Interpreting and Using the Validation Results from Automated Tools

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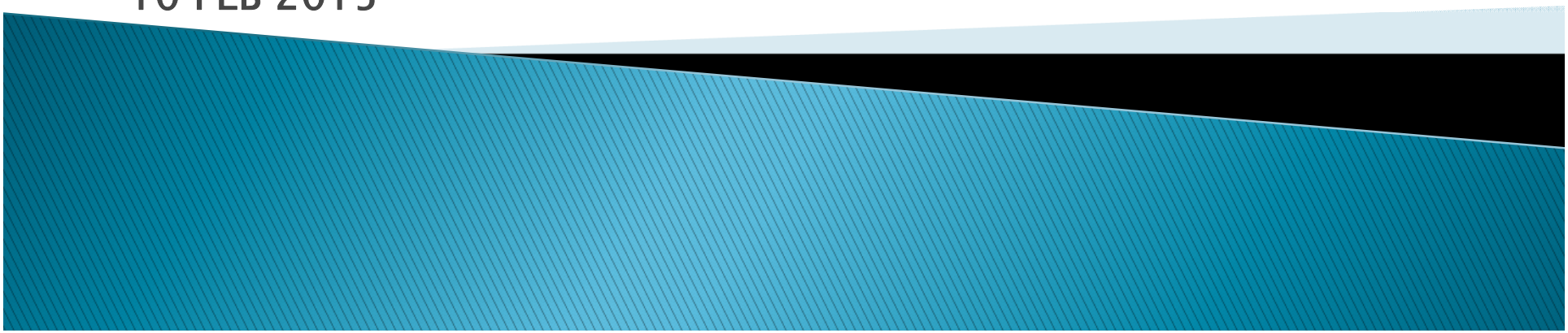
10 FEB 2015



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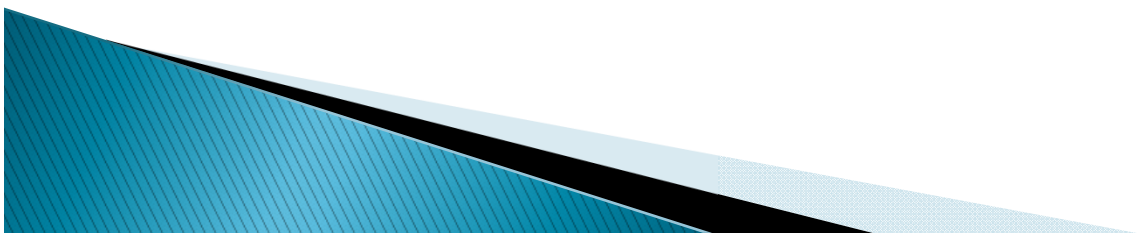
- Where are we today?



Current Environment

1) Submitting data electronically to the FDA and other regulatory agencies
2) eSubmission is in your future

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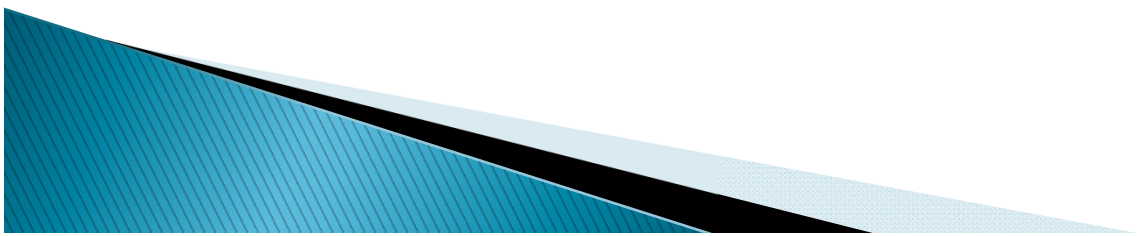
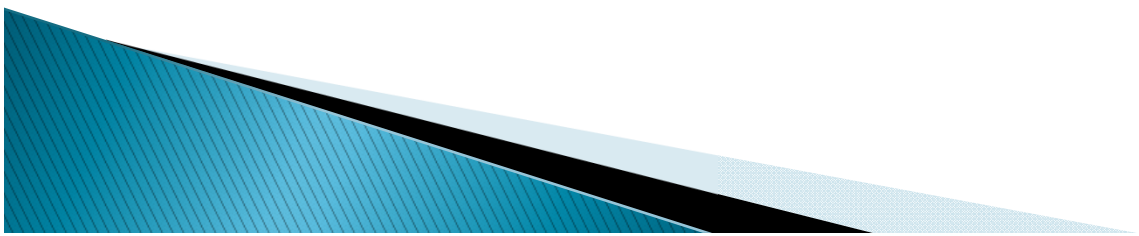
- Sas Transport files, define.xml, blankcrf, reviewers guides and a study data standardization plan is required for eSubmissions of study data



