



Society for Clinical Trials 32nd Annual Meeting

**Workshop P10
The Essentials of Clinical Data Management**

Sunday, May 15, 2011

1:00 PM - 5:00 PM

Georgia B

2011 Society for Clinical Trials Pre-Conference Workshop

Essentials of Clinical Data Management

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Agenda

- Review of Clinical Trials
- The role of a Clinical Data Manager
- Data management processes
- Essential Data Management documents
- Understanding database structures
- Regulations surrounding Clinical Data Management
- Standards used within Clinical Data Management
- Hands-on exercise
- Questions and Answer Session

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Meet Your Presenters

- Devin J. Hunt
 - Education
 - B.S. in Physics and Mathematics
 - M.S. in Epidemiology (in progress)
 - Experience
 - Manager, Statistical Programming and Clinical Data Management for EmpiriStat, Inc.
 - Over 7 years of experience in Data Management, Protocol Monitoring, Statistical/SAS programming, database development and testing for various clinical studies from Pre-clinical through Phase III

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Meet Your Presenters

- Jill Kuennen
 - Education
 - BA, Psychology and MA, Experimental Psychology
 - Experience
 - 1992-1994, Johnson Space Center, Houston, TX, Single subject vestibular research with astronauts and cosmonauts
 - 1995-2000, Substance Abuse Research Center, Detroit, MI, Single subject research with amphetamines, opiates, cocaine, and a clinical trial with sibutramine (meridia)
 - 2000-2003, PSU, Hershey, PA - Data Coordinating Center for ACRN and CARE networks sponsored by NHLBI

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Meet Your Presenters

- Jill Kuennen (continued)
 - Experience
 - 2003- 2006, Program Associate, Cancer Center, U of Iowa - Protocol administration for investigator and industry clinical trials.
 - 2006 – Current, Team Leader, Data Management, University of Iowa, Clinical Trials Statistical and Data Management Center -
 - Clinical Islet Transplant Studies sponsored by NIAID and NIDDK - clinical and data coordinating
- <http://www.ctsdmc.org/>
<http://www.citisetstudy.org/>

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Workshop Objectives

- Understand the key roles of a Clinical Data Manager
- Identify the processes involved with Clinical Data Management
- Identify and understand essential documents needed for Clinical Data Management Activities
- Be aware of the regulations for Clinical Data Management
- Identify the standards used within Clinical Data Management
- Get a hands on experience implementing the skills learned in this workshop

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Data Management Acronyms

- EDC = Electronic Data Capture
- CDM = Clinical Data Management
- CRF = Case Report Form
- CRFi = Case Report Form Instructions
- aCRF = Annotated Case Report Form
- CFR = Code of Federal Regulations
- FDA = US Food and Drug Administration
- ICH = International Conference on Harmonization
- DB = Database
- eCRF = electronic Case Report Form

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Review of Clinical Trials

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Review of Clinical Trials

- Sponsor means the person who takes responsibility for and initiates a clinical investigation
 - Individual, pharmaceutical company, government agency, academic institution, private organization or any other organization
- Contract Research Organization (CRO) means a person that assumes, as an independent contractor with the sponsor, one or more obligations of a sponsor
- 21 CFR 312

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Review of Clinical Trials

- Data
 - Food and Drug Administration (FDA)
 - "...Representations of facts, concepts, or instructions in a manner suitable for communication, interpretation, or processing by humans or by automated means."
- Data also includes metadata (information about data)
 - Variable type (character vs. numeric)
 - Variable format (65, 65.0, 065.0)
 - Variable length (2, 4, 5)
 - Variable name (HEIGHT, HGT, HT)
 - Variable label (Height)

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Review of Clinical Trials

- Pre-clinical/Animal trials
 - In vitro and in vivo testing
 - Various drug ranges and doses
 - Obtain preliminary efficacy, toxicity, and pharmacokinetic data
 - Decide if there is enough empirical evidence to warrant further testing of drug

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Review of Clinical Trials

- Pilot Studies/Phase I Studies
 - First testing in humans
 - Small sample of healthy volunteers (20 – 100 subjects)
 - Assess safety, pharmacokinetics, and drug tolerability, dose ranges
 - Usually conducted in an inpatient clinic for complete monitoring

