

Challenges in Implementing a Consistent SDTM Standard on Legacy Data

PhUSE SDE 17-April-13
Meike Best
UCB BIOSCIENCES



Alison, living with rheumatoid arthritis

Overview

- Rational for SDTM Remapping of Legacy Studies
- Quality SDTMs
- Short History of Cimzia®
- Consistency Challenges
- Project Methodology
- Conclusion

Rational for SDTM remapping of legacy studies

- ⑤ Have shelf-ready SDTMs for any upcoming pooled analysis purposes
 - Safety analysis e.g. for investigator's brochure update
 - Marketing requests
 - Submission of new indications
- ⑤ Project Scope: Legacy Studies
 - Clinical Study Report NOT based on SDTMs
 - Most studies not mapped to the SDTM standard before
 - In total 34 studies
- ⑤ By Product: Methods for Quality Assessment of SDTMs

Quality SDTMs

- ⊗ Full compliance with CDISC SDTM implementation guide
- ⊗ Consistent interpretation of Sponsor Decisions
 - Same Data Same Representation
 - Within Studies and Across Pool
- ⊗ Data represent information collected in CRF
 - All subinformation 100% kept
 - Meaning of Data preserved

Short History of Cimzia®

- Anti-TNF
- First marketed in
 - May 2008 for Crohn's Disease in US
 - May 2009 for Rheumatoid Arthritis in US
- Ongoing submission for Psoriatic Arthritis and Ankylosing Spondylitis
- Developing sponsor companies so far:
 - Celltech
 - Pharmacia
 - UCB (pre and post Schwarz merger)
- More than one decade of clinical trials on Cimzia®

Short History of Cimzia® - Challenges

- ⌚ Diverse Standards for CRFs and Raw Data
 - Each company had its own CRF and data base standard
 - Indication standards within the same company different
- ⌚ CDISC model evolved over time
 - Many studies conducted before model was introduced
 - Knowledge and Understanding of SDTM evolved

Consistency Challenges: Examples

- Crohn's Disease Activity Index: Background
- Efficacy endpoint for Crohn's Disease
- Score composed from

- Diary card one week before assessment
 - Number of liquid or very soft stools
 - Abdominal pain
 - General Well-being
 - Evening oral temperature
 - Concomitant medication as Loperamide...
- Crohn's Disease Assessment
 - Symptom list
 - Presence of abdominal mass
- Body weight
- Hematocrit value

Consistency Challenges: Examples

➤ Crohn's Disease Activity Index: Which Domain?

ucb		Visit 4		Subject's initials: _____					
QSCAT = CDAI CALCULATION									
CDAI CALCULATION									
QSSPID	1. Number of liquid or very soft stools								
	Day1	Day2	Day3	Day4	Day5	Day6	Day7	[NOT SUBMITTED]	Subtotal
QSORRES	+ + + + + + + = _____ x 2 = _____							QSTESTCD = CDCNL	
2. Abdominal pain		QSTESTCD =				FACAT = CDAI CALCULATION		FAOBJ = CROHN'S DISEASE	
	Day1	Day2	Day3	Day4	Day5	Day6	Day7	< Visit 4 WEEK 6 >	
	_____	_____	_____	_____	_____	_____	_____	CDAI CALCULATION	
3. General well-being		QSTEST				FASPID		FASCAT = SUBTOTALS	
	Day1	Day2	Day3	Day4	Day5	Day6	Day7	FAORRES	
	_____	_____	_____	_____	_____	_____	_____	Subtotal	
	+ + + + + + + = _____ x 2 = _____							+ + + + + + + = _____ x 5 = _____	
	+ + + + + + + = _____ x 7 = _____							+ + + + + + + = _____ x 7 = _____	
3. General		FATESTCD				FATEST			
	_____	_____	_____	_____	_____	_____	_____		
	NOSTOOL				Number Of Liquid Or Very Soft Stools				
	ABDPAIN				Abdominal Pain				
	RATWELL				General Well Being				

Consistency Challenges: Examples

- Crohn's Disease Activity Index: Which Domain?
- Final decision: Findings About (FA)
- Rational:
 - All data in one domain
 - Investigator assessment and interpretation

< Visit 4 WEEK 6 >

FACAT = CDAI CALCULATION
FAOBJ = CROHN'S DISEASE

CDAI CALCULATION

FASPID
FAORRES

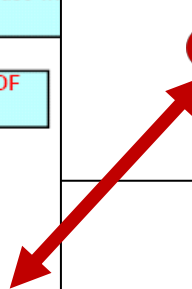
1. Number of liquid or very soft stools...FASCAT = SUBTOTALS <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 12.5%;">Day1</td> <td style="width: 12.5%;">Day2</td> <td style="width: 12.5%;">Day3</td> <td style="width: 12.5%;">Day4</td> <td style="width: 12.5%;">Day5</td> <td style="width: 12.5%;">Day6</td> <td style="width: 12.5%;">Day7</td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> </table> [NOT SUBMITTED] 2 = 2. Abdominal pain...(8) <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> <td style="width: 12.5%; border: 1px solid black; height: 20px;"></td> </tr> </table> [] + [] + [] + [] + [] + [] + [] = [] x 5 = 3. General <table style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; border: 1px solid black; height: 20px;"></td> <td style="width: 50%; border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> <tr> <td style="border: 1px solid black; height: 20px;"></td> <td style="border: 1px solid black; height: 20px;"></td> </tr> </table> [] + [] = [] x 7 =	Day1	Day2	Day3	Day4	Day5	Day6	Day7																														Subtotal
Day1	Day2	Day3	Day4	Day5	Day6	Day7																															

