Paul Hamilton
Sunil Kumar Pusarla

Selecting a Method for Creation of First DEFINE.XML

February 22, 2018

ABSTRACT

- Recently changes have included a requirement for DEFINE.XML
- While building a Supplemental submission, we had to switch from PDF to XML document format
- Will recapitulate the decision tree we transversed, examining the costs / risks associated with each decision
- Final outcome and resulting experience with the Agency will be revealed

INTRODUCTION

- FDA have always required the inclusion of a DEFINE.PDF document along with data domains
- Acts as a visual Table of Contents and guide to the data in the submission
- Recently this requirement grew to include a machine-readable form: DEFINE.XML
- Very similar outward appearance and structure
- Internal structure and means of production quite different

INTRODUCTION

- We submitted an NDA which lead to our first commercial offering
- Needed to submit a Supplement submission
- Only a DEFINE.PDF was provided in the original submission
- Since then the regulations matured and require the inclusion of DEFINE.XML
- Busy with preparing other parts of the submission package, we had little time to learn about DEFINE.XML

Resources

- First we surveyed our available resources
  - Use “Open CDISC” –Pinnacle21 software (open source)
  - Pursue justification and acquiring Pinnacle21(Enterprise edition)
  - Self-generate using SAS® Clinical Toolkit
  - Self-generate using JMP ® Clinical
  - Employ non-naïve contractor
  - Employ expert contractor
  - Completely outsource task to outside agency
- For each resource, evaluated probable cost and probability of successful outcome
- Constraints:
  - Time (very short)
  - Perceived probability of success needed to be very close to 100%

Resource # 1: “Open CDISC” –Pinnacle21

- Use “Open CDISC”
  - Pinnacle21 software (open source)
- Cost to acquire: $0.00
- Associated costs: $0.00
  - Already installed on our SAS server
- Pros
  - Familiar: already using the software on a daily basis to evaluate quality of generated SDTM and ADaM domains
- Cons
  - Unfamiliar: unsure just how to proceed to generate a DEFINE.XML.
  - Dedicated help not available
  - Possible (?) to find contractor with demonstrated success
  - How to validate?
  - Software already raising many false-negative messages, each of which must be explained in other documents

Resource # 2: Pinnacle21 Enterprise Edition

- Use Pinnacle21 software
- Cost to acquire: $$ <modest>
- Associated costs:
  - Have to arrange installation with our IT department
- Pros
  - Familiar: already using the free version on a daily basis to evaluate quality of generated SDTM and ADaM domains
  - Same software used by FDA for checking eCTD submissions
  - Dedicated training provided; help could be available
  - Increase confidence in evaluation of other CDISC documents
- Cons
  - Costs
    - Time to justify / obtain approval by senior management
    - Time to installation
  - Possible (?) to find contractor with demonstrated success

Resource # 3: SAS Clinical Toolkit®

- SAS Institute provides a set of macro tools claimed to be capable of producing DEFINE.XML
- Cost to acquire: $0
- Associated costs $0
  - Previously licensed and installed with SAS update
  - So far, unused at our site
- Pros
  - Familiar: we are a SAS-only shop with deep and broad experience
  - The power behind SAS® Clinical Data Integration?
  - Help available through SAS Consulting Services?
  - Time invested applicable to future studies / fillings – if successful
- Cons
  - Have to figure out how to use the macros
  - Time invested takes away from other critical tasks
  - Possible (?) to find contractor with demonstrated success

Resource # 4:Employ Non-naïve Contractor

- Work with various placement agencies to identify and hire a contractor with demonstrated success at producing DEFINE.XML
- Direct cost > $$
- Associated costs > $
  - Time to interview, vet, and select
  - Time to become familiar with our data, submission
- Pros
  - Hiring contractors is a common occurrence, many possible vendors
  - Easy to justify to management
  - Get to select candidate we think best for the job
- Cons
  - Contractor may have had previous success in another company, with their attendant resources and support systems
  - May not translate into current environment
  - High perceived risk