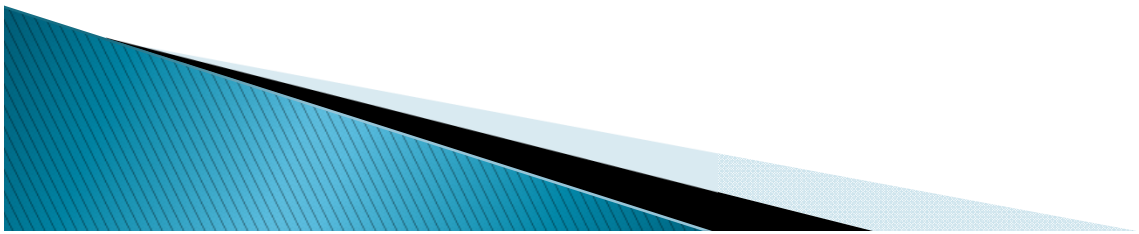
Submission Deliverables

- Not just datasets and define.pdf anymore
- Accuracy demands cross checks between
  - Datasets and define
  - Define and blankcrf
  - Data Standards plan, datasets and define
  - Between ADaM and SDTM



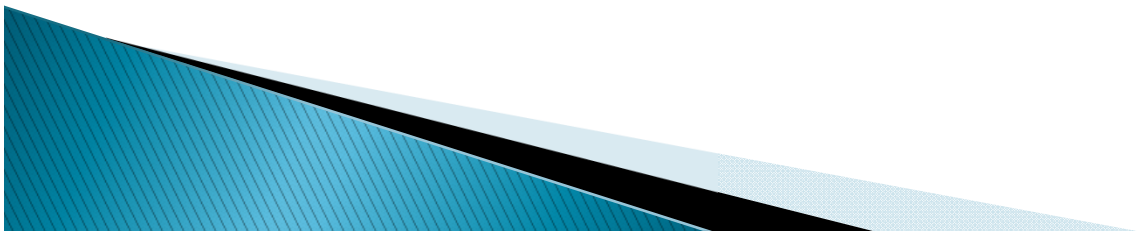
Required Submission Deliverables 2015

- Submission level
  - Data standardization plan
- Study level – SDTM and ADaM
  - SAS transport files
  - Define.xmls
  - Reviewers guides
- SDTM
  - blankcrf (annotated)



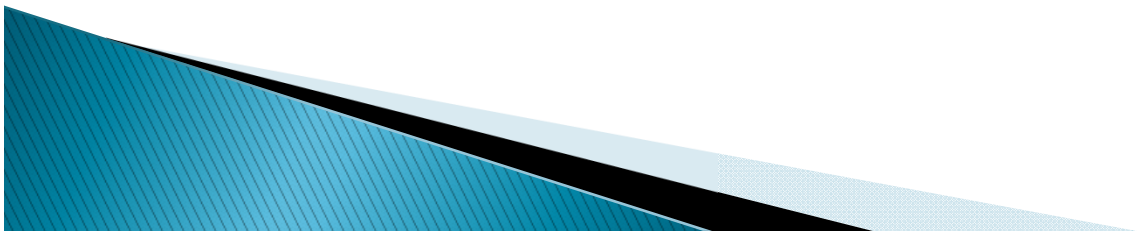
Submission Deliverables 2015 – 2

- There should be conformance to standards
- Integrity across and within each deliverable
- We want to pass the JumpStart Data Fitness test that FDA Computational Sciences will apply to NDA and BLA filings



