Paper DS 10

Define.xml Review: Failing to Plan is Planning to Fail

Robin Mann, GCE Solutions, Chandigarh, India
Parveen Kumar, GenInvo, Chandigarh, India

ABSTRACT

Imagine You are in the market to purchase a well-publicized book by a renowned author. You got the book at the nearby bookstore and It has a nice outer cover with beautifully written synopsis on the back. You started going through the Table of Contents to get more idea about the contents of the book.

Wait a minute, what is this?

You notice that the Table of Contents is wrong with spelling mistakes and incorrect section titles with wrong page information.

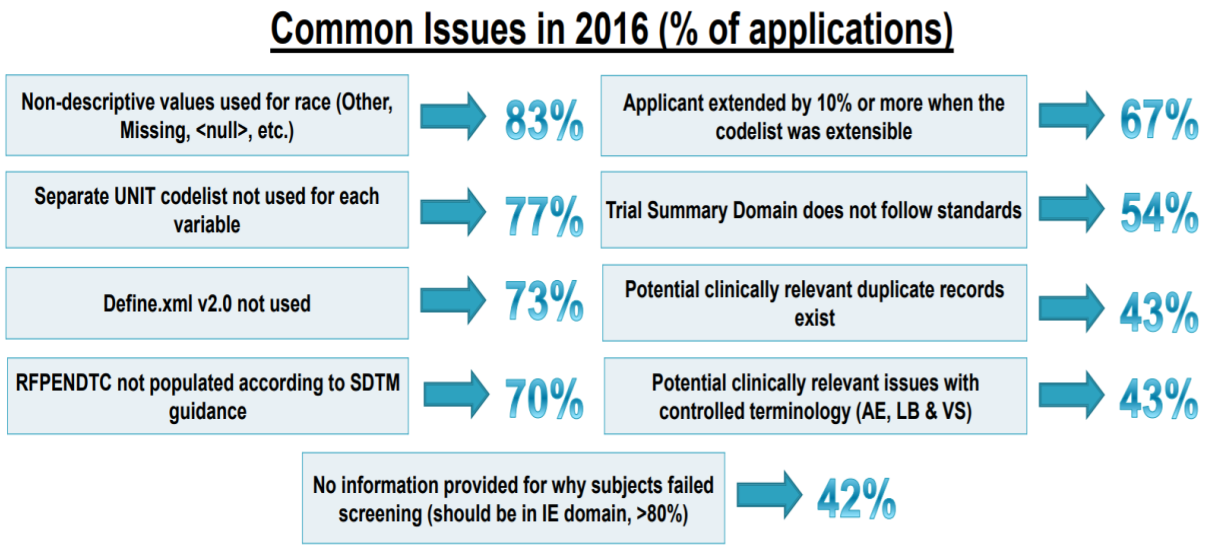
How would you feel? Would you purchase the book, or you now have doubts about the contents of the book?

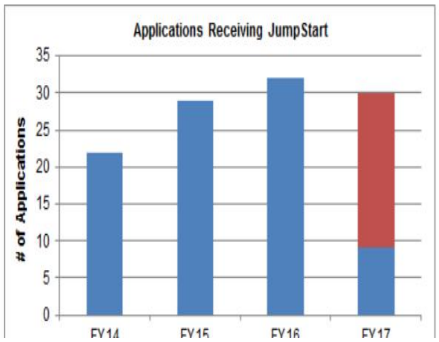
This is for sure the same sort of feeling that regulatory authority people have when they are provided with incorrect Define.xml.

Define .xml is the Table of Contents of the submission package and most useful document that describes the structure and content of the data submitted. A properly created and well defined Define.xml document can improve the efficiency of the Regulatory Review process, making the regulatory people and submission team happy, whereas a poorly created will hamper the speedy review with lot of cross questions.

INTRODUCTION

Despite Define-XML in the picture of data submission from more than a decade, the industry is still struggling with Define-XML. The proof is the “Data Quality Findings from Jumpstart” which highlighted that significantly large percentage of Define-XML submitted to Regulatory authorities with study data are still faulty.