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Review of Clinical Trials

- Phase II Studies
 - Typically a controlled study
 - Larger sample size than a Phase I study (20-300 subjects)
 - Designed to assess safety and efficacy
 - Sometimes divided up
 - IIA – assesses dosing requirements
 - IIB – assess efficacy
 - Healthy subjects and afflicted subjects

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Review of Clinical Trials

- Phase III/Pivotal Studies
 - Typically multi-center, randomized trial, controlled or uncontrolled
 - Large sample size (300 – 3000+ subjects)
 - Designed to study safety and efficacy of intervention compared to placebo or standard of care
 - Usually there is a requirement to complete two successful Phase III studies prior to filing a New Drug Application for the FDA

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Review of Clinical Trials

- Phase IV/Post Market Surveillance Study
 - Long term safety surveillance of drug use over long periods of time
 - Various requirements by regulatory authorities
 - Sometimes study results end with the drug being pulled from the market or requiring additional safety warnings

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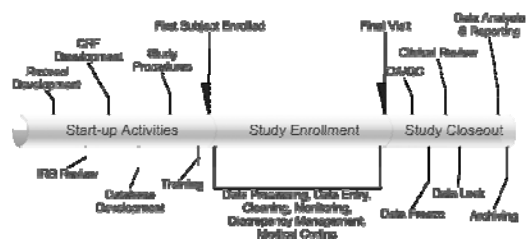
Review of Clinical Trials

- Types of clinical trials
 - Intervention/Treatment
 - Prevention
 - Diagnostic
 - Screening
 - Observational
 - Quality of Life

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Review of Clinical Trials

- Typical Progression of a Clinical Trial



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Roles of A Clinical Data Manager

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The Role of a CDM

- Data Managers work in all types of organizations
 - Private Organizations
 - Pharmaceutical companies
 - Biotechnology companies and Laboratories
 - Non-profit organizations
 - Universities and academic institutions
 - Contract Research Organizations (CROs)
 - Public Organizations
 - Universities and academic institutions
 - Various government agencies (DHHS, DoD, VA, etc)

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The Role of a CDM

- Data Managers work in all types of organizations
 - Contract Research Organizations (CROs)
 - Perform DM related activities for the sponsor
 - Act as a liaison between the sponsor and the study sites
 - Sponsor organizations
 - Review the work of the CRO
 - Ultimately responsible for DM related activities
- Clearly defined responsibilities for data management roles between the sponsor and CRO

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The Role of a CDM

- Data Managers work with all members of the clinical trial team
 - Clinical Operations
 - Biostatistics
 - Safety and Medical Monitoring
 - Project management
 - Information Technology
 - Regulatory Affairs
 - Scientists and other subject mater experts

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The Role of CDM

- Involvement with Clinical Operations
 - Ensure protocol is adhered to
 - Query resolution process
 - Report protocol deviations and violations
 - Source document verification and tracking of discrepancies
 - Data entry problems and issues
 - Ensure site staff are properly trained on DM activities

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The Role of CDM

- Interaction with Biostatistics
 - Review Statistical Analysis Plan (SAP) and Tables, Listings, and Figures (TLFs)
 - Review of Case Report Forms (CRFs) and annotated CRFs (aCRFs)
 - Review database design specifications
 - Review blinding, unblinding, and randomization procedures

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The Role of CDM

- Interaction with Safety and Medical Monitoring
 - Review the Safety Monitoring Plan (SMP)
 - Collaborate on the Adverse Event (AE) and Serious Adverse Event (SAE) reporting procedures and tracking
 - Compile and reconcile the safety database to the clinical database
 - Review AE CRF pages
 - Medical coding and medication coding

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The Role of CDM

- Interaction with Project Management
 - Various reporting needs
 - Enrollment
 - Drop-out/Early termination
 - CRF completion
 - Translation services if applicable
 - Overall study timeline review and adherence

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The Role of CDM

- Interactions with Information Technology
 - Database design specifications
 - Database testing and implementation
 - Database validations
 - Edit check programming
 - CRF development for Electronic Data Capture (EDC) systems
 - User access
 - Database Lock

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The Role of CDM

- Interactions with Regulatory Affairs
 - Study personnel training
 - Protocol review
 - CRF development meets regulatory standards
 - Reporting of AEs and SAEs
 - Current Good Practices (cGxP)

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The Role of CDM

- Interaction with Scientist and other subject matter experts
 - CRF development
 - Data reporting methods
 - Data collection methods
 - Electronic data formats

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The Role of CDM

- Many hats of a Data Manager
 - Manager
 - Liaison
 - Programmer
 - Detective
 - Trainer
 - Help desk support
 - Auditor
 - Data entry

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Data Management Processes and Documentation

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CDM Processes and Documentation

- Two sections or groups of processes and documents that CDM will work with
 - Study conduct related processes
 - Database related processes
- Data Managers are involved during the majority of the study, from start up to close out.