Resource # 5:Employ Expert Contractor

- Work with various placement agencies to identify and hire a contractor with demonstrated success at producing DEFINE.XML
- Direct cost > $$$
- Associated costs > $
  - Time to interview, evaluate, and select
  - Time to become familiar with our data, submission
- Pros
  - Hiring contractors is a common occurrence, many possible vendors
  - Easy to justify to management
  - Get to select candidate we think best for the job
- Cons
  - Very difficult to find true Subject Matter Expert, who happens to be available just when needed
  - Contractor may have had previous success in another company, with their attendant resources and support systems
  - Lowest perceived risk

Risk / Benefit Analysis

- Contact several placement agencies describing the nature and timing of our needs
- Recapitulated our perceived list of resources
- Queried to determine if other resources were overlooked
- One agency immediately presented three possible candidates
  - Two senior in SAS and pharma skills, but non-naïve in DEFINE skills
  - One very senior Subject Matter Expert with maximum DEFINE skills
- Given these opportunities, we decided to hire the senior SME
- Maximized probability of successful outcome
- Minimized lengthy and costly processes
  - Software justification
  - Software installation

Risk / Benefit Analysis

- Given these opportunities, we decided on the senior SME
  - Straightforward justification, on-boarding
  - Available immediately
  - Came with suite of self-developed macros tailored for producing DEFINE.XML (one-time use only)
  - Allowed sponsor personnel to focus on other submission tasks
  - Perceived highest probability of successful outcome
- Disadvantages / tradeoffs
  - Due to the nature of the contract, resources expended on this project would not be available for subsequent projects
  - eCTD submissions not a common event in our company
  - Next submission might occur in a very different set of circumstances, with attendant problems and financial resources

FDA Requirements

FDA Data Standards Catalog v4.10 (10-24-2017) - Supported and Required Standards

a listing of the data exchange, file formats and terminology standards supported at FDA. These standards have gone through all the steps necessary to make this part of the regulatory review process, including posting of e documents and associated implementation guidelines and technical specifications. The submission of standardized data using any standard not listed, or to an FDA Center not listed, should be discussed with the Agency in log is incorporated by reference in the guidance to industry, *Providing Regulatory Submissions in Electronic format-Standardized Study Data (http://www.fda.gov/downloads/Drugs/Guidances/UCM292334.pdf)*.

Data Exchange Standard	Exchange Format	Standards Development Organization (SDO)	Supported Version	Implementation Guide Version	FDA Center(s)	Date Support Begins (MM/DD/YYYY)	Date Support Ends (MM/DD/YYYY)	Date Requirement Begins (MM/DD/YYYY)	Date Requirement Ends	Regulatory Reference and Information Sources
(SDTM)	XPT	CDISC	1.4	3.2	CDER, CBER	08/17/2015		03/15/2018 [1] 03/15/2019 [2]		CDISC.org - SDTM
Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.0	CDER, CBER	Ongoing	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	CDISC.org - ADaM
Analysis Data Model (ADaM)	XPT	CDISC	2.1	1.1	CDER, CBER	03/15/2018		03/15/2019 [1] 03/15/2020 [2]		CDISC.org - ADaM
Standard for Exchange of Nonclinical Data (SEND)	XPT	CDISC	1.2	3.0	CDER	06/13/2011	03/15/2019 [1] 03/15/2020 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2019 [1] 03/15/2020 [2]	CDISC.org - SEND
SEND	XPT	CDISC	1.5	3.1	CDER	08/21/2017		3/15/2019 [1] 3/15/2020 [2]		CDISC.org - SEND
Define	XML	CDISC	1.0	N/A	CDER, CBER, CDRH	Ongoing	03/15/2018 [1] 03/15/2019 [2]	12/17/2016 [1] 12/17/2017 [2]	03/15/2018 [1] 03/15/2019 [2]	CDISC.org - Define-XML
Define	XML	CDISC	2.0	N/A	CDER, CBER, CDRH	08/07/2013		12/17/2016 [1] 12/17/2017 [2]		CDISC.org - Define-XML