Data Package Suggestions from JumpStart Findings

Define File

- Use Define.xml v2.0
- Include detailed description of data elements, for example:
  - Code lists that describe categories, subcategories, and reference time-points
  - Detailed and reproducible computational algorithms for all derived variables
  - Applicable value level metadata and description of SUPPQUAL domains
  - Explanations of sponsor-defined identifiers (i.e. – SPID, GRPID, etc)
- Provide separate unit code lists for each domain

Study Data Reviewer's Guide (SDRG)

- Provide SDRG for each data package with each section populated
- Fix all possible issues identified by FDA Validation Rules and include clear and detailed explanation for all "non-fixable" issues
- Provide Data Flow diagram that shows traceability between data capture, storage, and creation of datasets

WHERE IS THE GAP? WHY ARE WE STILL STRUGGLING WITH DEFINE-XML?

Often Study team is creating documents like metadata specifications from programming perspective and not from the perspective of reviewer. This can make the documents programming friendly but not reviewer friendly. There may be times when a programmer feels that the derivation is quite explanatory but for a person who is viewing the things with fresh eyes may feel it is too complex.

CASE FOR THOROUGH REVIEW?

A well created Define–XML provides detailed specification for datasets, variables, codelists, data origins, and derivations, which allows reviewers to interpret submission data faster and move through the process more quickly Whereas a poorly drafted will only start a Tennis match rally with Ball bouncing from one side to another.

Below we will discuss the approach for foolproof review of Define.xml. This step by step approach can be very handy for detecting common errors. The approach may not be covering all the possible issues but surely is a few steps towards clean and clear Define.xml.

DISCLAIMER

The scope of this paper is to present the opinions and suggestions of the authors. The interpretations of standards and procedures contained in this paper are those of the authors and they do not represent the position of their employer.

STEP BY STEP APPROACH

We will move step by step reviewing each and every part of Define.xml to make sure that the final document is as error free and explanatory as possible. 14 steps to clean and clear Define.xml.

STEP 1: DOCUMENT FOLDER CHECK

- Is the file named correct? - Define.xml

  The file must be named Define-xml irrespective of SDTM or ADaM define file.

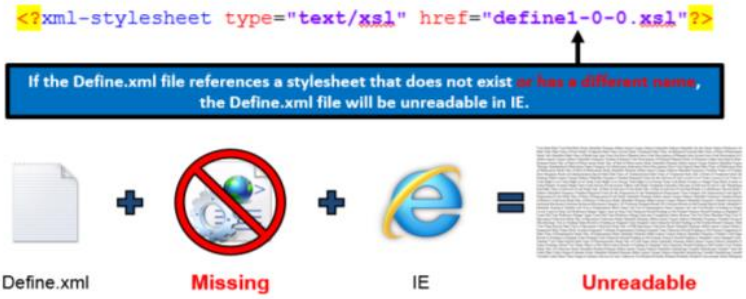
- Define.xml file is opening without issues?

  The Define.xml is intended to be both machine and human readable and contain information that different members from review team might need to reference.

- Style sheet (.xsl) file is present in the same folder with xml file?

  If a stylesheet reference is not provided, a browser will display the XML contents of the *define.xml* file.

A common issue which results in an unusable Define.xml file is using an incorrect stylesheet reference.



- Reviewer's guide is present (csdrg.pdf/adrg.pdf) and properly hyperlinked in Define.xml?

  The reviewer's guide complements the Define.xml and can be used to provide additional information about the datasets as well as convey information that does not have a place in define.xml or is not easily expressed in that format. The SDRG is focused on the tabulation datasets and data collection/mapping decisions or points of interest while the ADRG is focused around the analysis datasets, providing an overview of the analysis of the study and describing how the Statistical Analysis Plan (SAP) was implemented within the datasets.

- acrf.pdf is present (for SDTM)?

