



Finding Quality in Your Clinical Trials

Tuesday, June 7, 10am

Thanks for joining us



Answers before Questions

- Slides available by request
 - *Email Matt at mschutte@bioohio.com*
- Recorded version of this webinar will be available on BioOhio.com for BioOhio members; registrants will receive link...
if moderator remembers to hit “record”



Loretta Cipkus Dubray

President and CEO

Global Clinical Connections, LLC

Owner of clinical supplies consulting and coordination company, overseeing API manufacturing, drug product manufacturing, packaging, labeling, and distribution for Phase I-IV Clinical Trials for biotechs and pharmaceutical companies. Also working on training programs to educate companies about clinical supplies and clinical trials.

William Gluck, PhD

VP DATATRAK Clinical and Consulting Services



With more than 25 years of pharmaceutical/biotechnology industry experience, Dr. Bill Gluck heads DATATRAK Clinical and Consulting Services. He oversees DATATRAK's project management, trial design, clinical data management, clinical programming, customer solutions and learning solutions for all projects and phases of clinical studies.

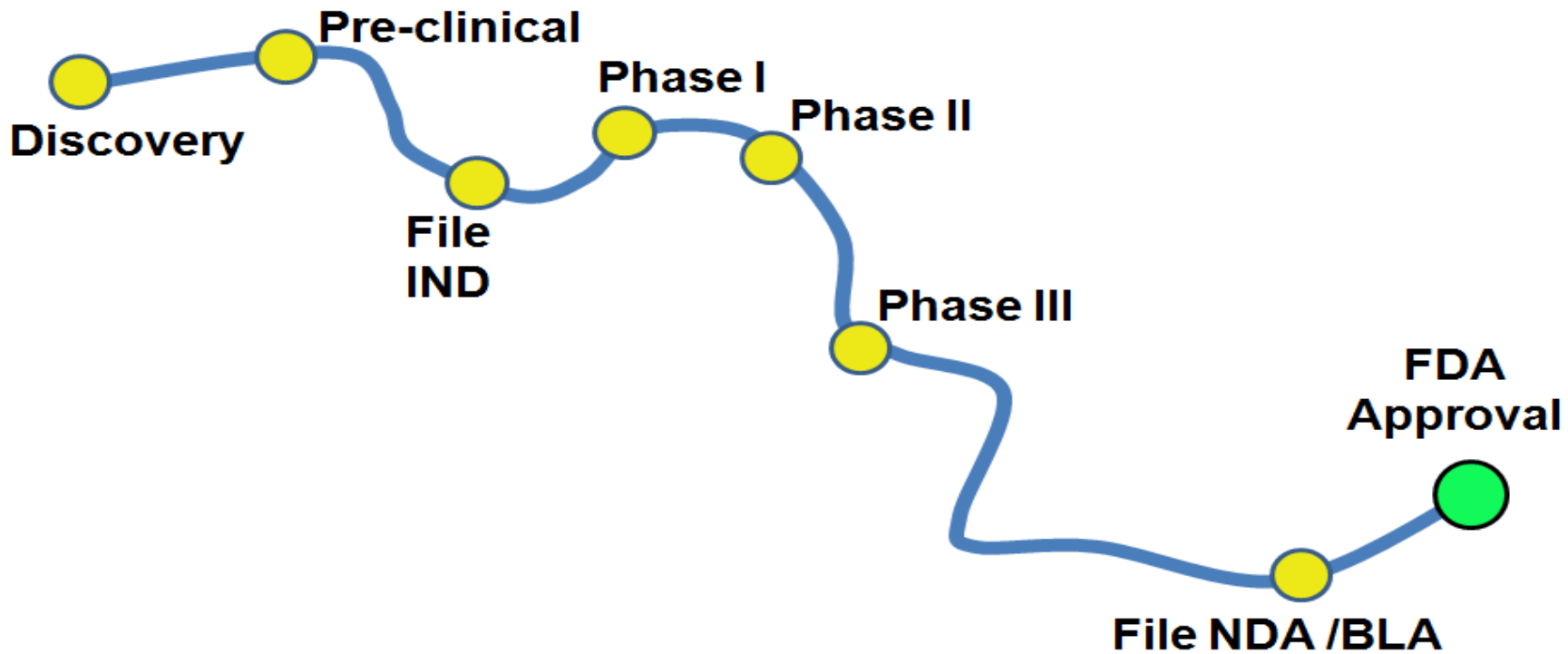
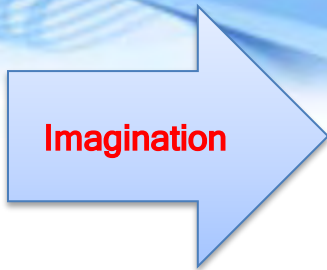


