Optimized SDTM process and SDTM related Tool Invention

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IMPROVE QUALITY
Outline

• Optimized SDTM Pre-process

• Optimized SDTM Post-process before deliverable

• Key points of SDTM- MSG

• Tool invention
Optimized SDTM Pre-process
Optimized SDTM Pre-process (1) --Senior Review CRF design

• CRF is the link between protocol, database and Statistical Analysis Plan (SAP)

• It gives programmers information on how the data are captured and collected

• Statistician and Programmers involved in the CRF finalization stage to ensure the data are collected in an appropriate manner to enable successful completion of study
Optimized SDTM Pre-process (1) -- Senior Review CRF design

- Understand the different version of CRF existed. For example, for RAVE study, there are four types of CRF could be approached at production
  1) Full eCRF – Annotated (used in the submission with SDTM annotations for regular sized studies)
Optimized SDTM Pre-process (1) --Senior Review CRF design

2) Full eCRF – Non-Annotated, Less pages. Full eCRF usually organized by VISITs
(3) Unique eCRF – Annotated (FDA prefer to have Unique eCRF with SDTM annotations provided during submission to reduce the review time, but double bookmark should be applied – VISIT and DOMAIN)

<table>
<thead>
<tr>
<th>Field Name</th>
<th>Data Type</th>
<th>Field Label</th>
<th>Units</th>
<th>Values</th>
<th>Pre-Filled Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVSTDAT</td>
<td></td>
<td>dd MMM yyyy Date of Visit</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Optimized SDTM Pre-process (1) -- Senior Review CRF design

(4) Unique eCRF – Non-Annotated, have much less pages

• Different type of EDC system may have result in given different type of eCRF
Optimized SDTM Pre-process (1) -- Senior Review CRF design

- Full eCRF would help to understand the whole study design.
- All CRF page numbers need to submit in the “Origin” field in Define XML file if the full eCRF is submitted.

<table>
<thead>
<tr>
<th>Name</th>
<th>Label</th>
<th>Origin</th>
<th>CRF Type</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMTRT</td>
<td>Reported Name of Drug, Med or Therapy</td>
<td>CRF Page 6</td>
<td>Unique eCRF</td>
<td>This is when Unique eCRF is submitted</td>
</tr>
<tr>
<td>CMTRT</td>
<td>Reported Name of Drug, Med or Therapy</td>
<td>CRF Page 6, 24, 42, 60, 78</td>
<td>Full eCRF</td>
<td>This is when Full eCRF is submitted</td>
</tr>
</tbody>
</table>
Optimized SDTM Pre-process (1)  
--Senior Review CRF design

• Dual Bookmark should be provided to Unique eCRF during Submission

• “By Visits” and “By Domain”

• “By Visits” should be ordered chronologically to Study Timepoints and Events Schedule

• “By Domain” should be ordered alphabetically. Within each topic, all applicable timepoints should also be ordered chronologically
Optimized SDTM Pre-process (1) -- Senior Review CRF design

• Check list when review the CRF:
  ➢ Ensure collected data answer the protocol questions
  ➢ Satisfy Analysis Requirements
  ➢ Code List displayed in CRF use or could be mapped to CDISC Controlled Terminology
  ➢ All collected fields have a Controlled Terminology associated
  ➢ Variable Names are not more than 8 characters
  ➢ Ensure alignment with Therapeutic Areas specificities
  ➢ Ensure consistency across associated Data Transfer Specification such for non-CRF data collected
  ➢ If the CRF is initiated from a similar previous study, then it is important to establish the differences from previous and current
Optimized SDTM Pre-process (1) -- Senior Review CRF design

- Other Points to review:
  - CRF design should be considered all possible values (e.g., Other, specify) and give the flexibility of entering non-listed text.
  - During the review of CRF design, programmer could start to make plans and think about how many SDTM domains should be draft and if there are any customized domain needed.
  - Review the Date-time format, if date and time has been collected separately.
  - For Laboratory part, understand if there are both Central lab and local lab tests have been collected for your study and how far away it is currently from CDISC standards (including test name, test units).
  - Review the parts of Protocol Deviation design. If any of the pre-listed protocol deviation collected on CRF. Are there both programmer-able and monitored protocol deviation have been planned for your study.
Optimized SDTM Pre-process (1)
--Senior Review CRF design

• Other Points to review (cont...):

  ➢ For early phase study, check the safety parameters have been designed per protocol, for late phase study, check both safety and efficacy has been designed correctly per protocol

  ➢ For pre-listed events, make sure you have –PRESP and –OCCUR variables designed in the domain.

