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FDA Pilot Standard Safety Data Request

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Meet the Speaker

Qianqian Cheng

Title: Statistical Programming Lead

Organization: Janssen China R&D, Johnson & Johnson

Qianqian Cheng graduated from Fudan University in 2012.
She had worked as Statistical programmer at Pfizer for more than 4 years. She Joined Clinical & Statistical Programming department at Janssen R&D as statistical programmer lead in 2017. She supported the approval of Darzalex clinical study in Multiple Myeloma and Amyloidosis. Currently, she focuses on BCMA CAR-T clinical study in Multiple Myeloma and has supported the NMPA submission and inspection.

Disclaimer

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Agenda

1. Background
2. What's the FDA Pilot Standard Safety Data Request?
3. Interpretation and Implementation
4. Summary

Background

- OCE(OHOP) and OOD Introduction
- Version History of Pilot Standard
- Why Does FDA Release This Standard?

OCE(OHOP) and OOD Introduction

OCE: Oncology Centre of Excellence

- Applicants submit applications to the product center, and those centers decide whether the product will be under an expedited program.
- The completed clinical review is sent to the product center, which makes the final application approval determination.

https://www.fda.gov/about-fda/fda-organization/oncology-center-excellence

OHOP: Office of Hematology Oncology Products

FDA Office of Hematology Oncology Products(OHOP) reorganized and renamed **Office of Oncologic Diseases(OCE)** in **Sep2019**

OOD: Office of Oncologic Diseases

- Oversees development, approval, and regulation of drug and biologic treatments for cancer and hematologic malignancies.
- OOD is responsible for making sure that these drugs and biologics to treat cancer are safe and effective for the U.S. public.

https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-oncologic-diseases-ood

History of Pilot OCE/OOD Standard Safety Data Request

Major Revision History Table :

Date	Version	Summary Changes
7-2019	1.0	Initial Version
11-2019	1.1	Modified several variable names for CDISC compliance; added notes for some OOD-specific variables
2-2020	1.2	Added ts.xpt; Added some additional explanations and standard CDISC variables
2-2021	1.3	Modified several variable names for CDISC compliance; added notes for some OOD-specific variables

Versions Link :

- V1.3: Pilot OCE/OOD Safety Team Standard Data Requests
  https://www.fda.gov/media/133252/download
- V1.0: Pilot OHOP Safety Team Standard Data Requests
  https://www.fda.gov/media/130532/download

Why does FDA release this Standard?

- Due to tremendous variability and inconsistency in the use of the CDISC ADaM data standard in safety datasets for oncology NDA/BLA applications submitted to FDA

- This variability leads to inefficiency in review for the FDA and multiple information requests to applicants during the review to resolve inconsistencies in analyses between FDA and applicants.

Note: datasets and variables defined in this standard are required for the Real Time Oncology Review (RTOR)

Under the RTOR program, when submitting complete ADaM datasets for key efficacy and safety tables/figures for the pivotal study, please refer to OOD Safety standard data specifications for the requested format of safety datasets.

RTOR: https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review

What's the Pilot OCE/OOD Standard Safety Data Requests?

- Overview of Standard Request
- Case Sharing - FDA Ad-hoc request from BLA/NDA Submission

Overview of Standard Request

➢ Which datasets are involved in?

Domain	Label	Define
ADSL	Subject level Analysis Dataset	adsl.xpt
ADAE	Adverse Events Analysis Dataset	adae.xpt
ADLB	Laboratory Analysis Dataset	adlb.xpt
ADEX	Exposure Analysis Dataset	adex.xpt
ADEXSUM	Exposure Summary Analysis Dataset	adexsum.xpt
ADCRSNT	Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT)	adcrsnt.xpt
TS	Trial Summary Table	ts.xpt

Overview of Standard Request

➢ Scenario #1

Variables that are typically not derived by sponsor (e.g.: JNJ)

