

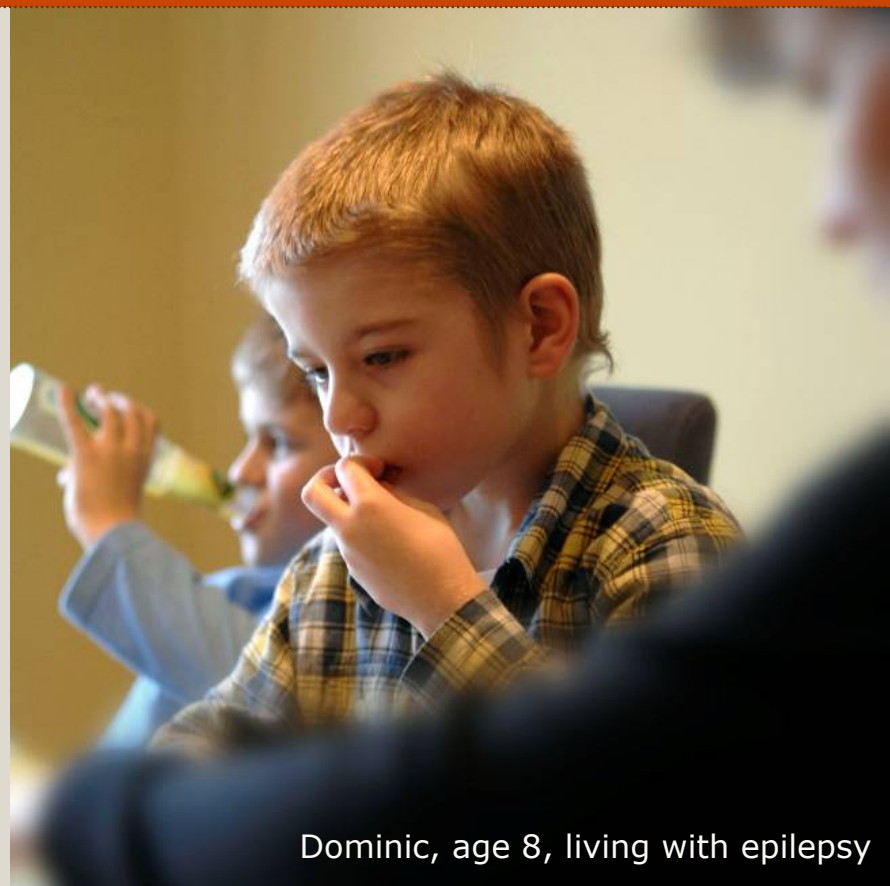
SDTM Implementation Guide : Clear as Mud

Strategies for Developing Consistent Company Standards

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Dominic, age 8, living with epilepsy



Objectives

- At the end of presentation you should understand:
 - Back to the basics: importance of consistent CRF annotation
 - “Data-in, data-out”
 - General rules to ensure basic consistent interpretations across as many studies as possible
 - Applying controlled terminology
 - Specific domain interpretations
 - Thinking ahead – the benefits of a sponsor defined interpretation of SDTM implementation

Why have an SDTM interpretation guide?

- Sponsor level clarification for some of the more vaguely defined SDTM variables outlined in the SDTM Implementation Guide (SDTM IG).
- Ensure consistency across studies.
- Easier to pool studies together for a CDISC SDTM-compliant repository.
- Will improve programming efficiencies.
- Can quickly shift resources from one study to another if necessary without losing quality.

- In order to have a success in developing an internal interpretation for SDTM IG, one must first start with consistent CRF design and annotation.
 - Demonstrate the connection between CRF and assigned SDTM variables.
 - Streamline annotations across similar styled studies.
- Through basic and consistent design, programming templates can be developed for common safety domains (such as AE, DM, MH, etc.)

