Introduction to the Principles and Practice of Clinical Research

National Institutes of Health

Data Management Overview

Part 1 of 4

National Institutes of Health

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Objectives

- Discuss activities associated with data management in clinical research
- Discuss the components of a Data Management Plan (DMP)

What is Clinical Data Management?

- A multi-disciplinary activity that includes:
  - Investigators
  - Research Nurses/Study Coordinators
  - Clinical Data Managers
  - Database Programmers
  - Biostatisticians
  - Monitors
  - Support Personnel
- Activities involving the handling of information outlined in the protocol to be collected and analyzed

Clinical Data Management Activities

- Data acquisition/collection
- Data abstraction/extraction
- Data processing/coding
- Data analysis
- Data transmission
- Data storage/security
- Data privacy
- Data quality assurance

What is the data used for?

- Analysis/support the objective(s) of the protocol
- Safety Reporting
- Regulatory Reporting
- New drug applications
- Support of labeling claims
- Publications
- Planning future protocols

Good Clinical Practice (GCP) Guidelines

- Trial management; data handling, record keeping
  - (2.10, 5.5.3 a-d)
- Subject and data confidentiality
  - (2.11; 5.5.3 g)

21 CFR Part 11

- Scope includes:
  - validation of databases
  - audit trail for corrections in database
  - accounting for legacy systems/databases
  - copies of records
  - record retention

Data Management Plans (DMP)

- Living paper or electronic records to document processes and procedures of how data will be handled
- Promotes consistent, efficient and effective data management practices at a study level

DMP Recommended Standards

- Have a plan in place prior to first participant being enrolled
- Assure the plan is in compliance with regulations and oversight agencies
- Identify and define personnel and roles involved in decision making, data collection, data handing and quality control
- DM processes should be described and defined throughout the duration of the study, from start to database lock

Components of a DMP

- Roles and responsibilities of all research team members who will handle data
- Description of the data that will be collected, data dictionaries or form annotations
- List of standards or terminologies that are used along with their version(s)
- How the data is acquired, processed and stored
- Where data will be stored
- Data handling rules
- Data sharing or access policy and processes

Summary

- Clinical Data Management is a multidisciplinary activity
- Data Management Activities
- Data Management Plans are often required
- Components of a Data Management Plan

Special Thanks to
Liz Ness, MS, BSN, RN, CRN-BC™
Director, Office of Education and Compliance
Center for Cancer Research
National Cancer Institute
For sharing her slides

Questions

- What activities are part of clinical data management?
- What is a Data Management Plan (DMP)?

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Data Management Overview

Part 2 of 4

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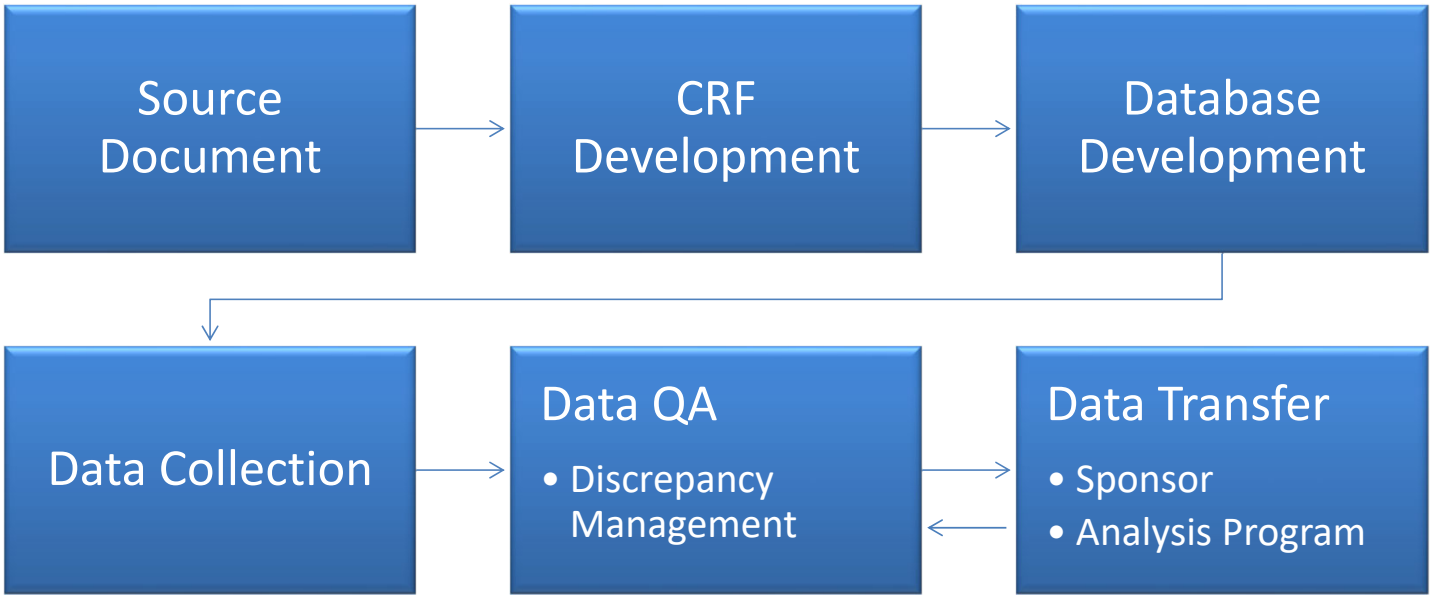
Objectives