Prepare Metadata

- SME provided data templates for entering CDISC domain metadata
- We filled out the spreadsheet provided by the set of compiled macros
- provide code lists
- external documents such as IE criteria
- aCRF
- Reviewer's Guide

Prepare Metadata: Tables

table	torder	tcrf_loc	structure	repeating	is_reference_data	purpose	class
VS	15	21	One record per vital sign measurement per	Yes	No	Tabulation	Findings
AE	11	61	One observation per adverse event per subject	Yes	No	Tabulation	Events
CM	9	17 64 67	One observation per recorded intervention occurence or constant dosing interval per subject	Yes	No	Tabulation	Interventions
DM	8	3 16	One observation per subject	No	No	Tabulation	Special Purpose
DS	12	60	One observation per disposition status or protocol milestone per subject	No	No	Tabulation	Events
EX	10	18	One observation per protocol-specified study treatment, constant dosing interval, per subject	Yes	No	Tabulation	Interventions
IE	14	14	One observation per inclusion/exclusion criterion not met per subject	Yes	No	Tabulation	Findings
MH	13	4 5	One observation per medical history event per subject	Yes	No	Tabulation	Events
TA	3		One record per planned Element per Arm	No	Yes	Tabulation	Trial Design
TE	4		One record per planned Element	No	Yes	Tabulation	Trial Design
TI	5		One record per I/E criterion	No	Yes	Tabulation	Trial Design
TV	7		One record per planned visit per Arm	No	Yes	Tabulation	Trial Design
XF	16	6 7 11 12 22 25 26 30 31 34 35 39 40 43 44 48 49 52 53 57 58	One record per finding per time point per visit	No	No	Tabulation	Findings

Prepare Metadata: Columns

table	column	param	paramrel	psas_format	pcrf_note	porigin
XF	XFTESTCD	ANTCSCG	XFORRES		10 29 38 47 56	
XF	XFTESTCD	ANTCSCG	XFORRESU		10 29 38 47 56	
XF	XFTESTCD	ANTCSCG	XFSTRESC		10 29 38 47 56	
XF	XFTESTCD	ANTCSCG	XFSTRESN	2.0	10 29 38 47 56	
XF	XFTESTCD	ANTCSCG	XFSTRESU		10 29 38 47 56	
XF	XFTESTCD	ANTCSCG	XFTEST		10 29 38 47 56	
XF	XFTESTCD	CRYVOICE	XFORRES		22	
XF	XFTESTCD	CRYVOICE	XFORRESU		22	
XF	XFTESTCD	CRYVOICE	XFSTRESC		22	
XF	XFTESTCD	CRYVOICE	XFSTRESN	1.0	22	
XF	XFTESTCD	CRYVOICE	XFSTRESU		22	
XF	XFTESTCD	CRYVOICE	XFTEST		22	
XF	XFTESTCD	IRISPATH	XFORRES		7 26 35 44 53	
XF	XFTESTCD	IRISPATH	XFORRESU		7 26 35 44 53	
XF	XFTESTCD	IRISPATH	XFSTRESC		7 26 35 44 53	
XF	XFTESTCD	IRISPATH	XFSTRESN		7 26 35 44 53	
XF	XFTESTCD	IRISPATH	XFSTRESU		7 26 35 44 53	
XF	XFTESTCD	IRISPATH	XFTEST		7 26 35 44 53	
XF	XFTESTCD	PUPDIAM	XFORRES	5.2		Derived
XF	XFTESTCD	PUPDIAM	XFSTRESN	5.2	7 26 35 44 53	
XF	XFTESTCD	PUPDIAM	XFSTRESC	5.2	7 26 35 44 53	