Back to Basics

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- In the example below, this basic layout can serve as a general template to many studies:

AE, Page 1 (AE1.02)

DATASET: AE QUALIFYV: 001	
Adverse Events	
Has the subject experienced any adverse events? ☐ Yes, record below ☐ No AEYN_L (\$) AEYN_N	
Adverse Event Number	0 : 1 AESPID (\$)
Adverse Event	AETERM (\$) DMODIFY (\$) Derived Questions SOC_S (\$) SOC_L (\$) HLGT_S (\$) HLGT_L (\$) HLT_S (\$) HLT_L (\$) PT_S (\$) PT_L (\$) LLT_S (\$) LLT_L (\$)
Date of Onset	AEST_D AEST_V DD MMM YY
Pattern of Event	☐ Intermittent AEPT_S (\$) AEPT_L (\$) AEPT_N ☐ Continuous
Serious Adverse Event?	☐ Yes AESR_S (\$) AESR_L (\$) AESR_N ☐ No
Intensity	☐ Mild AESV_S (\$) AESV_L (\$) AESV_N ☐ Moderate ☐ Severe
Relationship to Study Medication	☐ Related AERL_S (\$) AERL_L (\$) AERL_N ☐ Not related
Action Taken with Study Medication	☐ Dose not changed AEAN_S (\$) AEAN_L (\$) AEAN_N ☐ Drug temporarily interrupted ☐ Dose reduced AEAN_S (\$) AEAN_L (\$) AEAN_N ☐ Drug permanently withdrawn ☐ Dose increased AEAN_S (\$) AEAN_L (\$) AEAN_N ☐ Not applicable
Other Action Taken	☐ None AEON_S (\$) AEON_L (\$) AEON_N ☐ Concomitant medication AECM_S (\$) AECM_L (\$) AECM_N ☐ Hospitalization or prolongation of hospitalization AEHO_S (\$) AEHO_L (\$) AEHO_N ☐ Therapeutic or diagnostic procedure AEDP_S (\$) AEDP_L (\$) AEDP_N
Outcome	☐ Resolving AEOC_S (\$) AEOC_L (\$) AEOC_N ☐ Not Resolved ☐ Resolved ☐ Resolved with sequelae also complete: AEEN_D AEEN_V DD MMM YY ☐ Worsened ☐ Fatal
Did Adverse Event Lead to Dropout?	☐ Yes AEDO_S (\$) AEDO_L (\$) AEDO_N ☐ No

AE, Page 1 (AE1.02)

Adverse Events	
Has the subject experienced any adverse events? ☐ Yes, record below ☐ No [NOT SUBMITTED]	
Adverse Event Number	AESPID : 0 : 1
Adverse Event	AETERM
Date of Onset	AESTDTC DD MMM YY
Pattern of Event	☐ Intermittent AEPATT ☐ Continuous
Serious Adverse Event?	☐ Yes AESER ☐ No
Intensity	☐ Mild AESEV ☐ Moderate ☐ Severe
Relationship to Study Medication	☐ Related AEREL ☐ Not related
Action Taken with Study Medication	☐ Dose not changed AEACN ☐ Drug temporarily interrupted ☐ Dose reduced AEACN ☐ Drug permanently withdrawn ☐ Dose increased AEACN ☐ Not applicable
Other Action Taken	☐ None AEACNTH ☐ Concomitant medication ☐ Hospitalization or prolongation of hospitalization AEACNTH ☐ Therapeutic or diagnostic procedure
Outcome	☐ Resolving AEOUT ☐ Not Resolved ☐ Resolved ☐ Resolved with sequelae also complete: AEENDTC DD MMM YY ☐ Worsened ☐ Fatal
Did Adverse Event Lead to Dropout?	☐ Yes SUPPAE.QVAL where QNAM = AEDROP ☐ No

- CDISC compliant SDTM domains act only as the standardized source data for the study
- Strictly for reporting data, not correcting it!
- Do not add unnecessary imputations or algorithms that are not reflected on the annotated CRF (aside from the derivations or coded dictionaries outlined in the SDTM implementation guide).
- With this philosophy in mind, focusing only on reporting the data gives way to simple and concrete approaches.

General interpretation rules

- Communication: all groups involved in SDTM development need to discuss and agree on interpretations and internal guidelines.
- The sponsor defined interpretation guide for SDTM will be a “living document” that will need constant maintenance.
- The sponsor defined interpretation guide should only act as a companion to the CDISC compliant SDTM IG. It should not contradict nor challenge the CDISC rules or guidelines.
- Reinforce the motto: “Same name, same meaning, same value...” – SDTM variables that share the same variable name across domains must be identical in all attributes and values. This should also be reflected in the interpretation guide.