ADLB Variable Name	Variable Label	Type	Codelist/ Controlled Terms	CDISC Core	OCE/OOD Core (SDTM or ADaM)	CDISC Variable (ADaMIG v1.1 or SDTM v3.3 or OCE/OOD v1.3=FDA)	OCE/OOD Additional Information
ATOXGRL	Analysis Toxicity Grade Low	Char	0, 1, 2, 3, 4, Null	Perm	Req	ADaM	CTCAE grade (if applicable) if the toxicity grade is a low grade; if another grading system is used, provide details of this grading system in Study Data Reviewers Guide
ATOXGRLN	Analysis Toxicity Grade Low (N)	Num	0, 1, 2, 3, 4, Null	Perm	Req	ADaM	Numeric version of ATOXGRL
ATOXGRH	Analysis Toxicity Grade High	Char	0, 1, 2, 3, 4, Null	Perm	Req	ADaM	CTCAE grade (if applicable) if the toxicity grade is a high grade; if another grading system is used, provide details of this grading system in Study Data Reviewers Guide
ATOXGRHN	Analysis Toxicity Grade High (N)	Num	0, 1, 2, 3, 4, Null	Perm	Req	ADaM	Numeric version of ATOXGRH
AVALU	Analysis Value Unit	Char		N/A	Req	FDA	Include even if unit is included in PARAM description.

Overview of Standard Request

➢ Scenario #2

- Variables derived by sponsor with different naming convention.

ADSL Variable Name	Variable Label	Type	Codelist/Controlled Terms	CDISC Core	OCE/OOD Core	Source (ADaMIG v1.1 or SDTM v3.2 or OCE/OOD v1.3=FDA)	OCE/OOD Additional Information
LSTALVDT	Date Last Known Alive	Num		Perm	Req	ADaM	
NCTXSDT	Start Date of New Anti-Cancer Therapy	Num		N/A	Req	FDA	Start date of first subsequent anti-cancer treatment.

- Or different data structure.

ADEXSUM Variable Name	Variable Label	Type	Codelist/ Controlled Terms	CDISC Core (SDTM or ADaM)	OCE/OOD Core	CDISC Variable (ADaMIG v1.1 or SDTM v3.3 or OCE/OOD v1.3=FDA)	OCE/OOD Additional Information
AEVLINT	Analysis Interval for Evaluation	Char		N/A	Req	FDA	Describes the interval of time that was evaluated to derive AVAL, e.g., Overall, Cycle X, etc.
PARQUAL	Parameter Qualifier	Char		N/A	Req	FDA	Description of the treatment summarized on each record. Equal to EXTRT for summaries/ evaluations of individual treatments, or 'All' for summaries / evaluations across all treatments.

Case Sharing

- FDA Ad-hoc request from BLA/NDA Submission

- Add ADaM which is specific to CRS(Cytokine Release Syndrome) and NT(Neurotoxicity) analysis
- Add variables(AVALU, ATOXGRL, ATOXGRH) in the ADLB data
- Add evaluation flag variables (EVLLBFL) in the ADLB data

Dataset	Purpose and FDA specific requirements
ADSL Subject level Analysis Dataset	Key subject level information Specific FDA variables such as: - TRTEDY (Study Day of Last Exposure to Treatment) - DTH30TFL (Death Within 30 Days of Last Treatment) - DTA30TFL (Death After 30 Days of Last Treatment) - DTB30TFL (Death Within 30 Days of First Treatment) - NCTXSDT (Start Date of New Anti-Cancer Therapy) - CUTDT (Data Cut-off Date), this is redundant with the information in ts.xpt
ADAE Adverse Events Analysis Dataset	Specific FDA variables such as, variables related to individual 'experimental' drugs when using regimens made of combined treatments or the variable GRPID used, as per the specifications, "to tie together a block of records for a subject that belong to the same adverse event, e.g., grade 1 pyrexia which progresses to grade 2 should be identified with the same GRPID"
ADLB Laboratory Analysis Dataset	Specific FDA variables such as, EVLLBFL (Evaluable Lab Flag) to flag subject having both baseline and at least one on-study value
ADEX Exposure Analysis Dataset	Directly mapped from SDTM.EX Specific FDA variables such as: - EXDURD (Duration of Treatment (days)) - DOSREDFL (Dose Reduced Flag) - DOSINTFL (Dose Interrupted Flag) - DOSDELFL (Dose Delay Flag)
ADEXSUM Exposure Summary Analysis Dataset	BDS derived from ADEX containing summary information by subject and by subject/cycle (AEVLINT variable) Value metadata with details of all required parameters are also available, for example PARAMCD=RDOSINT (Relative Dose Intensity (%))
ADCRSNT Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT)	Derived from ADAE with additional flags e.g., FDAGT (CRS vs NT) The required structure is unclear, and an example would have helped, for instance the expected structure is "One record per subject per adverse event per start date" but from the specs some variables contain some statistics by subject e.g., "NT max tox grade by subject-period"

Interpretation and implementation

- Johnson & Johnson
- PHUSE Working Group

Johnson & Johnson

- This document is a pilot, it is not required per standard yet.

