

Handling protocol deviations – SDTM and ADaM

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Goal

Outlining a structured approach to report protocol deviations (PDs) within the CDISC framework for:

- Subject level PDs
- Country level PDs
- Site level PDs
- Covid-19 related PDs

Motivation

- According to the ICH E3 Guideline important PDs are to be reported in-text in the CTR and listed in Appendix 16.22.
- The CDISC, SDTM model provides guidance on how to collect subject level PDs. However, some PDs are site, country and/or trial specific and do not fit the CDISC, SDTM format since for these type of PDs USUBJID is not defined.
- An additional challenge is the inclusion and specific reporting of PD's related to the ongoing COVID-19 pandemic as summarized in the "PHUSE Clinical Data Scientists Guide to Studies Impacted by COVID-19".

PD process - Preparation

- Prior to FPFV a trial specific PD categorisation document is prepared describing trial specific examples of mandatory, PD categories and subcategories.
- The information described in the PD categorisation document is aligned across various sources capturing the PD information depending on the trial set-up.
- PDs collected during the trial are classified in important PDs and non-important PDs and categorized in 4 levels:
 - Trial – generally few
 - Country – generally few
 - Site – commonly seen
 - Subject – the majority

PD process – SDTM set-up

- A Standard program is processing the information from the "PD categorisation document" to make them available in SDTM.
- Independent of their classification or categorization all PDs are included in SDTM.
- The CDISC defined SDTM.DV and SDTM.SUPPDV domains are used to capture subject level PDs (*Table 2*).
- To capture PDs that are not delineated by USUBJID in Novo Nordisk we use the sponsor defined SDTM.XD and SDTM.SUPPXD domains (*Table 2*).
- Most of the specific information about each PD is stored in the QNAMs of SUPPDV/SUPPXD (*Table 3*).
- PDs related to COVID-19 will be prefixed in PDDESCzz (*Table 3*) according to the "PHUSE Clinical Data Scientists Guide to Studies Impacted by COVID-19" recommendations in order to enable us to identify this kind of PDs.

Conclusion

- Although not actually fitting the CDISC SDTM requirements non-subject related PDs for e.g. site, country or trial can be captured within the CDISC SDTM framework using sponsor defined SDTM domains.
- Adhering to this approach enables the creation and use of standard programs to create all outputs required for PD reporting.
- Special requirements for reporting of important and non-important PDs related to COVID-19 can easily be adhered to. Via this approach all PDs independent of their importance are collected in their respective SDTM domains.
- Special emphasis needs to be put on training of trial staff when flagging a PD as related to "COVID – 19", since different ways of spelling this prefix need to be captured programmatically.

Table 2: PD information in SDTM

Domain	PD Level	Comment
DV	Subject	CDISC SDTM domain for protocol deviation data, contains the variables: • DVTERM – Title of the PD • DVCAT – Assigned category • DVSCAT – Assigned subcategory
SUPPDV	Subject	Includes level of PD importance
XD	Non-subject	NN defined extension of the DV domain, contains the variables: • DVTERM – Title of the PD • DVCAT – Assigned category • DVSCAT – Assigned subcategory
SUPPXD	Non-subject	Includes level of PD importance
	USUBJID missing for all records	SUPPXD.PDLEVEL contains the non-subject PDs at the levels: • SITE LEVEL • COUNTRY LEVEL • TRIAL LEVEL

Table 3: QNAMs in SUPPDV and SUPPXD

QNA	Content
PDTYPE	• Important • Non-important
PDLEVEL	• Subject • Site • Country • Trial
PDCNTRY	• Country
PDSITERF	• Site ID
PDDESCzz	• PD description • Split text strings
PDACTzz	• PD action taken • Split text strings
PDSTDT	• Creation date
PDENDT	• Close date

PD process – Reporting

- Circumventing the creation of PD related ADaM datasets SDTM.DV, .XD and their respective subdomains (SUPPDV, SUPPXD) enable us to use a standard program to create subject level, important PD outputs.
- Since all PDs are collected in the same SDTM "like" framework, the same standard program can be used to create site-, country- and trial level important PD outputs.
- One challenge in PD reporting is the ongoing COVID-19 pandemic. According to the "PHUSE Clinical Data Scientists Guide to Studies Impacted by COVID-19" important as well as non-important COVID-19 related PDs need to be reported in order to judge their impact on trial results and patient safety. The process of capturing all PDs important and non-important in a CDISC SDTM like structure also caters the reporting of this class of PDs as they are readily available in SDTM.XD and SDTM.SUPPXD.
- With some adjustments to the standard PD reporting program the additional listings with their required orders can easily be produced.