- Discuss how clinical research data is handled
- Purpose of Source documentation
- Discuss Case Report Forms (CRFs)
- Data Standards

Data Handling Overview



Key Purposes of Source Documents

- Provide original documents, “raw” data and records
- Document existence of the subject
- Substantiate compliance with the protocol and integrity of the study data
- Serve as audit trail = recreate the progression of clinical trial

Hospital records/medical charts/clinical and office charts include:

- Physical exam findings
- Consent process
- Diagnostic reports
- Operative reports
- Laboratory reports
- Data recorded from automated instruments

Research records include:

- Subject diaries
- Quality Of Life (QOL) or other surveys
- Pharmacokinetics (PK) worksheets

Clinical Research Documentation

Documentation acceptable in clinical practice may need additional details when the patient enters a clinical trial.

Research source documentation is never by exception!

What is a Case Report Form (CRF)?

- A case report form (CRF) is a printed or electronic form used in a trial to record information about the participant as identified by the study protocol.

- CRFs allow us to:
  - record data in a manner that is both efficient and accurate
  - Record data in a manner that is suitable for processing, analysis and reporting

CRFs

- Data collection tool in clinical trials
- Paper based or electronic
- Allows for collection of study data in a standardized format:
  - According to the protocol
  - Complying with regulatory requirements
  - Allowing for efficient analysis
- Facilitates exchange of data across projects and organizations
- Accompanied by a completion/instruction manual

General Considerations for CRF Development

- Collect data outlined in the protocol
- Collect data required by the regulatory agencies
- Collect data with all users in mind
- Be clear and concise with data questions
- Avoid duplication
- Request minimal free text responses
- Collect data that allows for efficient computerization
- Develop version control procedures

Poorly Designed CRF

- Poorly designed CRFs will result in data deficiencies including:
  - Data not collected as per protocol
  - Collecting unnecessary data (i.e.: data not required to be collected per protocol)
  - Impeding data entry process
  - Database requiring modifications throughout study

CRF Development Process

During Protocol Development

- Pro: identification of problems with protocol procedures prior to protocol finalization
- Con: numerous versions of CRFs may be necessary

After Protocol Finalization

- Pro: fewer versions of CRFs and fewer reviews prior to finalization
- Con: if issues between CRF/data and protocol arise, protocol amendment may be required

Elements of a CRF

Header

- Key identifying Information
- Study Number
- Site/Center Number
- Subject identification number

Safety Modules

- Key identifying Information
- Study Number
- Site/Center Number
- Subject identification number

Efficacy Modules

- Unique modules
- Can be more difficult to develop
- Protocol dictates the elements
- Repeated battery of tests
- Define
  - Key efficacy endpoints of trial (primary and secondary)
  - Additional test to measure efficacy (e.g.: Quality Of Life)
  - Required diagnostics
- Includes baseline measurements

Standards

- Allows rapid data exchange
- Removes the need for mapping during data exchange
- Allows for consistent reporting across protocols, across projects
- Promotes monitoring and investigator staff efficiency
- Allows merging of data between studies
- Provides increased efficiency in processing and analysis of clinical data

Clinical Data Acquisition Standards Harmonization (CDASH)

- Clinical Data Integration Standards Consortium (CDISC)
- Standardize data collection fields intended to used on CRFs
  - Divided into sixteen domains
  - Applicable to all clinical studies regardless of therapeutic area or phase of development
- Link to site:
  - http://www.cdisc.org/standards

Summary

- Purpose of Source documentation
- Case Report Forms (CRFs)
- Data Standards

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Questions

- What is the purpose of Source Documentation?
- What is a Case Report Form (CRF)?