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Study Conduct Processes and Documentation

- Protocol Review
- Blinding and Randomization
- Study Specific Procedures and Standard Operating Procedures
- Safety Review Processes
- Training site staff on Data Management processes
- Clinical Review Processes
- Study conduct reporting

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Protocol Review

- Data managers review portions of the protocol to ensure it represents the true flow of data and data management related tasks
 - Data management system
 - Data flow from source documents to database
 - Data transfers to and from involved organizations
 - The study visit schedule
 - Specimen tracking
 - Safety management and clinical monitoring

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Blinding and Randomization

- Data managers review the blinding and randomization process, if applicable, to ensure a system is in place that can handle the needs to the study
- Blinding and Randomization can be performed with a paper based system (i.e. envelopes), but can also be done in a data management system
- Work with Statistician for randomization scheme to be implemented in the data management system
- Work with IT to ensure the blind is properly stored and no one has access to it. Also develop emergency unblinding procedures in case the blind needs to be broken

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SSPs and SOPs

- Site Specific Procedures (SSPs) and Standard Operating Procedures (SOPs) are developed in conjunction with the protocol to specify how the procedures in the protocol will be deployed and implemented.
- Data managers will often time help review and write SSPs and SOPs that relate to the responsibilities that they are accountable for.
 - Randomization and Blinding procedures
 - Data entry for Electronic Data Capture (EDC) Systems
 - Database Freeze and Lock

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Safety Review Process

- A safety review should be conducted by the medical monitor or safety officer prior to locking the database and finalizing the study
- A total review of all adverse events, serious adverse events, laboratory data, and other safety related measures reported during the trial
- Data managers will facilitate the review process and will be responsible for issuing any queries that are generated as a result of the review
- Some data management systems will have a capability to assist in this review as well

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Training Site Staff

- Prior to site coordinators and staff completing case report forms or entering data into the data management system, they will need to be trained on the proper procedures to carry out these tasks
- Data managers are responsible for conducting the training with the site staff on the proper way to complete case report forms, randomizing subjects, and blinding subjects and investigators
- Depending on the data management system used, data entry processes will need to be reviewed to ensure proper entry of study data

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Clinical Monitoring Process

- All studies need to be monitored by a qualified clinical monitor who is familiar with the protocol and procedures surrounding the conduct of the study
- Monitors review the completed case reports forms against the source documents at the site
- Data management systems may be able to facilitate the review of the source documents
- Data managers will review the visit report from the monitor and the source document discrepancies and produce queries or data clarification forms to fix the erroneous data

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Study Conduct Reporting

- Throughout the conduct of the trial, various people involved in the trial will need to review reports on the progress the trial is making
- Data managers will work with programmers and statisticians to generate study reports to provide to the sponsor and other people involved in the conduct of the trial
 - Enrollment and recruitment reports
 - Data collection reports/Missing forms reports
 - Interim analysis and data lock
 - Data safety and monitoring review boards and IRB reviews

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Database Processes and Documents

- Case Report Form and Case Report Form Instruction Development
- Database design, development, testing, implementation, and validation
- Data entry
- Data coding procedures
- Data cleaning, data quality, and audit of the database
- Database freeze, and database lock
- Data archiving

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CRF and CRFi Development

- Case Report Forms (CRFs) are paper or electronic forms and questionnaires created to collect from study sites relevant study data to assess the hypothesis, endpoints, and outcomes of a clinical trial
- Case Report Form instructions (CRFi) or Case Report Form completion guides (CCGs) are a set of instructions used by the site to guide them on the proper completion of the case report forms
- Data managers are responsible for the generation of the case report forms. If other study staff (programmer for EDC systems or administrative support for paper forms) the data manager is responsible for the oversight of these staff

