Out-of-(CSR) Body Experiences Tips on Assembling Appendices, **Datasets, CRFs, References**

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New Dataset Requirements

- Study Data Standards (CDISC) datasets required for **almost ALL M4, M5** studies
- NDAs, BLAs, ANDAs -Studies started after 12/17/2016 must submit CDISC
- Commercial INDs - Studies started after 12/17/2017 must submit CDISC

New Dataset Requirements

- **New high level technical rejection criteria**
  - **All datasets - legacy or CDISC**
  - Trial Summary (TS) dataset - M4, M5 studies
  - Demographic (DM) datasets with define.xml - M4, M5 studies
  - Subject level analysis dataset (ADSL) with define.xml - M5 studies
- 30 Day notice prior criteria becoming effective

M4, M5 Dataset Exceptions

- 4.2.2.7 Other Pharmacokinetic
- 4.2.3.7 Other Tox
- 5.3.1.4 Bioanalytical/Analytical Methods
- 5.3.5.3 Analyses Data More Than One Study
- 5.3.5.4 Other Study Reports
- 5.3.6 Reports of Postmarketing Experience

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New Dataset Info

CDER Small Business and Industry Assistance Webinar - Study Data Standards in eCTD: What You Need to Know about the New Technical Rejection Criteria - October 12, 2016

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm522121.htm

Technical Rejection Criteria for Study Data

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM523539.pdf

Study Data Technical Conformance Guide - Version 3.2 will be posted October 2016

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Clinical Datasets

- **Statisticians - key to quality and success**
- CDISC validated before handoff to publishing
- Files supplied by type, in appropriate folders
- **Publishers organize into submission tool**
  - Usually not a last minute "drop-in"
  - Supporting PDFs can have compliance issues
  - PDFs may require significant time/resources before submission ready

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Clinical Dataset Types

- **Tabulation datasets** - Raw data
  - Legacy
  - CDISC = SDTM - Study Data Tabulation Model
- **Analysis datasets -** Analysis of raw data
  - Legacy
  - CDISC = ADaM - Analysis Data Model
- **BIMO datasets** - Site specific data
  - Inspections - Office of Scientific Investigations

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Dataset File Types

- **SAS Transport** - XPT files
- **Data definition** - define file
  - Describes datasets and variables
  - **Legacy** - define.pdf - bookmarked and linked
  - **SDTM/AdaM** - define.xml and define.pdf
  - define.xml - internal and external xml links
  - define.xml supporting files - XSL, CSS, GIF
  - define.pdf for printing? bookmarks and links?

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Dataset File Types

- **Annotated CRF** - PDF
  - Tabulation datasets (SDTM/legacy)
  - Connects dataset variables back to CRF location
  - 16.1.2 Sample CRF - link to annotated CRF
- **Programs** - TXT
  - Analysis datasets (ADaM/legacy)
- **Reviewer guide, readme** - PDF
  - Any/all datasets (CDISC/legacy)

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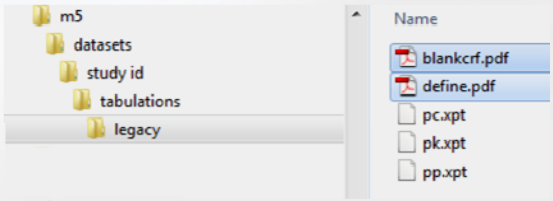
Legacy Tabulation Datasets



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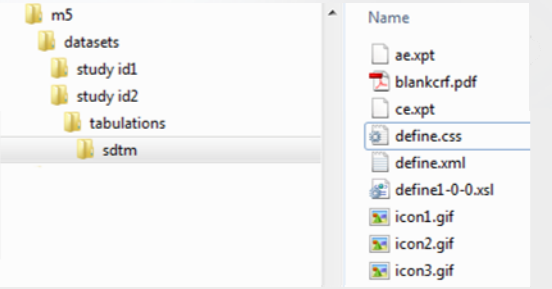
SDTM Tabulation Datasets



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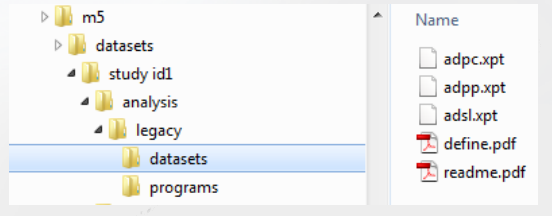
Legacy Analysis Datasets



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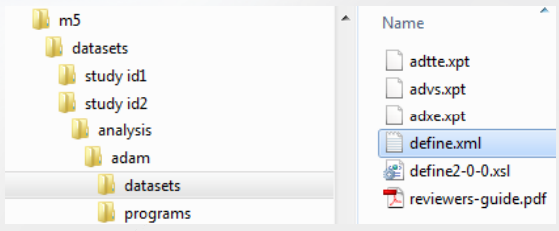
ADaM Analysis Datasets



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Case Report Forms

- **Identify, locate e-CRFs early - not at NDA**
- CRFs for all subjects not submitted
- CRF submission criteria
  - Deaths, serious AEs, withdrawals for AEs
  - FDA requested narratives
- Single file per subject - not CSR section 16.3
- 16.3 = CRF TOC linked to CRFs
- Links from narratives to CRFs

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Case Report Forms

- **Paper or electronic data capture system?**
- **Scanned paper CRF** - plan time/resources
- Submission ready = bookmarked and linked
  - Bookmark by visit/domain
  - Bookmark by domain/visit
  - Link data clarification forms to CRF page
- Manual / automated processes and QC

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Case Report Forms

- **CRFs from electronic data capture system**
- Generated by EDC system
  - Variety of e-Sub compliance issues
- e-CRF not designed like paper CRFs
  - Bookmarks visit/domain and domain/visit may not make sense
  - Audit pages instead of data clarification forms
- Time/resources variable - check early

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Literature References

- **Not part of the CSR**
  - All clinical references in module 5.4
- **Make decisions early**
  - To submit or not to submit CSR references?
  - Follow copyrights or not?
- **Acquire copies early**
  - Appendices compilation task
  - Assign responsibility to someone
  - Don't wait and let NDA linking drive process

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Literature References

- **Set reference document standards**
  - File name conventions = leaf title
  - Bookmark and link standards even needed?
  - Include FDA/ICH guidance documents?
  - "Blue" the CSR reference list text?
- **Submission readiness - unplanned resources**
  - Vendor references - excessive, noncompliant links
  - Noncompliant file properties - security settings

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Study Tagging File

- **Legacy CSR** - Report body, all appendices in one file
- **Granular CSR** - Report body, appendices in separate files
- STF - XML file = Backbone for CSR
  - CSR electronic table of contents
  - Report body and appendices
  - CRFs
  - Datasets

Thank You!

Questions?

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