**Finding Quality in Your
Clinical Trials:
Drug Supplies /
Clinical Protocol**

Loretta Cipkus Dubray

What will be covered?

- **The Lay of the Land**
- **Regulations**
- **Importance of Vendor Management**
- **Qualification of Vendors**
- **What is Clinical Supply Chain?**
- **What are the Deliverables from Supply Chain and the Clinical arena?**





REGULATED ENVIRONMENT

Example Regulations by Work Stream



Clinical

- **21 CFR 50**
(investigators/sponsors)
- **21 CFR 54** *(financial disclosure)*
- **21 CFR 312** (IND)
- **ICH E** *(GCP + trials + reports, etc)*
- **ICH M4** *(common technical document)*



Supply Chain

- **21 CFR 210 & 211** *(GMP)*
- **21 CFR 600** *(Biological products)*
- **21 CFR 800** *(medical devices)*
- EU GMP's - Annex 13
- **ICH Q1** *(stability)*
- **ICH Q5** *(biotech prod)*
- **ICH Q7** *(GMP)*

Consequences Are Real

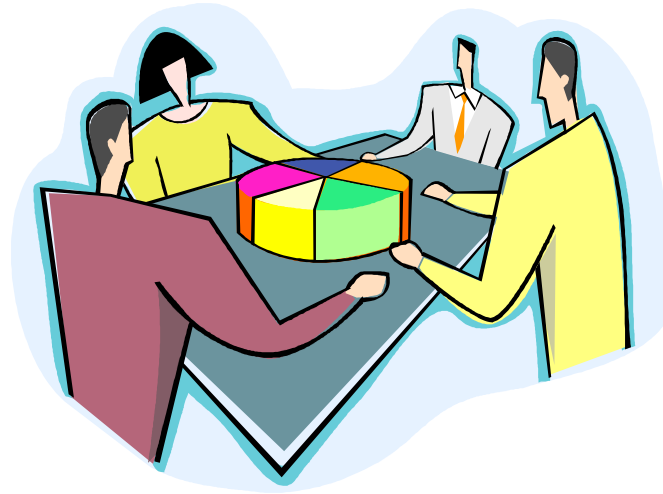
The FDA can **seize any products or devices from the field** if they are considered to be adulterated.

Adulteration means contaminated, co-mingled, mislabeled or product that is not in compliance with the regulations.