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Part 3 of 4

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Objectives

- Discuss Common Data Elements (CDEs)
- Attributes of Data Management Systems
- Data Privacy & Security
- Data Storage

Common Data Element (CDE)

- Set of descriptors for a variable
- Standardize the way in which data elements or questions can be asked, collected, stored, exchanged and reported
- Need to allow for version control
- Metadata can be easier to revise and reuse
- Cancer Data Standards Registry and Repository (caDSR) maintained by the NCI
  - Provides a data element inventory at both the individual element and the CRF level

Electronic CRFs

- Use of remote data capture (RDC) is increasing
- Generally, concepts for the design of eCRFs/RDC screens are the same as for paper
- Advantages:
  - Faster data collection
  - Cleaner data collection due to system built “checks”
  - Easier monitoring
  - Central database for storage of all trial data
  - Near real-time data access to authorized personnel
- Security (part of DMP)

CDMS v. CTMS

Clinical Data Management System (CDMS)

- Associated with traditional approach to clinical trial activities
- Heavy data management component
  - Collection of data on paper or electronic CRFs
  - Data is cleaned and transported to various reporting and care-associated destinations

Clinical Trial Management System (CTMS)

- Integrate data from many systems (e.g., labs, genomics, and adverse events), enter and clean the data in expedited steps, and store it in a repository that can serve multiple purposes over time
  - Key concept of 'services' or capabilities such as the ability to handle patient randomization at the same time as adverse event reporting and creating laboratory report alerts for the clinician.

Attributes of Data Management Systems

- Scalability
  - Ability to grow without loss of function or data
- Interoperability
  - Ability of systems to exchange data in ways that preserve the original meaning and intent of the data

Data Privacy/Security

- Federal Information Security Management Act (FISMA)
  - Process for detecting, responding and reporting security incidents
  - Periodic assessment of risk to a system
  - Security awareness training
- Protected Health Information (PHI)

Data Storage

- Paper
  - Locked cabinet and room
- Electronic
  - Back up servers and recovery system

Summary

- Discussed Common Data Elements (CDEs)
- Electronic data management systems are tools that enable health professionals to collect, store, exchange and share data in increasingly efficient and meaningful ways.
- Attributes of Data Management Systems
- Data privacy & security
- Data storage

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Questions

- What is a Common Data Element (CDE)?
- What are advantages of Remote Data Capture (RDC)?

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Data Management Overview

Part 4 of 4

National Institutes of Health

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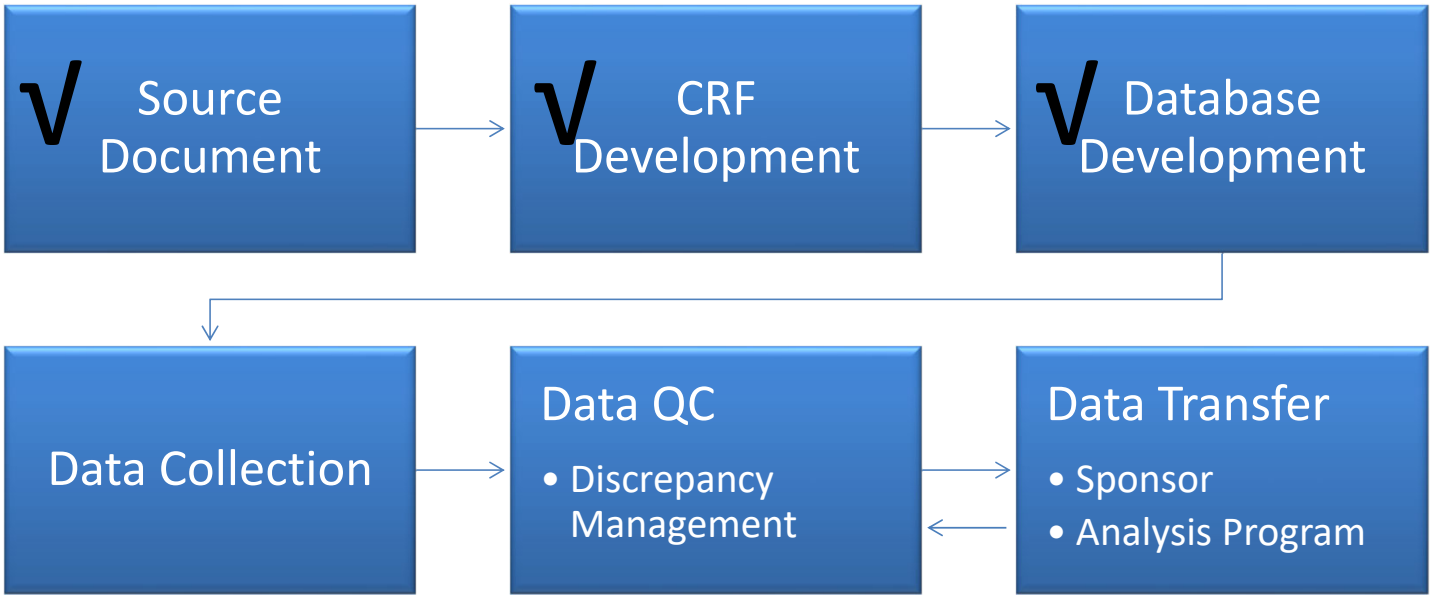
Objectives