  ➢ Review the VISITs, understand how many scheduled visits are there, how to treat unscheduled visits. How the final visits, early terminated visits or follow-up visits have been defined in the study. For example, there are two final visits defined for one study – Final visits – EOT – completes, and Final visits – EOS – Discontinues. Both of them could only happens once for each patient, and one patient shouldn`t have both of them occurred. This part can`t be validated through Pinnacle 21, hence you should have this checked performed as study specification

  ➢ Check the example of EOT and EOS in next slides
Optimized SDTM Pre-process (1) -- Senior Review CRF design

<table>
<thead>
<tr>
<th>Folder: FINAL VISIT: EOT - Completers</th>
<th>Form: VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generated On: 18 Jul 2016 12:15:37</td>
<td></td>
</tr>
<tr>
<td>Visit Date</td>
<td></td>
</tr>
<tr>
<td>Visit Type and Status:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinic</td>
</tr>
<tr>
<td></td>
<td>Phone</td>
</tr>
<tr>
<td></td>
<td>Missed Visit</td>
</tr>
<tr>
<td></td>
<td>Other Follow-Up</td>
</tr>
</tbody>
</table>

Please record any events on the Adverse Events Form occurring since Informed Consent

<table>
<thead>
<tr>
<th>Folder: FINAL VISIT: EOS - Discontinued</th>
<th>Form: VISIT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generated On: 18 Jul 2016 12:15:37</td>
<td></td>
</tr>
<tr>
<td>Visit Date</td>
<td></td>
</tr>
<tr>
<td>Visit Type and Status:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Clinic</td>
</tr>
<tr>
<td></td>
<td>Phone</td>
</tr>
<tr>
<td></td>
<td>Missed Visit</td>
</tr>
<tr>
<td></td>
<td>Other Follow-Up</td>
</tr>
</tbody>
</table>

Please record any events on the Adverse Events Form occurring since Informed Consent
Optimized SDTM Pre-process (2) -- DTS review

• DTS should consist:
  - Vendor Name, the purpose of document
  - Transfer type, Transfer method, if Password protected
  - Variables, Variable attributes, Field specification
  - Frequency of data transfer
  - Communication chain
  - Archiving plan
  - Project Team Contacts
Optimized SDTM Pre-process
--Intermediate program layer applied

• The intermediate program layer could be one SAS program or several programs

• One of the purpose of building intermediate program is to pre-process all source data – unify different data sources, for example: Create USUBJID in the program

• All importation program could be collected in the intermediate layer

• All Date variables could be converted to ISO8601. format before using in the SDTM programming, this would give most efficiency to the whole programming process

• Integrating coded data (from MedDRA or WhoDRUG) into intermediate datasets if the coding is not performed from EDC

• Much more could be done in the intermediate program, such as create a All visits datasets for all patients, etc. To suit the different needs of each study.
Optimized SDTM Pre-process -- Initial-check program

- Compare the raw datasets with previous data extracts
- Compare all data points with previous if CRF is upgrade
- Check the length of each variable to see if any text is beyond 200 characters
- Check the special character (for example, non-English characters)
Optimized SDTM Post-process before deliverable
Optimized SDTM Post-process
--Validation SDTM through Pinnacle 21

• When using Pinnacle 21, make sure the standards, configuration, the version of CDISC CT, and MedDRA version has been selected correctly

• Tips to read the Messages and resolve the issues from validation report
  ➢ Understand the issues mentioned in the reports, especially for Warnings and Errors
  ➢ Separate the Programming issue and Data Issue when review the report
  ➢ If the Pinnacle 21 report need to be submitted – with proper comments for each transfer during the study, it’s better to use different colour with your comments, this will make a easy and pleasure reading experience for clients
  ➢ Another good practice to help client read Pinnacle 21 report is given extra worksheet such as “AESTDTC missing”, “Unexpected AETERM” ..etc. It will help client understand which records have issues, also reminder Data Manager to solve it
  ➢ For large scaled study, Pinnacle 21 validator may have difficulty of creating reports, then you might have to split the patients in each domain to make it work
Optimized SDTM Post-process
--Validation SDTM through Pinnacle 21

<table>
<thead>
<tr>
<th>Colour instruction</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purple</td>
<td>- for Data Manager to investigate</td>
</tr>
<tr>
<td>Brown</td>
<td>- Coding related issues will report to Coder</td>
</tr>
<tr>
<td>Blue</td>
<td>- Data Manager has indicate that they need</td>
</tr>
<tr>
<td></td>
<td>programming support to pin point the records</td>
</tr>
<tr>
<td>Red</td>
<td>- comments need to consult with client</td>
</tr>
<tr>
<td>Black</td>
<td>- Programming Issue that need to be solved</td>
</tr>
</tbody>
</table>
Optimized SDTM Post-process -- Validation process for XPT file

• Create XPT file for deliverable purpose

• Post-process program should also convert the deliverable XPT file back into SAS and compare it with SAS file for production to make sure it`s the same. (This is something Pinnacle 21 validation can`t perform)

• Compare the deliverable package with previous deliverable, make sure the counts are reasonable
Key points of SDTM- MSG
Key points of SDTM- MSG --Package Components

• SDTM – MSG stands for Study Data Tabulation Model - Metadata Submission Guidelines. The Current released MSG is Version 1.0, released date as 2011-12-31.