What is Define.xml? -1

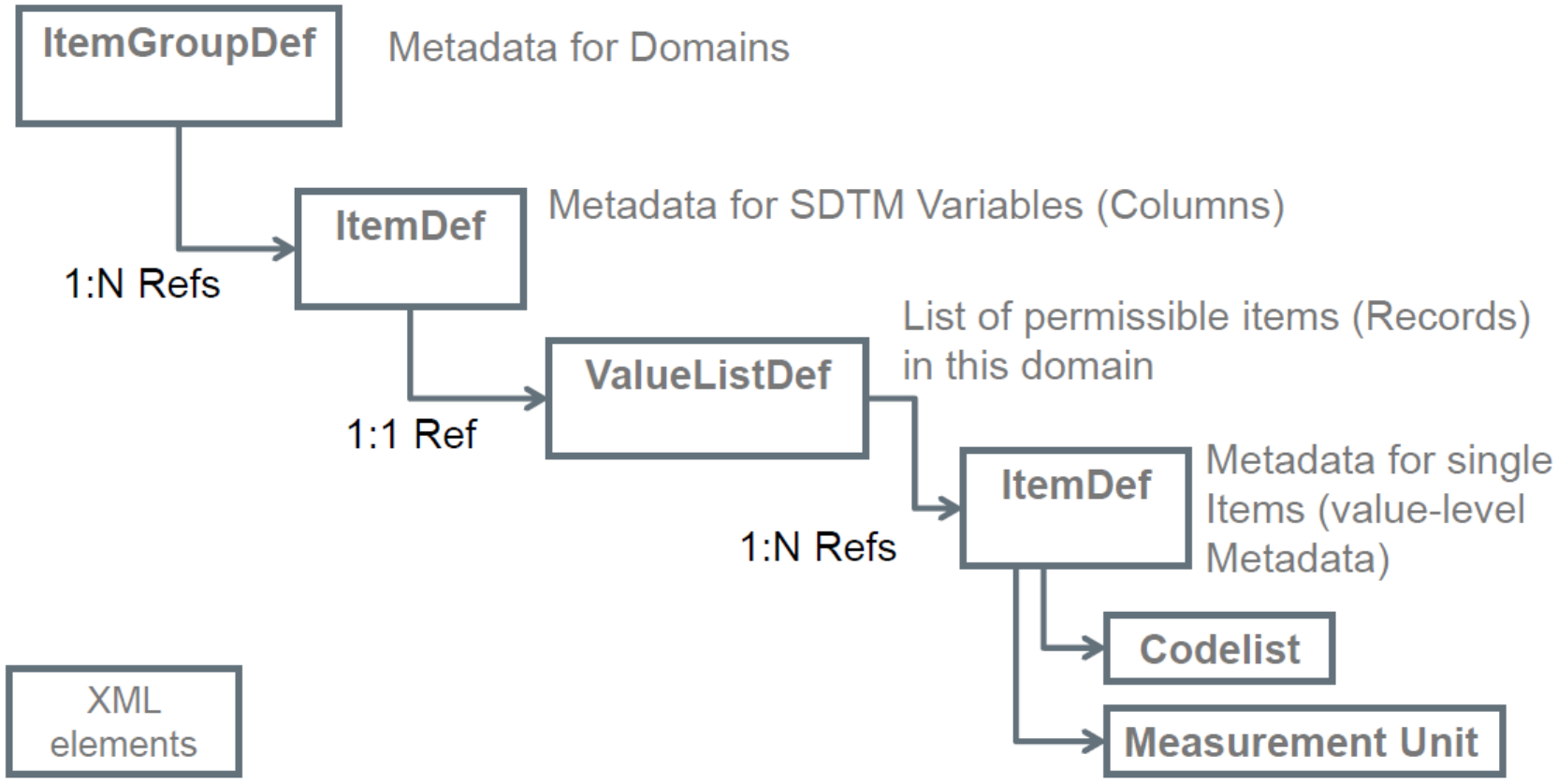
- **Metadata**
  - a description of the study data in a structured xml format designed to be machine and human readable
  - For a reasonable size SDTM grouping of datasets the define.xml may have up to 10,000 lines of xml text



