

Often these cases stem from lack of process or to lack of adherence to process, or to problems within the business organization.



Why We Care:

- Potential Regulatory Findings
- Unnecessary Work
- *They are cleverly disguised as IT Issues*

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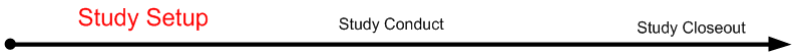
The Case of the Split Database Build

A "**Split Build***" is when a clinical team requests that an incomplete database be built so that a study can start collecting patient data, with the promise that the remainder of the DB be released later in the study.

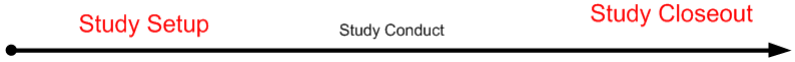
This is a deviation from **ICH Guideline E9** (*3.6 Data Capture and Processing)***



The Case of the Prodigal Data

Prodigal Data is clinical data that surfaces late* after database lock.

Data from 3rd Parties, such as CROs, Labs, and especially Central Readers** are often the culprit. The source of this problem is often a loosely defined guideline for timing in the study protocol.



Your Case Studies

- Group Exercise & Discussion

General Notes and Conclusion

- FDA is encouraging adoption of technology that streamlines process and eliminates paper. Complexity introduces risk to DI. Streamlined processes reduce risk. This requires embracing new technology and new risk.
- DI Risk Analysis must heavily involve Business Process Owners who understand the required application interactions. Process efficiency reduces DI Risk.
- FDA knows that resource constraints can adversely effect DI, thus they encourage a clearly defined risk-based approach (including early definition of failure modes).
- Data without Metadata is Meaningless. Audit Trails are considered Metadata.
- Version control is an acceptable alternative to audit trails.
- A CSV audit that focuses on Fit-for-Purpose Validation is synonymous with a 'Data Integrity Assessment/Audit', as Part 11 is a Data Integrity regulation
- Part 11 experts tend to be IT/Validation experts at sponsors, as the rule is generally considered a system rule rather than a DI rule.