• It is the documentation provide guidance for Compiling the eCTD module 5 “sdtm” folder

• The submission for SDTM should include –
  ➢ annotated blankcrf.pdf
  ➢ sdtm datasets in SAS version 5 transport format
  ➢ define.xml
  ➢ stylesheet – define2-0-0.xsl
  ➢ Reviewers` Guide
Key points of SDTM - MSG
--General Specification

• All SDTM related submission components should be located under “sdtm” folder. Name convention should follow FDA eCTD Guidance.
• Check the folder structure,
Key points of SDTM- MSG --General Specification

• Define.xml
  ➢ Dataset-level metadata
  ➢ Variable-level metadata
  ➢ Value-level metadata
  ➢ Controlled-Terminology as Codelist
  ➢ Stylesheets
  ➢ Define.xml validation
Key points of SDTM- MSG
--General Specification

• Annotated Blankcrf.pdf:
  - Annotation could be provided on entire CRF or Unique CRF
  - If the sponsor chooses to submit the entire CRF, then only the first occurrence need to be annotated. Subsequent pages should linked back to the first annotated occurrences
  - If the unique CRF is chosen to be annotated, then bookmarking will present the form as many times as needed.
  - Dual bookmark shall provided as mentioned earlier
  - When data recorded but not submitted to SDTM, the CRF be annotated with the text "NOT SUBMITTED".
  - To distinguish the domain level annotations from the variable annotations a slightly larger font can be used for the domain annotations
  - If more than one domain exists on a page as each domain annotation, and all of its variables, should be color-coded. Check the example in next slide
Key points of SDTM- MSG
--General Specification
Key points of SDTM - MSG
--General Specification

• In the documentation of “Study Data Technical Conformance Guide_March 2017.pdf”. It is mentioned: the printable define.pdf should be provided if Define.xml is not printable.

• It is also mentioned that the Define.xml with define2-0-0.xsl style sheet is preferable.
Key points of SDTM- MSG
--General Specification

• Define.xml use Define1-0-0.xsl style sheet is not printable. Hence the define.pdf file should also provided.
  ➢ After open Define1.xml with IE, Edit with Microsoft Word
  ➢ Arrange the page layout in Word and “Save As PDF”
  ➢ With this approach, the hyperlink is not working. It could only give appropriate outfit of the PDF file

• “Print to PDF” from web browser normally only gives first page of Define1

• The process may vary depends on PC setting

• With more complicated SAS approach, the hyperlink/bookmark could be created from Define1.xml file
Key points of SDTM- MSG
--General Specification

• Define.xml with Define2-0-0.xsl style sheet is preferable and printable
• Hence, in theory, the Define.pdf is not compulsory
• A fine version of define.pdf could be created from Adobe Acrobat Pro tool
• Convert Web page to PDF from Web Browser to keep all the hyperlinks
Key points of SDTM- MSG --General Specification

• The outfit is not always pleasant
• Modification with Tools from Adobe Acrobat Pro
Key points of SDTM- MSG
--Up-to-date resource

• Always check the eCTD important notices for any relevant

• MSG Version 2.0 is under development(https://www.cdisc.org/standards/foundational/study-data-tabulation-model-sdtm/sdtm-metadata-submission-guidelines-msg-v20)

• eCTD at FDA site (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

• eCDT Resources at FDA site (https://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm535180.htm)
Tool Invention
--Define XML creator invention

• Compatible with China regulatory rule and also the Chinese character
• Create XML from scratch (XPT, sas7bdat, Excel Spec)
• Edit XML file Visually
• One button to PDF, Excel Spec
Define XML Editor

- Compatible with China regulatory rule and also the Chinese character
- Easy Navigation at different levels
Define XML Editor

- Edit XML file visually
Define XML Editor

- XML file updated simultaneously
Import & Export

- Create XML from scratch (XPT, sas7bdat, Excel Spec)
- Define-XML export to PDF, Excel format
Define XML Editor

- One button to PDF file
- PDF with bookmarks, internal links
Thanks!