What is Define.xml? – 2

- **The Define contains the complete set of data definitions for:**
  - the meaning / scientific concept
  - ID / Label / short name
  - (Long) Name / description
  - References to external classification systems (e.g., MedDRA)
  - the type of data (integer, float, text, date, time)
  - the maximum length of the data value
  - the possible / permissible units of measure
  - permissible discrete answers (codelists)

Structure of Define.xml



Raw XML list of Define.xml

```
<?xml version="1.0" encoding="UTF-8"?>
<ODM FileOID="2" FileType="Snapshot" CreationDateTime="2013-03-13T20:41:31-07:00" Originator="Formedix" SourceSystem="Origin Submission Modeller" SourceSystemVersion="2.10.2" ODMVersion="1.2" xmlns:fdx="
http://www.formedix.com/ns/origin/2" xsi:schemaLocation="http://www.cdisc.org/ns/odm/v1.2 define1-0-0.xsd" xmlns:def="http://www.cdisc.org/ns/def/v1.0" xmlns:xlink="http://www.w3.org/1999/xlink" xmlns:xsi="
http://www.w3.org/2001/XMLSchema-instance" xmlns="http://www.cdisc.org/ns/odm/v1.2">
  <Study OID="AALL07P2">
    <GlobalVariables>
      <StudyName>Erwinaze</StudyName>
      <StudyDescription>Erwinaze</StudyDescription>
      <ProtocolName>ALL07P2</ProtocolName>
    </GlobalVariables>
    <MetaDataVersion OID="4" Name="Erwinaze" Description="Erwinaze" def:DefineVersion="1.0.0" def:StandardName="CDISC SDTM" def:StandardVersion="3.1.2">
      <def:AnnotatedCRF>
        <def:DocumentRef leafID="blankcrf.pdf"/>
      </def:AnnotatedCRF>
      <def:leaf xlink:href="blankcrf.pdf" ID="blankcrf.pdf">
        <def:title>blankcrf.pdf</def:title>
      </def:leaf>
      <def:ValueListDef OID="ValueList.DA.DACAT">
        <ItemRef ItemOID="DA.DACAT.STUDY MEDICATION" Mandatory="No" OrderNumber="1"/>
      </def:ValueListDef>
      <def:ValueListDef OID="ValueList1.DA.DACAT.STUDY MEDICATION.DATESTCD">
        <ItemRef ItemOID="DA.DACAT.STUDY MEDICATION.DATESTCD.TREAT" Mandatory="No" OrderNumber="1"/>
      </def:ValueListDef>
      <def:ValueListDef OID="ValueList1.IE.IECAT.EXCLUSION.IETESTCD">
        <ItemRef ItemOID="IE.IECAT.EXCLUSION.IETESTCD.EX01" Mandatory="Yes" OrderNumber="1"/>
        <ItemRef ItemOID="IE.IECAT.EXCLUSION.IETESTCD.EX02" Mandatory="Yes" OrderNumber="2"/>
        <ItemRef ItemOID="IE.IECAT.EXCLUSION.IETESTCD.EX03" Mandatory="Yes" OrderNumber="3"/>
        <ItemRef ItemOID="IE.IECAT.EXCLUSION.IETESTCD.EX04" Mandatory="Yes" OrderNumber="4"/>
      </def:ValueListDef>
      <def:ValueListDef OID="ValueList1.IE.IECAT.INCLUSION.IETESTCD">
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        <ItemRef ItemOID="IE.IECAT.INCLUSION.IETESTCD.IN02" Mandatory="Yes" OrderNumber="3"/>
        <ItemRef ItemOID="IE.IECAT.INCLUSION.IETESTCD.IN03" Mandatory="Yes" OrderNumber="4"/>
        <ItemRef ItemOID="IE.IECAT.INCLUSION.IETESTCD.IN04" Mandatory="Yes" OrderNumber="5"/>
      </def:ValueListDef>
      <def:ValueListDef OID="ValueList.LB.LBCAT">
        <ItemRef ItemOID="LB.LBCAT.CHEMISTRY" Mandatory="No" OrderNumber="4"/>
```
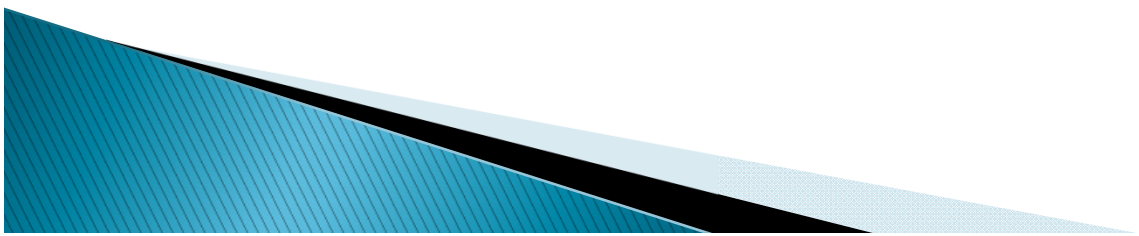
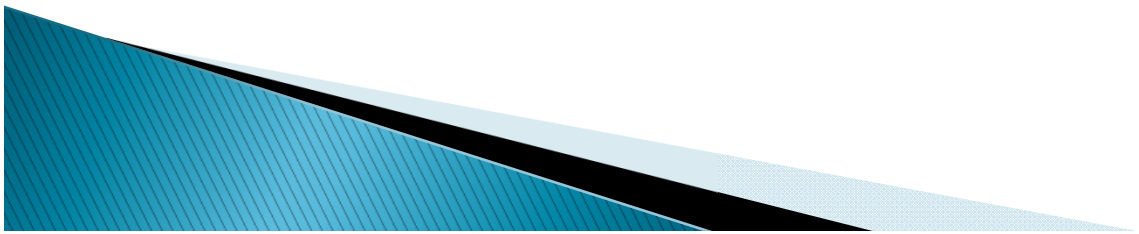