General interpretation rules: Controlled Terminology

- ▶ **Non-extensible codelists:** developing an interpretation guide will help illustrate how to remap the source values into SDTM compliant codelists.
- ▶ This will be vital when remapping from different study designs. Having this interpretation guide can outline how to remap in each situation.
- ▶ These codelists must be continuously maintained and ***communicated*** for every study and then added to the interpretation guide.

General interpretation rules: Controlled Terminology

- **Extensible codelists:** Even with an interpretation guide, these codelists are even more of a challenge.
- Decision of the sponsor to add codelists to the CDISC SDTM compliant codelists; however, the codes must remain consistent across studies!
- As previously stated with non-extensible codelists, the extensible codelists must be continuously maintained and ***communicated*** for every study and then added to the interpretation guide.
- Determine a method of recording and using the extensible codelist

Example: Extensible codelist for LBTEST/LBTESTCD

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	A	B	C	E	F
1	HEMATOLOGY (1) LABPANEL (101) SUBGROUP: WBC (3)				
2	Last LIC created:	103263	NEUTRO_ABS_MAN_CALC		
3					
4	NQuestion	N SAS	NUnit	SDTM Lbtestcd	SDTM Lbtest
5	ANC_CALC	ANC	G/L	ANCCALC	Calculated Absolute Neutrophil Count
6	AUER_RODS	AUER	--	AUERRRODS	Auer Rods
7	AUER_RODS_C	AUER_C	sibling		
8	AVG_CD3P	AC3P	%	AVGCD3P	Average CD3+
9	AVG_CD3P_ABS	AC3PA	cells/uL	AVGCD3PA	Average CD3+ ABS
10	BASOPHILS	BASO	%	BASOLE	Basophils/Leukocytes
11	BASOPHILS_ABS	BASOA	G/L	BASO	Basophils
12	BASO_ABS_MAN_CALC	BASOABMC	G/L	BASOABMC	Absolute Basophils Manual Calculated
13	BASOPHILS_ABS_O	BASOAO	G/L	BASO	Basophils
14	BASOPHILS_IMM	BASOIMLE	%	BASOIMLE	Immature Basophils/Leukocytes
15	BASOPHILS_IMM_ABS	BASOIM	G/L	BASOIM	Immature Basophils
16	BASOPHILS_MAN_DIFF	BASOMD	%	BASOMD	Basophils Manual Differential
17	BASOPHILS_MICRO	BASOM	%	BASOMCR	Basophils Microscopy
18	BASOPHILS_STIPP	BASOS	--	BASOSTP	Basophils Stippling
19	BASOPHILS_STIPP_QL	BASOSL	--	BASOSTPQ	Basophils Stippling (Qual)
20	BASOPHILS_STIPP_QL_C	BASOSL_C	sibling		
21	BLASTS	BLAS	%	BLASTLE	Blasts/Leukocytes
22	BLASTS_ABS	BLASA	G/L	BLAST	Blasts
23	BLASTS_UNDIFF	BLASUD	%	BLASTUN	Blasts Undifferentiated
24	CD14P	CD14P	%	CD14P	CD14+
25	CD14P_86P	CD14P86P	%	CD14CD86	CD14+ CD86+ Monocytes
26	CD16P_56P	C16P56P	%	C16P56P	CD16+CD56+
27	CD16P_56P_ABS	C16P56PA	cells/uL	C16P56PA	CD16+CD56+ ABS
28	CD16P_56P_86P	CD165686	%	C165686	CD16+CD56+CD86+
29	CD19	CD19	%	CD19LY	CD19/Lymphocytes
30	CD19_ABS	CD19A	cells/uL	CD19	CD19
31	CD19P	C19P	%	CD19P	CD19+
32	CD19PTB2	C19PTB2	%	C19PTB2	CD19+ Tube 2

Specific domain interpretations

- Determine key identifier variables and how to define them. Ex: USUBJID life cycle through multiple studies.
- Identify the SDTM core domains that are most commonly defined in every study.
- Develop a set of rules and guidelines for each of the SDTM core domains within each type of study design (phase 1 vs. phase 4, double-blind vs. open-label, ...).
- Consistency and compliance again becomes the focus with the specific domains.