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CRF and CRFi Development

- Data managers work with the sponsor, investigators, statisticians, and other subject matter experts to generate details of what data will be captured and how it is to be captured
 - Statisticians review CRFs against planned analyses
 - Programmers review CRFs against programming function
 - Scientific experts check for efficacy and safety endpoints
 - Regulatory experts ensure the forms follow any applicable regulatory guidelines
 - Pharmacovigilance review for proper data capture

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CRF and CRFi Development

- Develop CRFs on a stable draft of the protocol. Avoid creating CRFs too early as the protocol may change
- Data managers design the layout of the CRFs, keeping in mind the presentation of the questions, the responses to the questions, and the structure of the database
- Reviews of the CRFs are conducted and modifications are made until all parties are in agreement and sign off on the final version.
- Data manager creates annotated CRFs that will be used by programmers and statisticians to build and analyze the data stored in the database

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CRF and CRFi Development

- CRF development guidelines
 - Avoid collecting redundant data
 - Develop a layout that facilitates a simple flow through the form
 - Do not overcrowd the form with questions
 - Provide instructions for any questions that should be skipped depending on responses to prior questions
 - Questions should be clear and concise and must not lead the site on how to respond to a question

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CRF and CRFi Development

- CRF development guidelines (continued)
 - Avoid open text fields and comment fields. Provide a set of responses if possible
 - Use a "Yes/No" field instead of a "Check all that apply" approach. This Provides a definitive answer to each category or question
 - Use a standard order for responses and questions. This will lead to fewer errors in transcribing the data
 - Use a standard format for all responses (i.e. date and time fields, laboratory fields)

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CRF and CRFi Development

- CRF development guidelines (continued)
 - Avoid manually calculated fields. Collect the raw data and allow programmers to program the calculate value (i.e. Age)
 - Have a question asking if the assessment or visit was completed. Avoid Check if not complete questions
 - In general, do not pre-populate data on the CRFs unless the data will be the same for all subjects (i.e. medical history or physical exam body systems, visit numbers, or sequencing variables)

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CRF and CRFi Development

- Once the CRFs are developed the additional instructions can be produced
- CRFi need to provide a clear and concise understanding of how the data should be recorded on the CRFs
- CRFi should follow Good Clinical Practices where applicable
- Standardize the way in which the CRFi are produced and ensure they match with the CRF standards

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CRF Review Activity

- Study Background
 - Two treatment intervention groups for skin lesions
 - Treatment A: IV injection
 - Treatment B: Direct application
 - This CRF is completed at treatment intervention
 - Study Day 3, 7, and 10
- Work in teams to review this CRF and make suggestions on how the form can be improved upon from a Data Management perspective
- 15 minutes

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Database Design

- A properly designed database is essential to the successful collection and storage of the study related data
- A database design document (data management plan) should be assembled in order to provide database programmers with exact specifications for what is required and expected of the database
- Programmers review the design document, CRFs, aCRFs, and the CRF specifications to develop a layout of the data in the database
- Data managers should review the final structure of the database to ensure all variables are included and defined properly

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Database Design

Review the creation of the Data Management Plan and the CRF Specifications documents
- to create eCRFs.

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Database Design

- Once the data structure or back-end of the database is developed, the interface or front-end of the database will need to be developed. This should also be included in the design document
- The design of the interface will depend on the use of the data management system.
 - EDC system will need to be more intuitive and user friendly as study coordinators and other site staff will be interactive with the database
 - Paper based studies will have the data entry staff as main end user and can be a bit less "pretty"

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Database Development and Testing

- Database programmers develop the structure and interface of the database with the guidance of the data manager, the design document (data management plan), and CRF specifications.
- Once the data management system is developed, the database programmers and data manager will test the system to ensure it meets all requirements
 - Documentation needs to be in place to record the testing procedure and ensure industry standards are followed
 - All modifications and testing failures need to go back for fixes and the system needs to be retested

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Database Development and Testing

Review the creation of CRF Testing Plans.