Consistency Challenges: Examples

➤ Study termination: Correct Controlled Terminology Mapping?

please give the reason(s) why patient discontinued prematurely from the study:	
Patient required rescue therapy or hospitalisation for management of exacerbation of disease	☒ DSTERM = Patient required rescue therapy or for management of exacerbation of disease with DSDECOD = OTHER
Lack of improvement	☐ DSTERM with DSDECOD = LACK OF EFFICACY
	☐ DSTERM with DSDECOD = ADVERSE EVENT
	☐ DSTERM with DSDECOD = WITHDRAWAL BY SUBJECT
	☐ DSTERM with DSDECOD = CLINICAL DECISION
	☐ DSTERM with DSDECOD = LOST TO FOLLOW-UP

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Lack of improvement	☐ DSTERM with DSDECOD = LACK OF EFFICACY
Adverse event (regardless of association with the test treatment)	☐ DSTERM with DSDECOD = ADVERSE EVENT
Patient decision	☐ DSTERM with DSDECOD = WITHDRAWAL BY SUBJECT
Clinical decision	☒ DSTERM with DSDECOD = PHYSICIAN DECISION
Lost to follow-up	☐ DSTERM with DSDECOD = LOST TO FOLLOW-UP



Consistency Challenges: Examples

- ⊗ Study termination: Correct Controlled Terminology Mapping?
- ⊗ Final decision: DSDECOD=PHYSICIAN DECISION
- ⊗ Rational: No plausible reason for distinction

please give the reason(s) why patient discontinued prematurely from the study:

Patient required rescue therapy or hospitalisation for management of exacerbation of disease

**DSTERM = Patient required rescue therapy or for management of exacerbation of disease with
DSDECOD = OTHER**

Lack of improvement

☐ **DSTERM with DSDECOD = LACK OF EFFICACY**

Adverse event (regardless of association with the test treatment)

☐ **DSTERM with DSDECOD = ADVERSE EVENT**

Patient decision

☐ **DSTERM with DSDECOD = WITHDRAWAL BY SUBJECT**

Clinical decision

☐ **DSTERM with DSDECOD = PHYSICIAN DECISION**

Lost to follow-up

☐ **DSTERM with DSDECOD = LOST TO FOLLOW-UP**

Consistency Challenges: Examples

⌚ Adverse Event, Action taken: Legacy vs. Modern Standard Module

Event	Intensity	Relationship to Study Drug	Action Taken	Outcome	Seriousness
	mild = 1 moderate = 2 severe = 3	unrelated = 1 possible = 2 probable = 3 definite = 4	none = 0 *medication = 1 **other = 2 *** medication and other = 3	resolved = 1 improved = 2 unchanged = 3 worsened = 4 insufficient follow-up = 5 died = 6	non-serious = 1 ***serious = 2
	AESEV	AEREL	AEACN	AEOUT	AESER

Intensity	☐ 1 Mild ☐ 2 Moderate ☐ 3 Severe	AESEV
Relationship to Study Medication	☐ 1 Related ☐ 4 Not related	AEREL
Action Taken with Study Medication	☐ 1 Dose not changed ☐ 2 Dose reduced ☐ 3 Dose increased	AEACN
Other Action Taken	☐ 1 None ☐ 2 Hospitalization or prolongation of hospitalization	AEACNTH

Consistency Challenges: Examples

- Adverse Event, Action taken: Legacy vs. Modern Standard Module
- Final decision:
 - Generally map actions taken to AEACNOTH
 - Population of AEACN:
 - Check investigator texts for references to study drug
 - Defined items to be mapped to DRUG WITHDRAWN
- Rational:
 - AEACN=DRUG WITHDRAWN crucial for safety analyses
 - Most other actions taken reported not related to study drug

Project Methodology

- ⊙ Specification Management:
 - Central Readme and Issue Log
 - Close collaboration with Annotation Team
- ⊙ Quality Assessments:
 - Annotation Review
 - Open CDISC
 - Pooling checks

Project Methodology: Pool Check Example

- Check values used in variable AEACN

SAS Dataset Domain	SAS Variable	Value	Total freq	C8700	C8700	C8703	C8703	C8703	C8703	C8703
AE	AEACN		13561	1323	233	2132	1727	5299	2843	
AE	AEACN	DOSE INCREASED	27							
AE	AEACN	DOSE NOT CHANGED	10179							75
AE	AEACN	DRUG INTERRUPTED	203							
AE	AEACN	DRUG WITHDRAWN	559			97	45	57	50	7
AE	AEACN	MULTIPLE	1021				142	528	351	
AE	AEACN	NOT APPLICABLE	1662							62

- Value MULTIPLE not expected for variable AEACN
- Go back to studies, check raw data and CRF
- Referring to issue shown in last consistency example
- Resolution:
 - Correct mapping of actions taken to AEACNOTH if applicable

Conclusion

- Pool of shelf ready SDTMs for Cimzia® legacy studies
- Quality specifications
 - Consistency
 - Meaningful representation
 - Compliance with CDISC specifications
- Challenges
 - Evolving standards
 - Preserving the overview
- Methods applied
 - Central documentation
 - Annotation Review
 - Open CDISC
 - Pooling checks

Questions?