Specific domain interpretations

- Once study design has been identified, review each variable in each domain to determine clarification at the sponsor level.
- Develop a method to address these issues in a definitive manner for ease of understanding and development.
- Reminder that this will be a living document and will need constant attention and clarification to achieve maximum efficiency

Example: AE interpretations

Variable Name	Variable Label	Type	Term. or Format	CDISC Notes	Core	Sponsor Interpretation	Origin
AESEV	Severity/ Intensity	C	(AESEV)	The severity or intensity of the event. Examples: MILD, MODERATE, SEVERE.	Perm	Controlled terminology	
AESER	Serious Event	C	(NY)	Is this a serious event?	Exp	Controlled terminology:	
AEACN	Action Taken with Study Treatment	C	(ACN)	Describes changes to the study treatment as a result of the event. AEACN is specifically for the relationship to study treatment. AEACNOTH is for actions unrelated to dose adjustments of study treatment. Examples of AEACN values include ICH E2B values: DRUG WITHDRAWN, DOSE REDUCED, DOSE INCREASED, DOSE NOT CHANGED, UNKNOWN or NOT APPLICABLE	Exp	Controlled terminology If AEOUT="DOSE CHANGED" (or something similar), then one must review the actual dosing data to determine if the value should be assigned to the proper controlled terminology of "DOSE INCREASED" or "DOSE REDUCED".	
AEACNOTH	Other Action Taken	C		Describes other actions taken as a result of the event that are unrelated to dose adjustments of study treatment. Usually reported as free text. Example: "TREATMENT UNBLINDED. PRIMARY CARE PHYSICIAN NOTIFIED."	Perm	Sponsor terminology: NONE HOSPITALIZATION OR PROLONGATION OF HOSPITALIZATION CONCOMITANT MEDICATION THERAPEUTIC OR DIAGNOSTIC PROCEDURE If more than one value was populated, then the value of AEACNOTH = "MULTIPLE" and separate SUPPAE records will need to be populated for each corresponding value Example: MEDICATION and THERAPEUTIC OR DIAGNOSTIC PROCEDURE is checked. In AE, the variable AEACNOTH="MULTIPLE". In SUPPAE, the corresponding values are QNAM="AEACNOT1" and QVAL="MEDICATION" and another record of QNAM="AEACNOT2" and QVAL=" THERAPEUTIC OR DIAGNOSTIC PROCEDURE"	
AEREL	Causality	C	*	Records the investigator's opinion as to the causality of the event to the treatment. ICH E2A and E2B examples include NOT RELATED, UNLIKELY RELATED, POSSIBLY RELATED, RELATED. Controlled Terminology may be defined in the future. Check with regulatory authority for population of this variable	Exp	Sponsor approved terminology: RELATED POSSIBLY RELATED UNLIKELY RELATED NOT RELATED If the source data is missing (or NA, NR) then that value shall be retained in the SDTM instead of being mapped to one of the above choices.	
AEPATT	Pattern of Adverse Event	C	*	Used to indicate the pattern of the event over time. Examples: INTERMITTENT, CONTINUOUS, SINGLE EVENT.	Perm	Sponsor approved terminology: INTERMITTENT CONTINUOUS	

Thinking Ahead: Benefits to Interpretation Guide

- Easier to create universal SDTM repositories.
 - Easy to add new studies.
 - Rapid response to regulatory authority inquiries.
- More likely to achieve CDISC SDTM-compliance through clarified instructions.
- Pooled analyses (ISS, ISE) will be easier to derive.
- Study teams become much more efficient.
- Streamline programming tools to help in development and validation of SDTM

- ▶ In this presentation we have provided you with an introduction to the challenges and benefits of developing an sponsor defined interpretation guide for the CDSIC SDTM Implementation Guide:
 - Consistent CRF design and annotation
 - “Data-in, data-out” philosophy to help simplify the SDTM creation process
 - General interpretation guidelines that can be applied to all SDTM development
 - Get a good understanding of codelists and dictionaries and the methods of delivery to the SDTM domains
 - Specific domain guidelines
 - “Quick-wins” in terms of building a consistent SDTM repository that can serve many purposes.

Questions