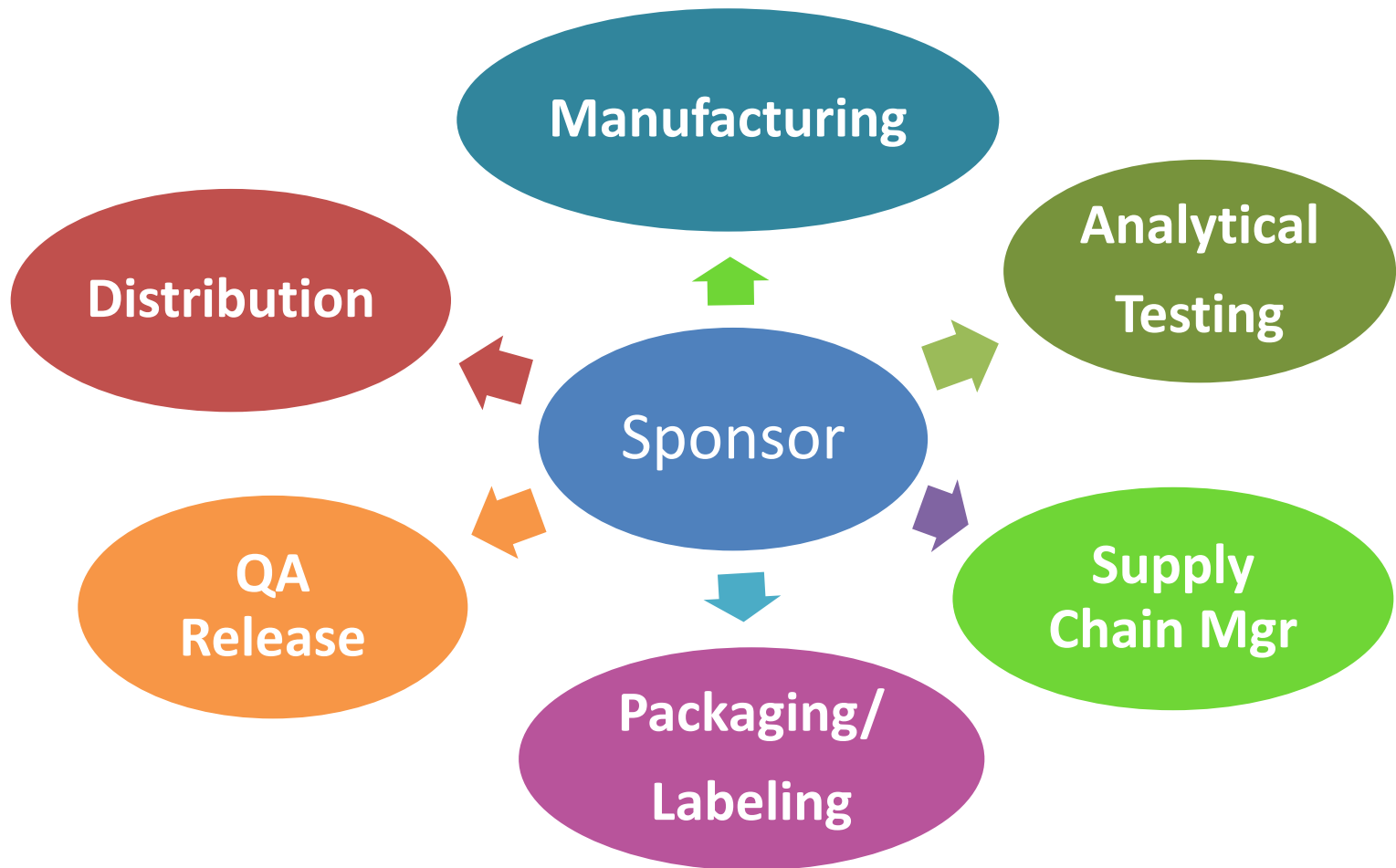


Vendor Management

As a small company, you can't do it all yourself!



What Supply Chain Functions are You Outsourcing?



Vendor Management Sponsor Accountabilities

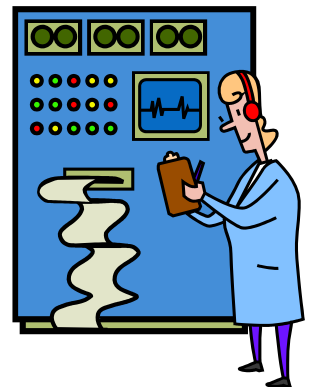
It is the Company's responsibility as the sponsor to follow the regulations set forth by the FDA (and other regulatory agencies).

If delegation of activities to contract organizations is used – the Company must ensure that the contracted organizations adhere to the regulations.



Consequences of a Lack of Oversight

If you are not monitoring your vendors:



Vendor Management Consequences are Real

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- **Adulteration means contaminated, co-mingled, mislabeled** or product that is not in compliance with the regulation.