  The annotated CRF provides a regulatory reviewer with an understanding of the relationship between the data collected on the CRF and the submitted tabulation datasets. Each field should be annotated with the corresponding dataset and variable in the submitted datasets or should be annotated as "NOT SUBMITTED" if not included in the submitted datasets.

- Transport files (SAS Datasets) are named correctly?

  SDTM Datasets example -- AE.xpt where AE is the domain

  ADAM Datasets example – ADAE.xpt, Prefix AD is required for ADaM.

- Check for broken hyperlinks in the Navigation Pane

  Define.xml file can be a very long document with many segments, easy navigation is important. The navigation pane running along the left-hand side of the Define.xml file is critical to a reviewer to help manage the size of the document. Broken hyperlinks are most common issues detected in Define.xml.

- Check the hyperlink “Go to the top of the define.xml” is taking to the top of the document and not broken.

  Go to the top of the define.xml

STEP 2: METADATA LEVEL INFORMATION CHECK

- Check that standard version (SDTM or ADaM), Study name, Study description, Protocol name listed at the top of the file are correct and matches exactly with csdrg or adrg.
- Make sure that Pinnacle 21 validator has been run on Define.xml and there are no major issues or rejection criteria present. All acceptable messages are appropriately explained in the csdrg /adrg as applicable.
- Make sure that Pinnacle 21 validator has been run on the datasets with the Define.xml file specified and there are no major issues or rejection criteria present. All acceptable messages are appropriately explained in the csdrg/adrg as applicable.

STEP 3: DATASET LEVEL INFORMATION CHECK

- All domains(.xpt) presented include data and are not empty?
- Dataset labels are as per Implementation guides and are not missing in actual data or Define.xml.
- Domain label matches with the actual dataset (xpt) label?
- All attributes (structure, class or keys) are present?
  - Order of domains in define.xml and csdrg/adrg is correct:
  - SDTM: TDMs, Special Purpose, Interventions, Events, Findings, Finding about, Relationship
  - ADaM: ADSL, followed by all other alphabetically by Dataset name.

- The order of domains is same as the order in csdrg/adrg?

- The key variables are valid and natural and not surrogate. For eg. USUBJID, AESEQ is invalid as AESEQ is surrogate key.

STEP 4: INDIVISUAL DATASETS / VARIABLE LEVEL METADATA CHECKS

- Check that the list of variables is consistent with the content of datasets (xpt).
- Check that the metadata is Study Specific and not general as shown in the example below.

Example of an Algorithm with Limited Detail:

Variable	Label	Derivation/Comment
RFPENDTC	Date/Time of End of Participation	Last date of contact

Example of an Algorithm with Added Detail:

Variable	Label	Derivation/Comment
RFPENDTC	Date/Time of End of Participation	Last known day of contact with subject; If DM.DTHDTC is not NULL then RFPENDTC = DM.DTHDTC. Else RFPENDTC is equal to MAX of --DTC, --STDTC, and --ENDTC variables from all domains.

- Variable data types are among Define.xml. Data types acceptable values are defined in section 4.2.1 data type considerations of the CDISC Define-xml-2.0- specifications.pdf
- The variables attributes (label, type and length) are consistent between actual Datasets (xpt) and the Define-XML file.
- Variable order of the Define file is consistent with the Data (xpt)
- Check for any raw data references in your derivations or comments. always remember the review team do not have access to your raw database.
- Check for blindly copied derivations and comments from the mapping spec into the Define.xml that are often coding language and raw data references.
- Check for missing descriptions for Study specific sponsor variables like --SPID (Sponsor ID), --GRPID (Group ID), etc. if sponsor did not fully describe these variables (e.g., meaning, source, computational algorithms, etc.), then there is no way to understand the submitted data. The biggest value of Define file is to provide descriptions for study specific data elements.

