Validation of Derived Data via Cross Validation Methods

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The Problems

- A data element may appear more than once in the eCRF
- To derive data based on calculation of previously collected data
- Continuation Studies needing subset of patient data from parent study
- Transfer of patients from a screening study to a registry type study

Within same study

- Examples of same data across different CRFs: Can they all be derived?
  - Patient Initials
  - Patient Age in the same year
  - Patient Weight, Height in the same month
  - Patient Initial Medication loading dose
  - Patient procedure method (PCI through radial or femoral) at baseline

Within same study

- Need to collect BMI
  - Can ask for it from clinic (they calculate and enter)
  - Can ask for component details and derive

Cross Studies

- Same study number but new schema/ setup
- Subset of existing patients going forward
- New CRFs going forward
  - ➢ New CRFs leverage some existing data
  - ➢ Want to pull data forward into new CRF plate from existing “older” study plate data

Cross Studies

- Transfer of Patient to New Study
  - ➢ Screening study with PHI data records
  - ➢ Patient is identified for specialized study
    - ❖ Want to transfer only certain patient record data to specialized study

So What Now?

- Can we just copy data from plate to plate?
- Or from study to study?
- Or derive data as needed?
- What do we need to worry about?

Points to Consider

- What does regulatory guidance say?
- What does the study protocol say?
- What are the risks to the patient?
- What are the risks to the study results?
- What are the mechanisms to do this?
- What verification or validation is needed?

Regulatory Guidance

- FDA 21 CFR Part 11

- Determine predicate rule requirements
- Assess the risk related to derived variable
- Implement appropriate Part 11 controls
  - Specify what's to be done (requirements)
  - Test/Validate correctness of what's being done
  - Control process (change management, documentation)

Regulatory Guidance

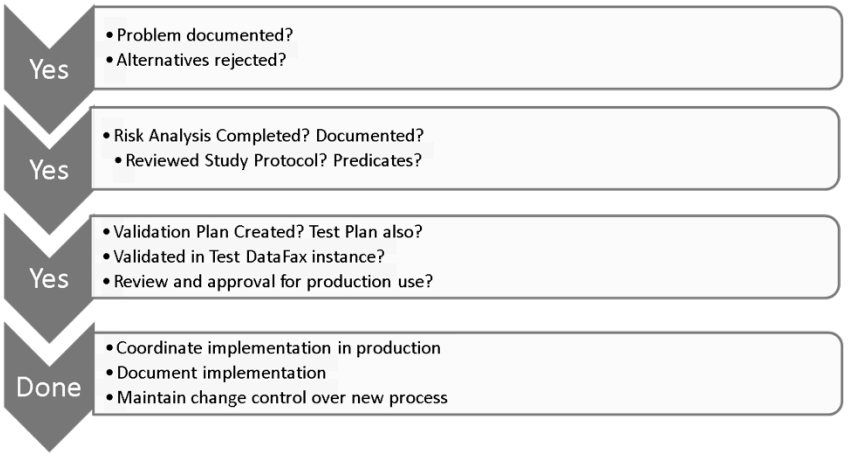
- FDA Guidance for Industry Computerized Systems Used in Clinical Investigations

- Study protocols
- SOP Source documentation and retention
- Internal security safeguards

Risks

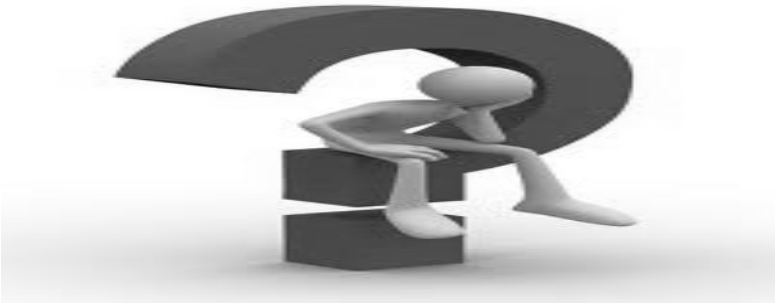
- NEVER hard code values in programming
  - ➢ If Patient initial on visit 1 equals “XYZ” then set Patient initial on visit 2 to “ABC”
- NEVER assume same data collection request is equivalent across CRFs(refer to study protocol)
  - ➢ Patient blood pressure on 3 CRFS for visit 2
- Data corruption during copy or calculation
- Audit trail clarity on “who” did “what”