Prepare Metadata: Column Parameters

table	column	cpkey	csas_format	cdescription	ccrf_note	corigin
AE	AEACN	.			62	CRF
AE	AEACNOTH	.			62	CRF
AE	AEACT	.			62	CRF
AE	AEBODSYS	.		MEDDRA		Assigned
AE	AECONTRT	.			62	CRF
AE	AEDECOD	.		MEDDRA		Assigned
AE	AEENDTC	.				CRF
AE	AELOC	.				CRF
AE	AEOUT	.			62	CRF
AE	AEREL	.			62	CRF
AE	AESDDFL	.			63	CRF
AE	AESDFL	.			63	CRF
AE	AESDTH	.				Derived
AE	AESEQ	.				Derived
AE	AESER	.				CRF
AE	AESEV	.			62	CRF
AE	AESHOSP	.				Derived
AE	AESTRFD1	.				CRF
AE	DOMAIN	.		AEDOMAIN		Assigned
AE	EPOCH	.		AEEPOCH		Derived
AE	STUDYID	.				Assigned
AE	AESTDTC	3				CRF
AE	AETERM	2				CRF
AE	USUBJID	1				Derived
AE	AEENDY	.	3.0	STDY		Derived
AE	AEENRF	.		ENRF		CRF
AE	AESTDY	.	3.0	STDY		Derived

Execution

- The macro batch file produced
  - define.xml version 2.0
  - define.xml version 1.0.
  - define.html (visually easier)
- Macros also provided additional functionality:
  - comparing the metadata against study data
  - comparing current study's metadata with similar, older study's metadata
- This was verified against
  - Xerces software (open source?)
  - Pinnacle 21 community version
- and was issue free.
- Version 2.0 was submitted to the FDA as part of the eCTD package

Resulting Product

- Static screenshot

Date of Define-XML document generation: 2017-04-30T10:29:58

Stylesheet version: 2015-01-16

Standard	SDTM-IG 3.1.2
Study Name	OMS302-ILR-007
Study Description	A randomized, double-masked, parallel-group, phenylephrine-controlled study of the effect of OMS302 added to standard irrigation solution on intraoperative pupil diameter ar acute postoperative pain in children ages birth through three years undergoing unilateral cataract extraction with or without lens replacement
Protocol Name	OMS302-ILR-007
Metadata Name	OMS302-ILR-007, Data Definitions
Metadata Description	Study OMS302-ILR-007, Data Definitions

Tabulation Datasets for Study OMS302-ILR-007 (SDTM-IG 3.1.2)

Dataset	Description	Class	Structure	Purpose	Keys	Location	Documenta
SE	Subject Elements	Special Purpose	One record per actual element per subject	Tabulation	USUBJID, SESTDTC	SE.xpt	
SV	Subject Visits	Special Purpose	One record per actual visit per subject	Tabulation	USUBJID, SVSTDTC, VISITNUM	SV.xpt	
TA	Trial Arms	Trial Design	One record per planned Element per Arm	Tabulation	STUDYID, ARMCD, TAETORD	TA.xpt	
TE	Trial Elements	Trial Design	One record per planned Element	Tabulation	STUDYID, ETCD	TE.xpt	
TI	Inclusion/Exclusion Criteria	Trial Design	One record per I/E criterion	Tabulation	STUDYID, IETESTCD	TI.xpt	
TS	Trial Summary	Trial Design	One record per trial summary parameter value	Tabulation	STUDYID, TSSEQ, TSPARMCD	TS.xpt	
TV	Trial Visits	Trial Design	One record per planned visit per Arm	Tabulation	STUDYID, VISITNUM	TV.xpt	
DM	Demographics	Special Purpose	One observation per subject	Tabulation	USUBJID	DM.xpt	
SUPPDM	Supplemental Qualifiers for DM	Special Purpose	One record per IDVAR, IDVARVAL, and QNAM value per subject	Tabulation	STUDYID, RDOMAIN, USUBJID, IDVAR, IDVARVAL, QNAM	SUPPDM.xpt	
CM	Concomitant Medications	Interventions	One observation per recorded intervention occurence or constant dosing interval per subject	Tabulation	USUBJID, CMSTDTC, CMCAT, CMTRT, CMDOSE	CM.xpt	

CONTACT INFORMATION

- Your comments and suggestions are welcome:

Names	Paul Hamilton Sunil Kumar Pusarla
Enterprise	Omeros Corporation
Address	201 Elliott Avenue West Seattle WA 98101
Work Phone	(206) 676-5000
E-mail	phamilton@omeros.com skumar@omeros.com