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Database Implementation

- Upon passing all testing the data management system can be placed into a production environment
 - The system is now available for users to enter data
 - Only users that have been trained on the system should be allowed to use it
- Modifications to the system after initial production release need to be documented, archived, and properly tested prior to release
- Database implementation document or SOP should be in place to describe how to place a database into production

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Data Entry Process

- There are two main types of data entry processes depending upon the type of data management system used
 - Electronic Data Capture (EDC) vs Paper based studies
- In an EDC system, the study site usually enters the data directly into the database
 - Edit checks are performed in real time in order to prevent erroneous data from being entered into the database
 - Clinical monitors review the database with the source documents during a site visit

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Data Entry Process

- In a paper based study, data entry staff enter the data in to the database from the paper CRFs
 - Double data entry should be performed
 - Data is entered twice by two independent data entry personnel trained on the process
 - Data is compared across first and second pass and discrepant values are resolved by a third party
 - Edit checks are performed on the data to ensure valid data is reported in the system
 - Clinical monitor compares source documents to CRFs

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Data Coding Procedures

- Medical coding is performed on Adverse Event verbatim terms and Concomitant medication drug names to categorize and standardize the way in which medical terminology is reported and stored
 - AE verbatim term is coding using Medical Dictionary for Regulatory Activities (MedDRA)
 - Preferred Term and System Organ Class
 - Concomitant Medications are coded using World Health Organization Drug (WHODrug) Dictionaries
 - Drug names as generic or trade name

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Data Coding Procedures

- Auto-encoders can be used to automatic the coding process
- Unknown or ambiguous terminology needs to be reviews by a coding expert to select the proper terminology
- Prior to finalizing the database, a complete review of the verbatim terms and the coded terms should be conducted by a medical expert
- Errors need to go back to the coding team to recode the terms according to the medical experts
- Data managers will facilitate the process of the review and will work with coders to enter the data into the database

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Data Cleaning Procedures

- Data cleaning is the process in which the data in the clinical database is reviewed to ensure it is accurate and complete
- There are many ways in which data cleaning can be conducted, depending upon the type of data management system used (EDC vs. paper based)
- Edit checks are run to check for valid ranges on numeric dates, times, and laboratory values. Edit checks also review unexpected missing responses, check for invalid responses based upon responses to other questions (crosschecks), and check for missing forms

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Data Cleaning Procedures

- Once edit checks are run, any errors or inconsistencies that need further explanations are sent to the site via a data clarification form or query
 - This is a documented query that includes the identifying information for the subject, the problem or query, and the site's response to resolve the query
- The query is then resolved by entering the resolution into the database and the edit checks are run again
- Edit checks are run until there are no queries that are generated for the site to review

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Data Cleaning Procedures

- Many EDC edit checks are run immediately when the user enters the data
 - Out of range values and invalid date, time, or result formats
 - Crosschecks with previous question responses
- EDC systems typically have a missing forms report that can be generated in real time
- Some EDC systems have a query tracking and resolution module built in
- Edit checks are also run after the data is in the database

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Data Cleaning Procedures

- Paper based studies have edit checks that are run after the data is entered into the system
 - This leads to more queries on average as most simple errors are not immediately caught
 - Edit checks will be programmed to look for the same items as an EDC system
 - Data Clarification Forms or queries are sent out via paper, fax, or email

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Data Validation and Audit Process

- After edit checks are run and all queries have been resolved, the database must be validated or audited
- A Data Validation Plan (DVP) details the process that will be used to review/audit the data
- This only applies to a paper based study and not an EDC system because the data in the database has already been reviewed against the source documents by the monitor
- This process compares the data in the database with the data reported on the case report forms to ensure the data is accurately entered into the database

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Data Validation and Audit Process

- All study end points, outcomes, and safety data should go through a 100% review, while other data should have a random sample review
- All discrepancies between the CRFs and the database must be documented and fixed in the database
- A database error rate is calculated. This formula is $(\# \text{ of incorrect entries} / \# \text{ of reviewed fields}) * 100$
- There should be an error threshold defined in the Data Validation Plan (i.e. 0.1% or 1/1000 fields) where a more thorough review of the data will occur the the threshold in reached

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Annotated CRF Activity

- Annotated CRFs reflect the structure of the underlying database
- Use the knowledge of database structures to annotate two CRFs
- Include
 - Data table name
 - Variable names
 - Variable type
 - Variable formats and a code list
 - Variable lengths
- 30 minutes

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Database Freeze and Lock Procedures

- Database freeze is when all users have their permissions removed and the data can no longer be changed in the database
- Approval from PI, DM, Statistician, Monitor, and RA
- Reconciliation is done between the safety database for adverse events and the clinical database
- A clinical review of the data can be performed to catch any last minute inconsistencies or errors
- If any errors are found at this point, the database can be unfrozen, modified to fix the errors and then frozen again

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Database Freeze and Lock Procedures