- Avoid confusing and irrelevant information which can be misleading as shown in example below:

Example with Extraneous Information:

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
EFFEVT	Efficacy Event (Y/N)	text	1	["N" = "No", "Y" = "Yes"] <No Yes Response>	If VTESTAT.THRMSTT in (1, 2) and VISITN = 84 then EFFEVT = 'Y'. Else 'N'. UDPATED 01JAN2018: per Stewart, we need to change this to check the status at last available visit as some subjects may not have imaging done at Day 84. E.g. subject 8274-2847's last image is at Day 63, so we need to check that visit in that case. Also, need to exclude subjects who do not have any post-baseline imaging.

Improved Version:

Variable	Label	Type	Length / Display Format	Controlled Terms or Format	Source/Derivation/Comment
EFFEVT	Efficacy Event (Y/N)	text	1	["N" = "No", "Y" = "Yes"] <No Yes Response>	Sort XA domain by USUBJID, XADTC and keep the last available date where XATESTCD = "THRMSTT". If XA.XASTRESC is "REGRESSION" or "UNCHANGED" then EFFEVT = "Y". Else if XA.VISITDY > 0 then EFFEVT = "N". Else if XA.VISITDY <= 0 then EFFEVT = " " (null).

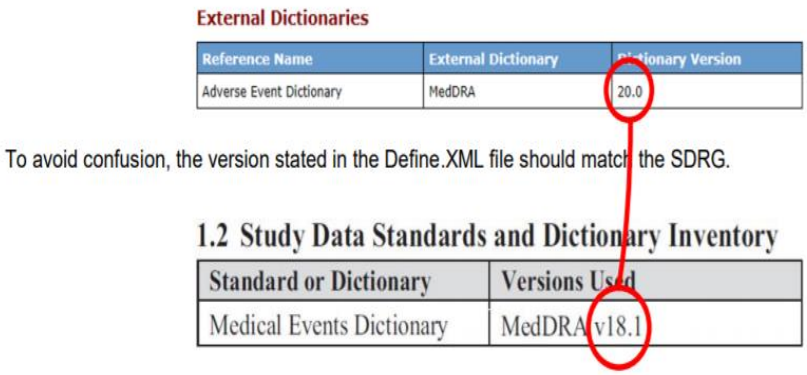
STEP 5: VALUE LEVEL METADATA CHECK

- Check every SDTM/ADaM Dataset has its corresponding value level metadata?
- The length attribute is required when Data Type is integer, float, or text. Especially in case of ISO8601 date format.
- The Significant Digits attribute is required when Data Type is float.

STEP 6: EXTERNAL DICTIONARIES CHECK

- CM, AE, MH (and any other domain where data was coded) drug dictionary name and version should match with csdrg.
- Check the dictionary versions mentioned in Define-xml are matching with csdrg and adrg

The MedDRA version used in the coding of the adverse events needs to be specified in every application.



External Dictionaries

Reference Name	External Dictionary	Dictionary Version
Adverse Event Dictionary	MedDRA	20.0

To avoid confusion, the version stated in the Define.XML file should match the SDRG.

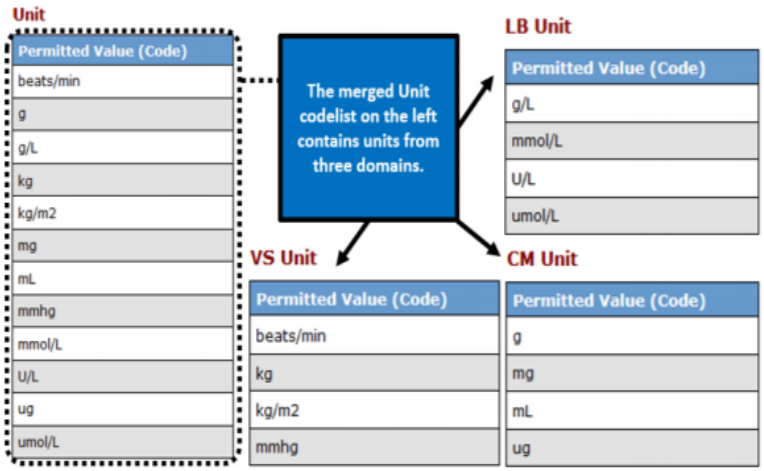
1.2 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
Medical Events Dictionary	MedDRA v18.1

STEP 7: CONTROLLED TERMINOLOGY/ CODELISTS

Controlled Terminology (CT) tables in the Define.xml file, also known as codelists, help reviewers quickly examine terminology used by applicants and provide a reference for any coding reviewers might encounter during their investigation of study data. Missing codelists can cause errors during validation due to the lack of information to help reviewers understand how data was collected.