Vendor Qualification

FDA (CFR Part 211,) requires that you:

- Qualify** the vendors that you use
 - questionnaire
 - audit
 - site visit

- **Monitor** the vendors you use



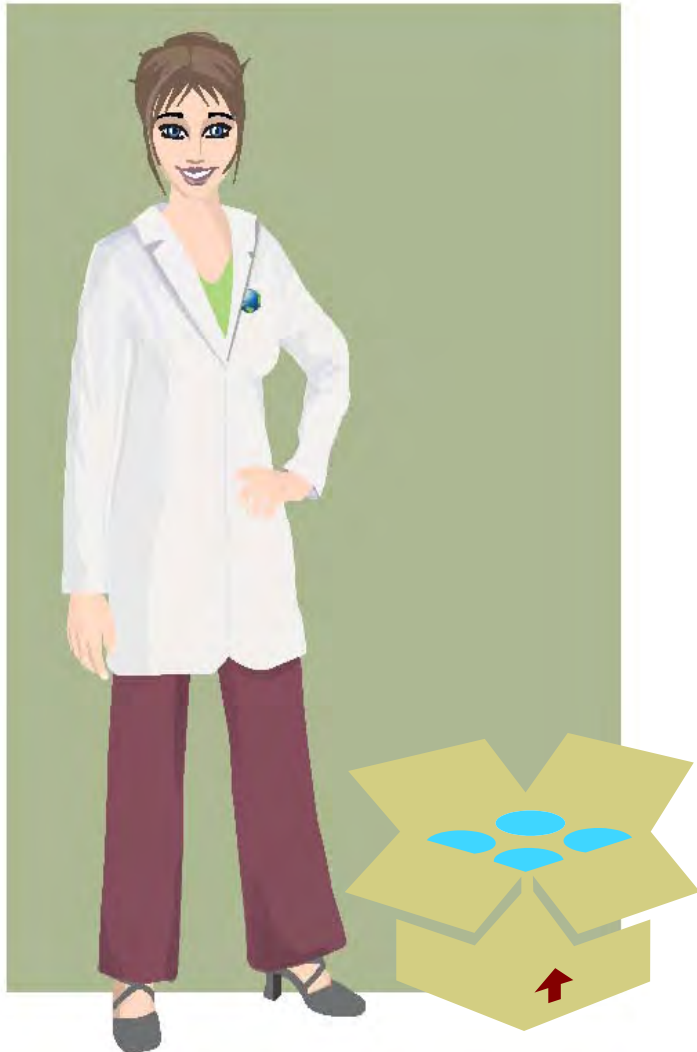
Vendor Management

When in doubt—
consult with experts!



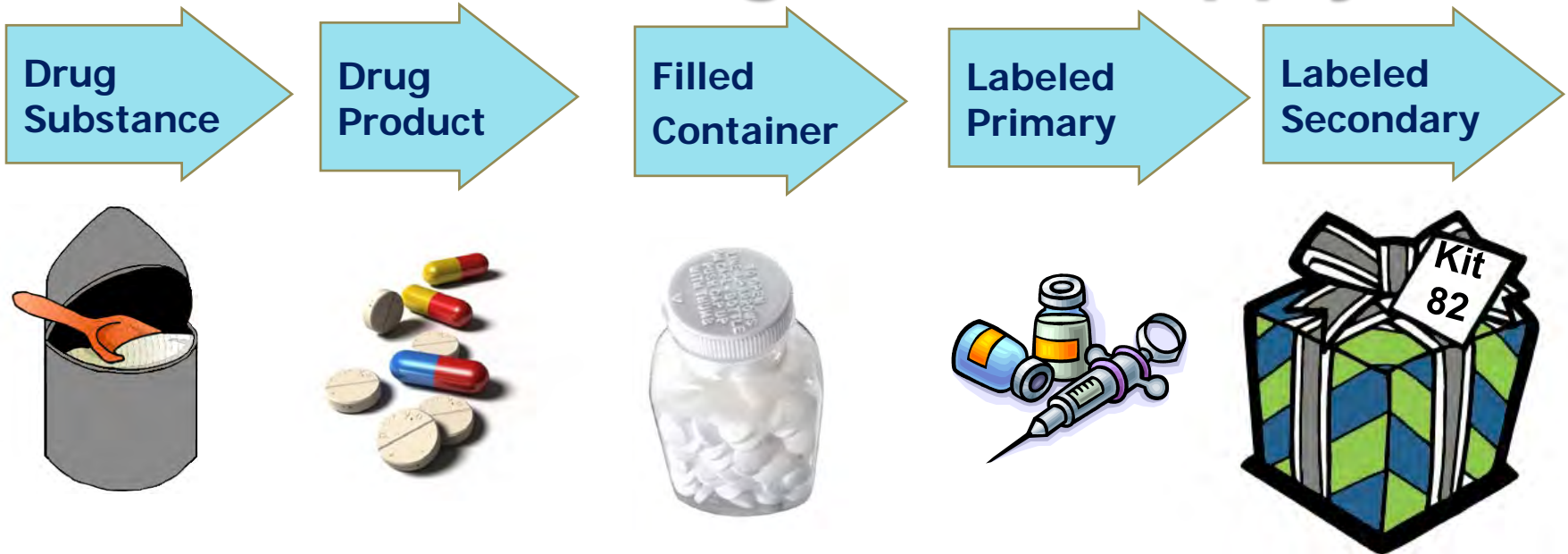
Your Company is **ultimately and legally responsible to** adhere to the regulations.