- After the data is frozen and all reconciliation has been performed and there are no errors or omissions the database can be locked
- The study is unblinded if applicable
- Approval from PI, DM, RA, Statistician, Monitor, and Safety to lock the database
- Once the database is locked, no changes can be made to the database unless it is unlocked
 - Highly suggest never unlocking a database unless there are major errors in the data as this may introduce bias

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Data Archiving

- After the database is locked and all analyses have been performed, the data can be archived
- This will depend upon the IT staff and the organizational SOPs
- Archiving is removing the database from an active server and placing it into an archived location
- The database will need to be retrieved from the archive if requested for additional analyses or for auditing by regulatory authorities

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Essential Data Management Documents

- Procedural Documents
 - Protocol and Amendments
 - Manual of Procedures (MOP)
 - Standard Operating Procedures (SOPs)
 - Study Specific Procedures (SSPs)
 - Data Management Plan (DMP)
 - Safety Management Plan (SMP)
 - Clinical Monitoring Plan (CMP)
 - Study timelines

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Essential Data Management Documents

- Data Collection and Processing Documents
 - Case Report Forms (CRFs)
 - Case Report Form Instructions (CRFi)
 - Data entry guidelines
 - Self-evident corrections
 - Medical coding guidelines
- Database documents
 - Design and system validation
 - Code lists, formats, and data dictionary
 - Annotated CRFs

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Essential Data Management Documents

- Data Collection and Processing Documents (con.)
 - Randomization Master List
 - Laboratory Normal Ranges
 - Subject Enrollment Log
- Data Quality
 - System Validation Plan
 - Data Validation Plan (DVP)
 - Edit checks
 - Data clarification forms (DCF)/queries

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CDM SOPs

- SOPs provide the sponsor and other vested parties assurance that the data and other tasks will be consistently handled and performed
- SOPs add a level of assurance that the final data and product will be of the highest quality
- SOPs define who is responsible for the various tasks associated with Data Management activities
- Elements of an SOP include the title, scope and purpose, responsible parties, procedures, cross-references to other SOPs and policies

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CDM SOPs

- DCF Generation and Resolution
- CRF Development
- Database Design
- Database Lock
- Database Closure and Archiving
- Data Entry and Verification
- CRF Receipt and Tracking
- CRF Completion Guidelines
- Coding Adverse Events
- Training Procedures
- Electronic Data Transfers
- Data Management Plan
- Data Validation Plan and Audits

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Data Management Plan (DMP)

- DMP Table of Contents
- Purpose of DMP
 - Provide a focus for the data management activities to be performed, who will be responsible for performing those activities, and what is to be produced as documentation
 - The activities detailed in the DMP assist in the production of quality data for any interim and final statistical analyses
- Responsibilities within the DMP
 - A detailed list of all responsibilities and what organization is responsible for each

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Data Management Plan (DMP)

- DM Software and System
 - Description of all systems that will be used during the course of the trial
- Schedule of events
- CRF information
 - Sample CRFs
 - Retrieval and transmission of data
 - Tracking methods
- Database structure

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Data Management Plan (DMP)

- Data Validation
 - Data validation plan reference
- Discrepancy Management
- Medical Coding
- AE and SAE reconciliation
- DB Lock procedures

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Data Validation Plan (DVP)

- A user-defined comprehensive list of the edit checks and field calculations for the study
- Auditing procedures
 - Error thresholds
 - Resolution plan
- "Living" document throughout the study conduct
 - Finalized at study closeout – for archiving

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Understanding Database Structures

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Database Design

- Relational database
 - Data tables that refer to or link to other data tables using numbers or characters

Visit ID	Visit Name
1	Screening
2	Baseline

Subject	Visit ID	Date	Time
SUB001	1	12May2010	1356
SUB001	2	14May2010	1032
SUB002	1	10May2010	1421
SUB002	2	11May2010	1503

Subject	Visit ID	Date	Time
SUB001	Screening	12May2010	1356
SUB001	Baseline	14May2010	1032
SUB002	Screening	10May2010	1421
SUB002	Baseline	11May2010	1503

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Database Design

- Database normalization
 - Designing a database to remove anomalies or inconsistencies within the data

Subject	Visit	Lab Test	Result
SUB001	Screening	Glucose	112
SUB001	Screening	Creatinine	45
SUB001	Baseline	Glucose	95
SUB001	Baseline	Creatinine	46