Implementation Process



Options of data collection

- Manual Data Entry from original CRFs
- Edit Checks
- DFexport/DFimport



Edit Checks

- Pro
  - Programmatically efficient
  - Control Stays within DataFax System
  - Data stays within the DataFax System
  - Audit trail fully maintained
  - Lower cost
- Con
  - Introduces concern of 21 CFR Part 11
  - More coordinating time

DFexport/DFimport

- Pro
  - Simple to understand
  - Can be automated to process large data sets
  - Can be under the control of the study teams
  - Can be used to bring data into richer set of programming tools than edit check language
- Con
  - Introduces risk of data movement out of DataFax
  - Introduces risk of programming outside of DataFax
  - Audit trails do not show the originator. It shows only the person who does the import

DFexport/DFimport (cont)

- Con
  - Introduces concerns of 21 CFR Part 11
  - Requires conversion of export to import format
    - Will study teams use Excel to convert formats?
    - Will IT Department be leveraged to convert formats?

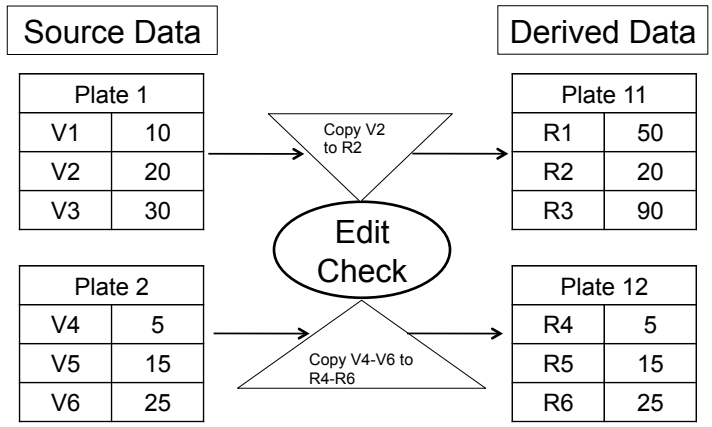
FDA requirements

- FDA issued 21 CFR part 11
  - Audit trails
  - System controls
- Guidance for industry computerized systems used in Clinical Investigations
- Standard operating procedures: create, modify and maintain data
- Training of Personnel

Cross Validation Procedures

- Standard edit check testing
  - Raw data testing (Cross plate checking)
  - Sample data testing
- R statistical programming language
  - R's language has a powerful, easy to learn syntax with many built-in statistical functions
  - R is open-source and runs on UNIX, Windows and Macintosh
  - Performs dataset comparisons easily

Example: Internal Cross Plate Data Transfer Using Edit Checks



*Source and destination fields must be defined the same

DFexport/DFimport Example

- Patient Screening Study 1 identifies candidates
- Candidate patient approved for Study 2
- Specified plate data is exported from study 1
- Exported data may need to be filtered (filtering criteria can be complicated)
- Exported plate data massaged into an import record
- Massaged record is tested/validated using Unix scripts (perl, awk, etc)
- Validated record is imported into Study 2
- Validation is done after import
- Scheduled jobs to do the export/import

How to maintain

- If the original study data management plan doesn't include this process initially, add an amendment
- Database is managed centrally, any modification and update of database setup will immediately inform the central personnel and proper procedure will be performed to ensure the integrity of database
- Risk assessments for all database changes

Are the risks acceptable?

- Should we even be doing this ?

Questions?