  Sponsors are not required to follow this standard, but J&J Oncology team has made the decision to proactively adopt FDA's pilot

- Included most of the "Required"/"Cond" variables into ADaMs standard metadata and developed the standard codes to derive them.

- Implemented in all new oncology studies.

- Had a few experiences in submitting data package by including those OCE/OOD variables.

Example of FDA's OCE/OOD variables in ADSL

ADaM metadata update

DATASET	VARNAME	VARLABEL	LNGTH	ORIGCOM	DERVCOPY	SASMCR	SASCDREF	NOTES
ADSL	DTH30TFL	Death Within 30 Days of Last Treatment		Set to "Y" if a subject died within 30 days of last dose. If DTHDT (where DTHFL= 'Y') <= ADSL.TRTEDT+30 then DTH30TFL='Y', else DTH30TFL="N".	Derived	%ADDTHTRTFL		OOD REQ
ADSL	DTHA30FL	Death After 30 Days of Last Treatment		Y if death occurred after 30 days of treatment end (DTHDTC > TRTEDT+30); If DTHDTC is partial: Y if the month and year are greater than the month and year of TRTEDT + 30. Y If only the year of available and greater than the year of TRTEDT + 30. Y, If DTHDTC is fully missing and DM.DTHFL is not missing	Derived	%ADDTHAB30FL		OOD REQ
ADSL	DTHB30FL	Death Within 30 Days of First Treatment		Y if death occurred within 30 days of starting treatment (DTHDTC <= TRTSDT+30); If DTHDTC is partial: Y if the month and year are less than the month and year of TRTSDT + 30. Y If only the year of available and less than the year of TRTSDT + 30. Y, If DTHDTC is fully missing and DM.DTHFL is not missing	Derived	%ADDTHAB30FL		OOD REQ
ADSL	DTHCAUSP	Cause Spec for Death		*STUDY-SPECIFIC*	Derived	*STUDY-SPECIFIC*		OOD REQ
ADSL	DCTFL	Subject Discontinued Treatment Flag		Y if DSSCAT has text containing 'TREATMENT' and if DS.DSCAT='DISPOSITION EVENT' and DS.DSECOD not equal to " COMPLETED".	Derived	%ADDCT		OOD REQ
ADSL	DCTDT	Treatment Discontinuation Date	8	DS.DSSTDTC if DSSCAT has text containing 'TREATMENT' and if DS.DSCAT= 'DISPOSITION EVENT' and DS.DSECOD not equal to " COMPLETED".	Derived	%ADEOT		OOD REQ
ADSL	DCTADY	Study day of discontinuation		DS.DSSTDY if DSSCAT has text containing 'TREATMENT' and if DS.DSCAT='DISPOSITION EVENT' and DS.DSECOD not equal to " COMPLETED".	Derived	%ADDCT		OOD REQ
ADSL	DCTREAS	Reason for Discontinuation of Treatment		If DSSCAT has text containing 'TREATMENT' and DS.DSCAT equal to 'DISPOSITION EVENT' and DS.DSDECOD not equal to 'COMPLETED', then DCTREAS equal to DS.DSDECOD.	Derived	%ADEOT		OOD REQ
ADSL	DCTREASP	Reason Specify for Discont of Treatment		If DS.DSSCAT has text containing 'TREATMENT' and DS.DSCAT equal to 'DISPOSITION EVENT' and DS.DSDECOD is equal to ('OTHER', or contains 'WITHDRAWAL BY') then set DCTREASP to DS.DSTERM	Derived	%ADEOT		OOD COND
ADSL	DCTREASP	Reason Specify for Discont of Treatment		If DS.DSSCAT has text containing 'TREATMENT' and DS.DSCAT equal to 'DISPOSITION EVENT' and DSSTDTC is not missing and DS.DSDECOD is equal to ('OTHER','PROTOCOL DEVIATION','PHYSICIAN DECISION','SUBJECT REFUSED FURTHER STUDY TREATMENT' or contains 'WITHDRAWAL BY') then set DCTREASP to DS.DSTERM	Derived	%ADEOT		OOD COND
ADSL	DCP01RS	Reason for Discont from Period 01		*STUDY-SPECIFIC*	Derived	*STUDY-SPECIFIC*		
ADSL	DCP01RSP	Reason Spec for Discont from Period 01		*STUDY-SPECIFIC*	Derived	*STUDY-SPECIFIC*		