VS

Subject ID	Visit ID	Lab Test ID	Result
1	1	1	112
1	1	2	45
1	2	1	95
1	2	2	46

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Database Design

- Horizontal vs. Vertical structure
 - One record per observations version multiple records per observation

Subject	Visit	Glucose Result	Glucose Abnormal	Creatinine Result	Creatinine Abnormal
SUB001	Screening	114	Yes	44	No
SUB001	Baseline	98	No	45	No

VS

Subject	Visit	Lab Test	Result	Abnormal
SUB001	Screening	Glucose	114	Yes
SUB001	Screening	Creatinine	45	No
SUB001	Baseline	Glucose	98	No
SUB001	Baseline	Creatinine	46	NO

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Database Design

- Which is best for a clinical trial?
 - Depends...
 - Type of CRF
 - Type of data being recorded
 - Amount of processing of the data after it is collected
 - Typically...
 - Second Normal Form, and use code lists
 - Horizontal vs. Vertical depends on type of CR
 - Collect as few variables as possible

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Edit Check Activity

- Using the annotated CRFs (supplied), generate edit checks to ensure proper data is being collected
- Specify the CRF, the edit check criteria in sentence form
- Make an attempt to write the SAS code implementing your edit check
 - Develop the conditional 'IF' statement
 - numeric missing values: .
 - character missing values: "
 - logic statements: <, lt >, gt <=, le >=, ge =, eq ^=, ne
 - character results surrounded by quote: 'NO'

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Regulations and Good Practices in Clinical Data Management

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Data Management Regulations

- Food and Drug Administration (FDA)
 - 21 Code of Federal Regulations (CFR)
 - Guidance Documents
 - GxPs
- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)
- European Directives
- Good Clinical Data Management Practices (GCDMP)

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Data Management Regulations

- 21 CFR
 - Part 11: Electronic records; electronic signatures
 - Regulations as to when the FDA will accept digital records and digital signatures in lieu of paper forms and wet signatures
 - Data is trustworthy and reliable
 - Data that is created, modified, maintained, archived, retrieved, or transmitted electronically
 - Part 50: Protection of human subject
 - Informed consent process and procedures
 - IRB duties

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Data Management Regulations

- FDA Guidance for Industry
 - Collection of Race and Ethnicity Data in Clinical Trials
 - Computerized Systems Used in Clinical Investigations
 - on Part 11, Electronic Records; Electronic Signatures-- Scope and Application
 - General Principles of Software Validation
 - Pharmacogenomic Data Submissions
 - Providing Regulatory Submissions in Electronic Format-- Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications

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Data Management Regulations

- ICH Guidance Documents
 - ICH E6: Good Clinical Practice: Consolidated Guidance
 - ICH E2A: Clinical safety data management: Definition and Standards for Expedited Reporting
 - ICH E8: General considerations for clinical trials
- The Health Insurance Portability and Accountability Act (HIPAA)

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Standards within Clinical Data Management

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CDM Standards

- Various standards within CDM
 - Within an organization
 - SOPs
 - CRFs
 - Database Design
 - Across organizations and data standards
 - MedDRA
 - CTCAE
 - WHO Drug
 - CDISC

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Data Standards

- When we talk about data standards, we are really talking about metadata standards
- Organizations or companies usually develop proprietary data standards
- Data standards can vary based upon industry, company, therapeutic area, product
- Sometimes there are no data standards

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Data Standards – Advantages

- Efficiency
 - Database development
 - Data entry
 - Data review
 - Data analysis
- Pooling or combining data
- Transferring data to partnering organizations or companies

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Data Standards – Challenges

- Coming to a consensus by all stakeholders
- Creating a robust standard that applies to all situations and needs
- Large initial investment of time and money to develop the standards
- Dissemination of standards to all stakeholders
- Enforcement of standards by all users

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Data Standards

- Greater efficiency and uniformity can be gained from developing a data standard
- Need a large effort to develop standards
- Companies develop proprietary standards, but is it possible to standardize an entire industry?
 - Clinical Data Interchange Standards Consortium (CDISC) is attempting to do this

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Coding Dictionaries

- MedDRA
- ICD-9
- WHO Drug Dictionary (Enhanced)