Supply Chain



GMP – Good Manufacturing Practices must be followed during the preparation (manufacturing & packaging), testing and distribution of clinical trial materials to be administered to human/ target animal clinical studies

Common GMP Regulations Apply



- Clean facility and equipment
- SOPs ; trained personnel
- Written instructions approved by QA
- All ingredients & packaging materials are qualified
- Written record
- QA disposition

Distribution Route (The Supply Chain)



Clinical Protocol

GCP – Good Clinical Practices must be followed for all clinical studies that could affect the safety and well-being of human participants.



Work stream Accountabilities

Clinical

Trial design
Site qualification
Enrollment
Patient data Mgmt

Supply Chain

Supply design
Label approval
Distribution strategy
Inventory management

Example Regulations by Work Stream



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Good Clinical Practice Deliverables

FUNCTION	DELIVERABLES	KEY ROLES
Clinical	Protocol Site selection IRB approval Case report form Informed consent Investigator meeting Enrollment	Project manager Biostatistician IRB review board Site monitor Data manager Medical writer
Regulatory	IND NDA EU Dossier	CMC preparation Submission writer Submission manager



What's next?

We will drill down deeper to look at an aspect of Clinical Trials Management:

Clinical Data Management

We will look at a practical examples of different companies' approaches and the end results.

Want More Information?

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The Clinical Trial

Dr. Bill Gluck

Discussion Points

- Defining Data and Quality
- Influences to Quality Data
- Defining a Data Hierarchy
- Case Study: Two Clinical Data Management Teams' Approaches to Achieve Quality Data
- Summary and Questions





Definition

Data (Records):

All collected and recorded information on patients considered for enrollment or actually enrolled in a trial.

Source:

http://www.nap.edu/openbook.php?record_id=9623&page=70



The Cascading Effect of Data

The FDA relies on data to make regulatory decisions.

A Sponsor relies on data to support their claims about the product.

A Physician and/or Patient relies on data to make treatment choices.

Definition

Quality (ISO 9000)

The **quality** of something can be determined by comparing a set of inherent characteristics with a set of requirements.

If those inherent characteristics meet all requirements, high or excellent quality is achieved

If those characteristics do not meet all requirements, a low or poor level of quality is achieved.



Characteristics of Quality Data

- Quality Data are strong enough to support conclusions and interpretations equivalent to those derived from error-free data.
- Error-Free data while possible is not probable.
- Certain data points are more important to interpreting the outcome of a study than others, and these should receive the greatest effort and focus.

Influences on Achieving Quality Data

- Corporate Culture plays a key role (conservative vs. risk-accepting)
- ‘Win by an Inch’ – Know the regulations and simplify the process to meet regulations
- Use of standards is essential.
 - Protocol template
 - Standard data structures, eCRF layouts, edit checks, etc. (CDISC, CDASH)



Defining a Data Hierarchy

- **Define critical data**
 - Safety
 - Efficacy
- **Work Backwards**
 - Biometrics/Biostatistics determine tables, figures/graphs and listings (TFL's) for the clinical study report from the protocol
 - Collect only data included in the TFL's or that will be reported

Leaner and Cleaner Data – An Approach

- A risk-based plan on cleaning data
 - Primary Endpoint or Critical Data
 - Edit Checked; Manual Review; SDV; Freeze; Data Lock
 - Secondary Endpoint Data – Level 1
 - Edit Checked; SDV; Freeze; Data Lock
 - Secondary Endpoint Data – Level 2
 - Edit Checked; SDV; Data Lock
 - Secondary Endpoint Data – Level 3
 - Edit Checked; Data Lock