Before Validation Tools

- In the beginning…
  - Manual work
  - Custom programs / applications
  - Spreadsheet specifications to check and re-check

- There were no regulatory standards for validation until Nov 2014
  - OpenCDISC started with Janus Rules and WebSDM conformance

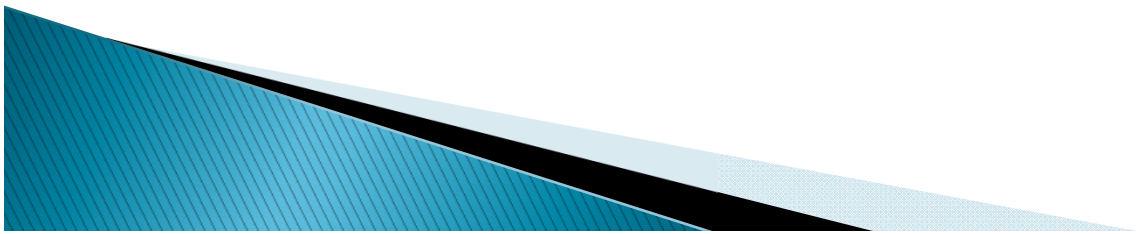


- Using Automated Validation Tools



Benefit of Tools

- Decreases time and increases accuracy
- Allows you to accomplish the impossible
  - Define.xml is metadata file that is hierarchical and based on ODM to support human and machine readability
  - A reasonable size study define.xml up to 10,000 lines of xml statements
- May tell you some things about your data you did not know



Limitations of Tools

- Extensible codelists create false errors
- Legacy studies have non-conformant terminology
- False positive results
  - Tests without units
- Different tools yield different results
- There is NO substitute for knowing your data structure and content
- There is NO substitute for consultation with Regulatory agencies