- Check the code list contains all the planned CRF options and not just those present in the data.
- Check that the codelists pertains to specific Data package and does not contain codelists meant for other data packages like ADaM codelists in SDTM Define.xml, and vice versa.
- The most mistake found in Define-xml is having one UNIT codelist for all unit variables/values across the data package- Check this is not happening as when a reviewer clicks on EXDOSU codelist, they want to see only the units in the EX domain, not units across EX, LB, VS, etc.



- Controlled Terminology values contain only elements used in the submitted data (xpt) for a given dataset and not the full code list elements (e.g. UNIT code list will be split into UNIT(EGRESU) , UNIT (LBRESU) etc.)

- Whenever a code list is a CDISC controlled Terminology, the title should include the code list code – e.g. "AGE UNIT [CL.AGEU, c66781]"

- If the codelist is extended **" * Extended Value"** is specified below the table and next to extended codelist elements.

Standardized Disposition Term [CL.NCOMPLT, *C66727*]

Permitted Value (Code)
ABNORMAL LABORATORY VALUE(S) [*]
ADMINISTRATIVE PROBLEMS [*]
ADVERSE EVENT [*C41331*]
COMPLETED [*C25250*]
DEATH [*C28554*]
INFORMED CONSENT OBTAINED [*]
PROTOCOL DEVIATION [*C48251*]
SCREEN FAILURE [*C49628*]
UNSATISFACTORY THERAPEUTIC EFFECT [*]
WITHDRAWAL BY SUBJECT [*C49634*]

* Extended Value

- Don't create codelists with all values from CDISC CT when many values are irrelevant to your data package. when a reviewer clicks on EXDOSU codelist, they do not want to see all 500+ units from CDISC CT.

- Check for missing codelists for study specific data elements, often sponsors populate codelists only for variables that have standard CDISC Control Terminology (AEACN), but do not create study specific codelists. For example, for Category (--CAT), Subcategory (--SCAT), or EPOCH variables.

- Missing codelists for Value Level metadata – SUPPQUAL domains are typically described using value level metadata but sponsors often leave out codelists for supplemental qualifiers that have controlled terminology.

- Codelists created for variables collected as a free text –Create codelists only for variables where data was collected, derived or assigned based on a list of pre-specified terms. For example, if CMDOSU is collected using values from a drop-down menu in EDC system, it should reference a codelist in Define.xml file. However, if CMDOSU was collected as free text, a codelist is not necessary as it will result in presence of several hundred unique terms.

STEP 8: COMPUTATIONAL ALGORITHMS (SDTM) / ANALYSIS DERIVATIONS (ADAM)

- Computational algorithms are clear, well defined and are in plain English language.

- Computational algorithms are consistent with specifications.

- Derivations should be in Plain language and need not be from programming perspective.

- The review team attempting to analyze the data package, who is not only unfamiliar with the study, but also unfamiliar with the sponsors' own internal standards, will need a define.xml that correctly and clearly describes all origins and derivations.

- In common practice, the define.xml is created just prior to a submission, generally by someone who is very close to the data and derivations. In other cases, the define.xml is created while the study is still ongoing, where data and derivations often change as protocol amendments are made. Both cases require careful quality control and review processes to ensure common mistakes are avoided.