PHUSE Working Group

- FDA Oncology Safety Data Standards

Purpose:

- To obtain broad industry feedback on the current publicly available OCE/OOD standard safety data request
- To assist sponsors with implementation of these data specifications.
- To identify specific gaps between FDA and industry to collaborate and close those gaps.

Stakeholders:

The Stakeholders include FDA reviewers and analysts, industry, CROs, and software developers.

Team members:

Representatives from industry

PHUSE Data Standard Group

➢ Comments collected:

PHUSE group FDA Oncology Safety Data Standards is involved in evaluation of "Pilot OCE/OOD Standard Safety Data Requests" document and gathering feedback from the participating sponsors. J&J has an active representation in this PHUSE group.

Overview
This file contains the consolidated comments from the FDA Oncology Safety Data Standards Project Team. The goals of this phase of the project was to obtain broad industry and CRO feedback on version 1.3 of the OCE/OOD standard safety data request. The comments in the following tabs should not be considered as the consolidated opinion of the project team but the complete set of feedback collected from project team members for consideration to be included in a future version of the specifications. No indication is given to the status of the comments.

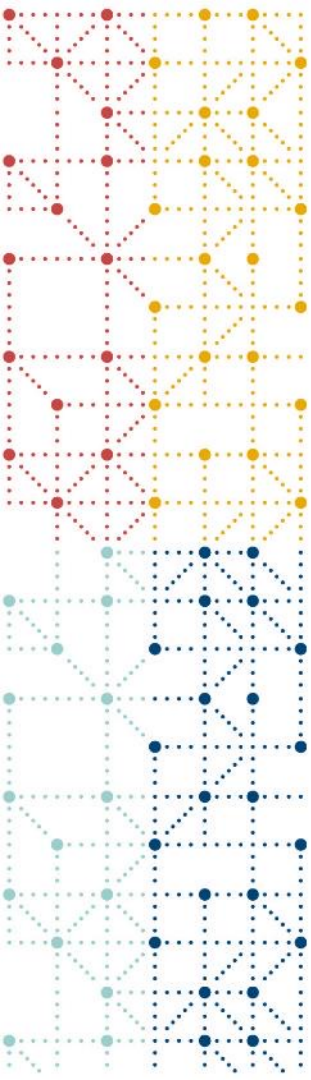
Standard Safety Data Requests
ADAE
ADCRSNT
ADEX
ADEXSUM
ADLB
ADSL
TS

https://advance.phuse.global/display/WEL/FDA+Oncology+Safety+Data+Standards

Summary

Proactive adoption of this FDA pilot standard safety data request

- Help sponsors to minimize Ad-hoc request after submission
- Improve efficiency of FDA review process
- Support Real Time Oncology Review (RTOR)
- Harmonize the internal TA (oncology) standards



Thank You!

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Details about Standard Request

➢ Which Cases are involved?

- New SDTM Domain should be included.
  - TS: Trial Summary Table (ts.xpt)
  - Structure: One record per trial summary parameter value;

Includes Trail Randomization/enrolled/dosed patients' Num, Therapeutic Area, Indication, Blinded or Unblinded, Start/End date, Treatment Arms, Data Cutoff Description, primary/second/exploratory endpoints …..

Trial Summary Codes

TSPARMCD	TSPARM	TSVAL (Codelist or Format)	Record with this Parameter	OCE/OOD Additional Information
TITLE	Trial Title	Char		
STUDYID	Study Identifier	Char		
REGID	Registry Identifier	Char		NCT number
STUDYIND	IND Where Trial Conducted	Char		IND number under which trial was conducted
SPONSOR	Clinical Study Sponsor	Char		
INDIC	Trial Disease/Condition Indication	Char		Use SnowMed terminology
INDICP	Proposed Indication	Char		Use proposed label indication
STYPE	Study Type	Char	Interventional, observational	
NARMS	Planned Number of Arms	Num		