Interpreting the Validation Results – 1

What automation can for you

- dataset structure – variable names / labels
- data integrity
  - checks reference to DM subjects
  - presence of baseline flags
  - dates after disposition
  - Results units consistency
  - Terminology checks
- referential integrity
  - Start date before End date
  - Disposition references – sometimes

Interpreting the Validation Results – 2

What you still have to do

- dataset structure
  - do you have the right variables per spec?
  - custom domains
- data integrity
  - baseline flags – does not see 2 per subject?
  - Review Terminology flags, If a codelist is expandable – is it correct?
- data validation more content focused
  - right subjects
  - right dates
  - right codelists
  - right test codes

Interpreting the Validation Results – 3

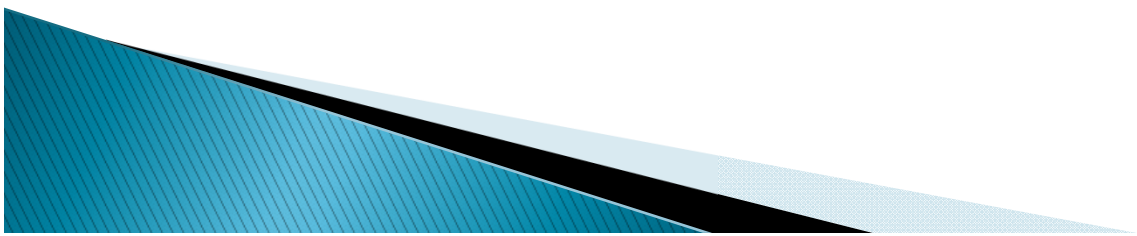
- False positive results may occur
  - Lab tests without units will generate errors e.g. Urine pH = 5, specific gravity 1.012
  - Terminology
    - Extensible codelists with non matches in the terminology file where the sponsor has added codes / values not present
      - E.g. Oxygen Saturation as O2SAT VSTESTCD
  - Some program bugs may generate false error messages
    - Report these!

Suggested Process for OpenCDISC Validator

- Review Setup / Parameters
  - Confirm SDTM Version
  - Confirm MedDRA version
  - Confirm Terminology version
  - Include the define.xml file if present
  - Set report parameters
    - Study Name / Number / Dates / other text / Excel message limit
- Run validation
- Review Error report
  - Update Issue Summary tab with Comments
  - Refer to details tab as needed
  - Identify / report any new bugs
  - Consider submitting an update to terminology team
- If final dataset for submission then include in reviewers guide data conformance section with explanations

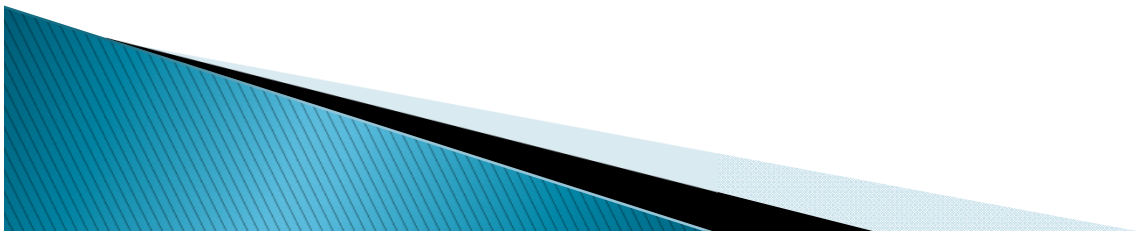
Lessons Learned – 1

- Focus on content more!!!
  - You know your studies, the data collected and analyzed better than anyone else
- Older studies more likely to be non-conformant
  - If the data was collected using non-standard terminology or older efficacy measures know the strengths and weaknesses of what you have



Lessons Learned – 2

- Understand the exceptions and their meaning
  - False positives
  - Non standard terminology
- Involve study team experts to understand and explain complicated clinical questions that are contained in
  - Statistical Analysis Plans
  - CRF Data and other source data



Lessons Learned – 3

- Provide documentation to explain what is known
  - Reviewers Guide
    - Hard codes
    - Non Conforming data
- Fix what is possible
- Be prepared to answer questions about legacy data

Thank you!

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