STEP 9: COMPUTATIONAL ALGORITHMS THAT REFERENCE INTERNAL DATASETS

- All “Derived” variables must have clear and detailed description of computational algorithms so reviewers can understand how values were derived and can independently reproduce them if needed. However, majority of submissions still have missing or poorly documented computational algorithms. Quite often sponsors provide “generic” algorithms for Study Day and Baseline Flag variables, but do not provide any information for important study specific derivations like EPOCH, SESTDTC, etc.

- Sometimes in computational algorithms sponsors refer to non-available information like raw data from EDC system or external look-up conversion tables, additional documentation which is not included in submission data package. Ensure that all Derived variables and Value Level have clear, correct and detailed computational algorithms, which only use data elements and information included in the data package. Check that the computational algorithms does not contain references to internal applicant datasets or variables which are not submitted in the data package.

Example of an Algorithm with References to Internal Datasets and Variables:

Variable	Label	Derivation/Comment
BRTHDTC	Date/Time of Birth	cat(put(demo.brth_year,4.),'-',put(demo.brth_month,z2.),'-',put (demo.brth_day,z2.))

This algorithm references a dataset (demo) and variables (brth_year, brth_month, brth_day) that cannot be found in any submitted data.

A PhUSE working group is developing a "Define.xml Completion Guide".
http://www.phusewiki.org/wiki/index.php?title=Define-XML_V2.0_Completion_Guidelines_%26_Style_Sheet_Recommendations

- Sometimes the computational algorithm/derivation is too long or too complex for Define-xml. we can create an additional pdf document named complex algorithms and document the complex algorithms there or simply document the complex algorithms in reviewers guide.

STEP 10: ANALYSIS RESULTS METADATA (ARM – ADaM) CHECK

- Hyperlinks have been added as applicable and are working (e.g. Hyperlink on AVAL is bringing to the AVAL value level metadata of the appropriate analysis data section).
- All outputs selected for ARM are present.
- Analysis result is consistent with output titles.
- Analysis parameters are listed as necessary when input dataset is BDS. All parameters used in data references (including selection criteria) and in programming statements are listed with the format: PARAMCD = “<paramcd>” (<param>).
- Analysis variable is consistent with what is used in programming statements.

STEP 11: ORIGIN CHECK

- ORIGIN values are defined in accordance with the Origin Guidance document for all variables (SDTM and ADaM)
- If ORIGIN = CRF, check if variable is annotated on CRF. If a variable is annotated on the CRF, then it should have origin CRF or Assigned (e.g. SITEID, USUBJID, SUBJID) either at the variable level or at the value level metadata.

Note: Site and Subject are assigned a number by the sponsor system. We can set ORIGIN to assigned for all occurrence of variables SITEID, USUBJID, SUBJID.

- Was the data collected on CRF, derived, or received from laboratory? If collected on CRF, then on what pages? If derived, then with what method?
- When the Origin = “Derived”, detailed derivation algorithm should be specified in Define.xml.
- When a variable has more than one ORIGIN value, the column ORIGIN should be left blank in the “Tabulation Dataset” section and described in the Value Level Metadata.

LB – Laboratory Test Results

Variable	Label	Key	Type	Length	Controlled Terms or Format	Origin	Derivation/Comment
LBORRES	Result or Finding in Original Units		text	8			

Value level Metadata

Variable	Where	Type	Length / Display Format	Controlled Terms or Format	Origin	Derivation/Comment
LBORRES	LBCAT = "CHEMISTRY" and LBSCAT = "LIVER FUNCTION TESTS" and LBSPEC = "SERUM" and LBTESTCD IN ("ALB" (Albumin) , "ALP" (Alkaline Phosphatase) , "ALT" (Alanine Aminotransferase) , "AST" (Aspartate Aminotransferase) , "BILDIR" (Direct Bilirubin) , "BILI" (Bilirubin) , "BILIND" (Indirect Bilirubin))	integer	4		eDT	
LBORRES	LBCAT = "CHEMISTRY" and LBTESTCD = "ALDSTRN" (Aldosterone)	integer	5		CRF Pages 40 - 41	