- Discuss data collection
  - CRF Completion
- Quality Control
- Data Transfers
- Data Flow among team and sponsor

Data Handling Overview



CRF Completion

- Per GCP Guidelines (4.9.1), investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported on the CRFs including:

  - all sections have been completed
  - all alterations have been properly made
  - all adverse events are fully recorded and that for all serious adverse events, any specific documentation has been completed

Timeliness of CRF Completion

- Ideally CRFs should be completed as soon after the subject's visit as possible
- Ensures that information can be retrieved or followed-up on while the visit is still fresh in the healthcare provider's mind, and while the subject and/or the information is still easily accessible
- 2 weeks post study event

Common Errors

- Logical
- Inaccurate information
- Omissions
- Transcription errors
- Abbreviations
- Spelling errors
- Illegible entries/”write-overs”
- Writing in margins

Making Corrections

- Paper CRFs
  - Draw one horizontal line through the error;
  - Insert the correct data;
  - Initial and date the change;
  - **DO NOT ERASE, SCRIBBLE OUT, OR USE CORRECTION FLUID OR ANY OTHER MEANS WHICH COULD OBSCURE THE ORIGINAL ENTRY**
- Electronic CRFs
  - Make correction and the system does the rest
  - May need to include justification for change

Tips…

1. Use the CRF completion/instruction manual
2. Make sure appropriate protocol, investigator and subject identifying information is included in the Header
   - Pre-populated for RDC
3. Ensure data is entered in the correct location or data field
4. Use the appropriate units of measurement (UOM), and be consistent
5. Use only the abbreviations authorized per manual

...Tips

4. Double check spelling
5. Watch for transcription errors
   - E.g.: sodium level should be “135” and entered as “153”
6. Use “comments” section to elaborate on any information, ***but keep to a minimum***
7. Perform quality control and logic checks

REMINDERS

Data cannot be entered onto a CRF if it is not in the medical record or another source document

- If the individual completing the CRF, finds missing or discrepant source data they should:
  - Notify the health care provider who then will provide the data/correct the data
  - If applicable, contact outside source (i.e.: outside lab or doctor's office)