CASE STUDY –

A Clinical Data

Management Perspective

Study Team Focus on Data

- Clinical Operations
 - Protocol specific endpoints
 - Protocol conduct
 - Regulatory compliance and note deviations
- Biometrics
 - Protocol specific endpoints
 - Data collection and management
- Drug Safety
 - Serious Adverse Events
 - Adverse Events and Coding
- Regulatory
 - Process and procedure
 - Compliance





CDM Case Studies: Team 1

Approach

- CDM oversight (1 FTE to 2-3 studies)
- Out-source EDC application development
- Review
- Testing
- Approval with primary CDM input
- Some study team input
- Deviations to standards noted

CDM Case Studies: Team 1

Approach

- Held until data were 100% clean (per internal QC process and procedures)
- Programmed edit checks inside the EDC application as well as SAS programmed edit checks outside of EDC application (total checks ~ 1500 per study)
- Additional query management system needed
- Manual reviews
- Documentation intensive

Team 1 Approach

- Hand-off to Statistical Programming
- Statistical Programming programs and performs redundant data quality checks
- Few new discrepancies

Data review meetings held **after** data lock with study team plus medical writers to clarify questions regarding data items

Corrections if needed are made via hard-coding corrections in SAS code with appropriate documentation

Team 1 – Pros and Cons

- **Pros**

- Data at each hand-off are clean and reliable
- Intra-group resource shifting is easier (work flow is group specific and more process and procedure driven)

- **Cons**

- Group driven, resource and time intensive (CDM perspective)
- Tendency to over program and depend solely on electronic/programmed edit checks – inefficient use of an EDC application
- Some disconnect between clinical programming of the EDC application and direct input from the study team
- Tendency to over-document and hold data
- Lack of team trust in data; redundant checking after hand-off occurs

Team 1 - Conclusion

At the end of the day...

- **High data quality** is achieved.
- **Low number of data issues** noted in Regulatory Compliance audits of Clinical Study Reports and outside audits.
- Potential **need for reconciliation** of programming to final clinical database due to interim hard-coding.

CDM Case Studies: Team 2

Approach

- Matrix oriented approach
 - CDM oversight (1FTE to 4-6 studies),
 - Dynamic In-house EDC application development with full study team participation (simplify data collection to only critical data defined by study team)
 - Interactive Team review, testing and approval
 - No deviations to standards allowed
 - CDM programmed edit checks within the EDC application with few outside checks programmed using SAS (total edit checks ~ 300)
 - Manual data reviews conducted using patient listings and profiles with entire study team

Team 2 Approach

- Hand-off from CDM to Statistical Programming
 - Statistical Programming programmed and performed unique data quality checks – some new discrepancies noted
- Data review meetings held **after data freeze and before** data lock with study team plus medical writers to discuss Clinical Study Report strategy, clarify questions regarding data items
 - Corrections, if needed, made to database prior to lock, little hard-coding

Team 2 – Pros and Cons

- **Pros**

- Matrix driven, constant cross-functional group interaction and communication
- Direct input from the study team (simplify data collection to only critical data) – maximize EDC application capabilities
- Data hand-offs are streamlined and dynamic due to interaction and distribution of data review and cleaning responsibilities

- **Cons**

- Matrix driven, harder to shift resources
- Tendency under check programmatically (CDM perspective, especially with laboratory data edit check) - document enough to meet regulatory requirements
- Potential for data discrepancies if there are changes to the matrix/team membership – breaks in continuity

Team 2 - Conclusion

At the end of the day...

- **High data quality** is achieved.
- **Low number of data issues** noted in Regulatory Compliance audits of Clinical Study Reports and outside audits.
- The matrix approach done right is efficient and effective (**doing more with less**) due to the strong cross-functional group interaction.



Summary

Data hierarchies do exist – driven by several factors.

Each member of the study team has an individual perception and/or focus of data quality and how to achieve it.

No matter the approach, both teams achieved the same goal of high level data quality in their clinical studies.



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