STEP 12: ANNOTATED CRF

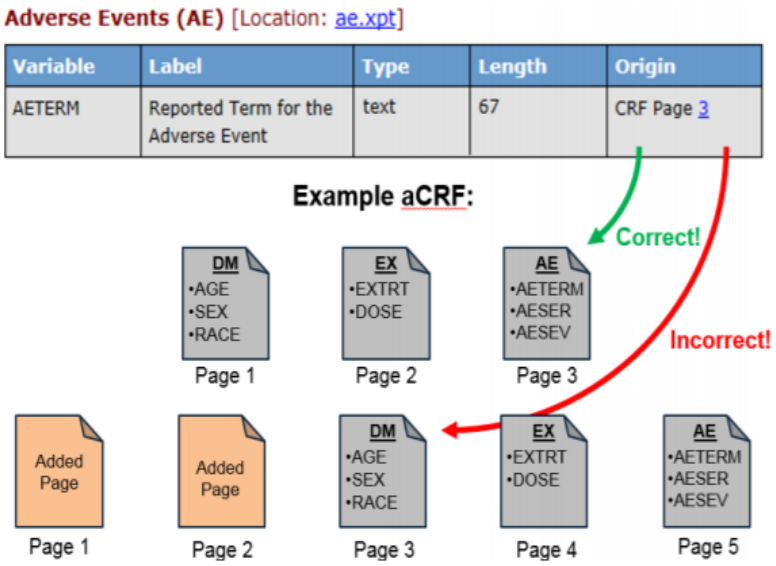
An Annotated Case Report Form (aCRF) documents how the data was collected and how it was mapped to SDTM datasets. When Origin attributes in Define.xml are properly populated, a reviewer can simply click on a hyperlink and be taken directly to the CRF page where the dataset variable was original collected. This greatly improves reviewer's ability to understand the source of data. It also shows traceability to ensure that all collected data has been submitted (except the data that is clearly marked as NOT SUBMITTED).

Common issues encountered with annotated CRFs:

- Missing or incorrect annotations
- Annotations that were not created with PDF Annotation feature, but instead are represented by highlighted text or PDF form fields
- Annotations reference EDC database fields instead of variables in SDTM

STEP 13: INCORRECT ACRF LINKS

One of the most useful functions of the Define.xml file is its ability to link a variable's record in the file to the page where the information was collected in the annotated Case Report Form (aCRF). A common issue is an incorrect aCRF link. This may be caused when a file name for an aCRF is changed without updating a reference in Define.xml file. For example, original "blankcrf.pdf" or "acrf-study-1.pdf" renamed to new "acrf.pdf". Another cause can be adding pages to the aCRF without updating links in the Define.xml file.



STEP 14: MISCILLEANOUS CHECKS

- Is there any derivation that is specified at multiple places or too long but can be added to adrg/ csdrg and can be referenced as "SEE section x.x.x in adrg/csdrg" instead of complete derivation at each occurrence?
- Are baseline flags populated in SDTM, if not then check whether derivation algorithm specifies correct reason for not deriving at SDTM Level?
- Do create a separate PDF file for large derivations that require formatting – the Define.xml standard does not account for formatting (e.g., new line characters, numbered lists, bullet points, etc.)

CONCLUSION

Define-XML must be created from a reviewer perspective keeping in mind that any complex or ambiguous information will only delay the approval. Reviewer should be able to get required information from Define.xml without reading the Protocol and other study documents in detail. Always keep in mind that the reviewer may or may not be a programming person so keep the things as plain and simple as possible.

People should know that the end consumers of the define.xml:

- Does not have access to raw data
- Have not read the Study documents in detail

- May or may not be a programmer
- Not familiar with the Study data
- Relying heavily on Define.xml accuracy

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CONTACT INFORMATION

Your comments and questions are valued and encouraged.

Contact the authors at:

Robin Mann

GCE Solutions

Robin.mann@gcesolutions.com

Parveen Kumar

GenInvo

Parveen.k12@geninvo.com