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MedDRA Standards

- MedDRA = Medical Dictionary for Regulatory Activities
- Medical terminology used to classify adverse event information
- Allows health authorities and the biopharmaceutical industry to more readily exchange and analyze data related to the safe use of medical products
- Developed by the International Conference on Harmonisation (ICH)

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MedDRA Standards

- Data format
 - Verbatim terminology
 - System Organ Class (SOC)
 - High-level Term (HLT)
 - Preferred Term (PT)
 - Lower-level Term (LLT)
 - Numeric codes for each term
- Auto encoders
- Frequent updates to the dictionary

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WHO Drug Standards

- World Health Organization Drug Dictionary
- Comprehensive dictionary of medicinal product information
- Identifying drug names, their active ingredients and therapeutic use
- Majority of entries refer to prescription-only products, but some are over-the-counter (OTC) or pharmacist-dispensed

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WHO Drug Standards

- Types of products
 - Medicinal product
 - Herbal remedy
 - Vaccine
 - Dietary supplement
 - Radio-pharmaceutical
 - Blood product
 - Diagnostic agent
 - Homeopathic remedy

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WHO Drug Standards

- Benefits of using WHO Drug include
 - Consistent, quality-assured, and up-to-date information entry
 - A hierarchical structure that allows easy and flexible data-retrieval and analysis at different levels of precision
 - Chemical and therapeutic groupings - using the WHO drug record number system and the ATC classification
 - Available in software-independent electronic format for easy implementation in user systems

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WHO Drug Standards

- Coding includes
 - Common drug/substance name
 - Anatomical Therapeutic Chemical classification (ATC) codes
 - Ingredient table
 - Manufacturer

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What is CDISC?

- Non-profit organization focused on developing an industry standard since 1997
- Supported by more than 170 organizations
 - Biotechnology and pharmaceutical companies
 - Contract Research Organizations (CROs)
 - Information technology providers
 - Academic institutions
 - Government agencies
 - Non-profit organizations

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What is CDISC?

- Multinational effort to develop industry standards for various regulatory authorities
 - United States
 - European Union
 - Japan
 - Australia
 - China

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CDISC - Mission

- "...develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of healthcare."

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CDISC Principals

- Lead the development of standard data models that improve process efficiency while supporting the scientific nature of clinical research
- Recognize the ultimate goal of creating regulatory submissions that allow for flexibility in scientific content and are easily interpreted, understood, and navigated by regulatory reviewers

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CDISC Principals

- Acknowledge that the data content, structure and quality of the standard data models are of paramount importance, independent of implementation strategy and platform
- Maintain a global, multidisciplinary, cross-functional composition for CDISC and its working groups

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CDISC Principals

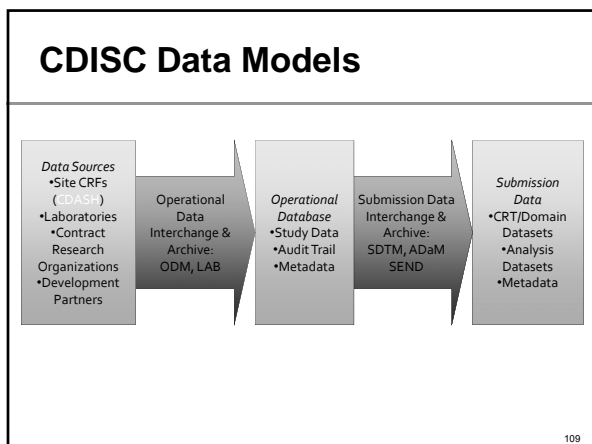
- Work with other professional groups to encourage that there is maximum sharing of information and minimum duplication of efforts
- Provide educational programs on CDISC standards, models, values and benefits
- Accomplish the CDISC goals and mission without promoting any individual vendor or organization

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CDISC Collaborations

- CDISC is working with multiple organizations to develop the data standards
 - Data management (SCDM, NCDM, ACDM, DMB, ARCS)
 - Drug Information Association (DIA)
 - Medical Writers Associations (AMWA, EMWA)
 - NIH/NCI
 - HL7
 - C-Path
 - AMIA
 - PhRMA
 - EMEA
 - WHO

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In Summary...

- Data managers are involved in many aspects of the clinical trial
- Data managers do more than just manage data
- Data managers need to a wide amount of experience in order to be effective within their role of the clinical trial
- There is not necessarily one “right” way to do things
- Documentation is very important

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Additional Questions?

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