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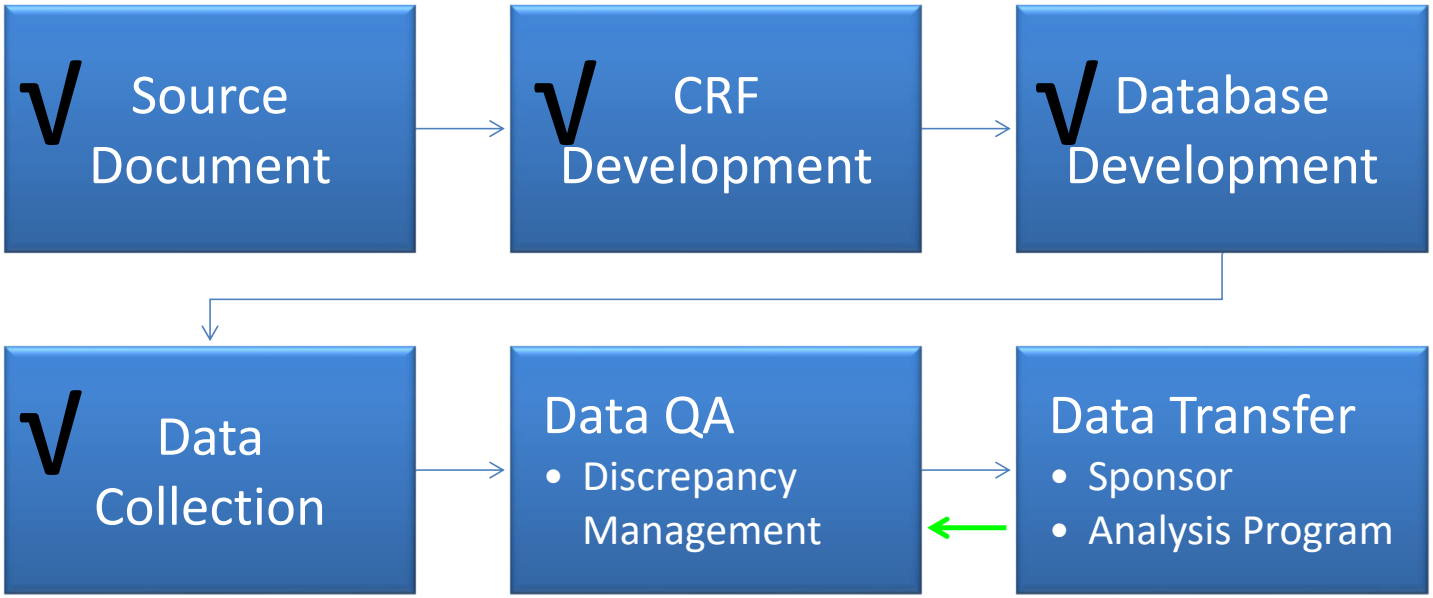


Quality Control
GCP Guidelines 5.1.3

QC should be applied to each stage of data handling to ensure that all data:

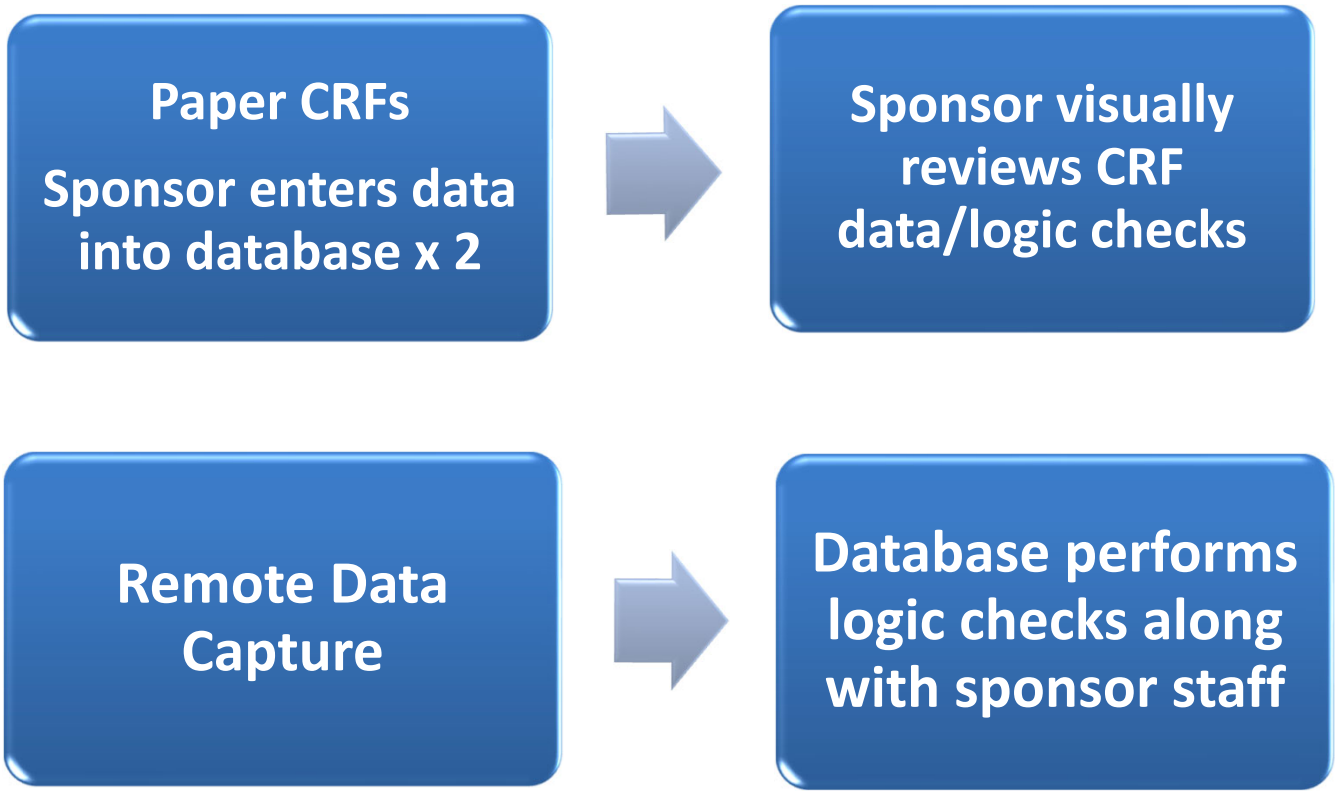
- Are reliable
- Have been processed correctly

Data Transfer

- Analysis program
- Sponsor

Data Flow for Research Team

Data Flow for Sponsor

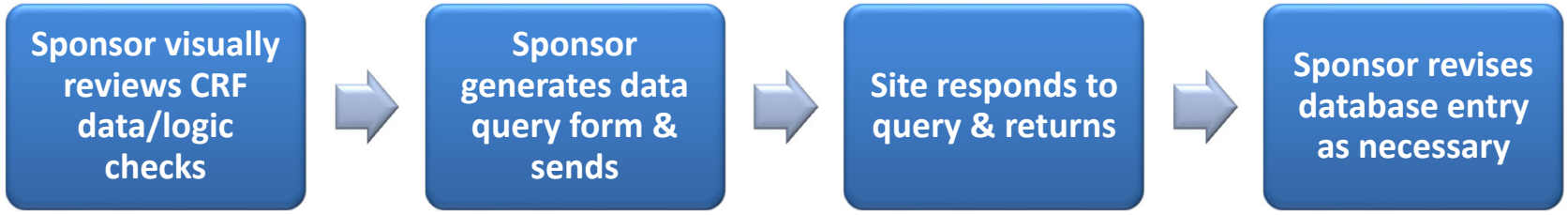


Handling Data Issues

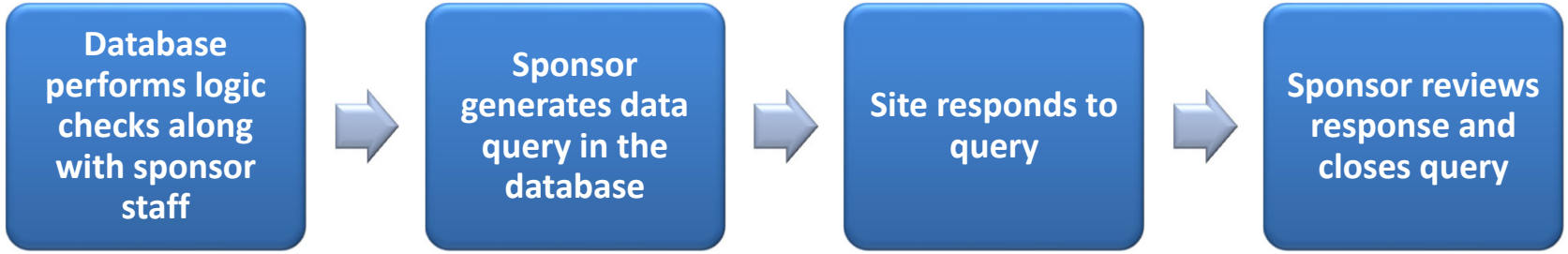
- Electronic
- Manual
- Sponsor generated
- Database generated
  - Univariate
  - Multivariate

Data Query Flow

Paper CRFs



RDC



Data Queries

- Data queries generated by sponsor/CRO for resolution by site
- Formally authorized staff for query responses
- Completed queries must be signed by investigator or authorized staff
- Copy of completed data queries filed at site
- Query records in sponsor’s permanent database

Summary

- Data is the foundation of research
- Data collected in a database should always match the original source document
- Tips for completing CRFs
- Data quality is critical, and QC is the responsibility of all members of the research team

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Questions

- When should CRFs be completed?
- Who is responsible for data quality?

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