Implementation of RTOR Standards at AstraZeneca

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Presented by Robert Zollinger, Senior Statistical Programmer I, Oncology R&D, AstraZeneca



Meet the Speaker

Robert Zollinger

Title: Senior Statistical Programmer I

Organization: AstraZeneca

I am a Senior Statistical Programmer at AstraZeneca with four years of experience in the Pharma industry on Early Oncology studies. A year ago, I transitioned from full-time study work into a study-facing standards development role within Oncology. I have a degree in Mathematics and Computer Science from MIT in Cambridge, Massachusetts, USA.



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- The views and opinions expressed in this presentation are those of the authors and do not necessarily reflect the official policy or position of CDISC.
- The authors are employees of AstraZeneca and have stock ownership or options in AstraZeneca.



Agenda

- 1. What is RTOR? Why is it important?
- 2. What standards guidance has the FDA provided for RTOR?
- 3. What questions did AstraZeneca encounter while creating RTOR standards, and how did we answer them?
- 4. Conclusion: So, we've created the "perfect" RTOR standards...

What is RTOR? Why is it important?

Real-Time Oncology Review (RTOR)

RTOR is an FDA program initiated in February 2018 "to facilitate earlier submission of top-line results (i.e., efficacy and safety results from clinical studies before the study report is completed) and datasets, after database lock, to support an earlier start to the FDA application review."

Studies must meet several criteria to apply:

- Evidence indicates that drug may provide substantial improvement over other existing therapies
- Easily interpretable endpoints (e.g., overall survival, overall response rate)
- Straightforward study design



The business case for RTOR compliance

RTOR compliance provides many benefits to sponsors.

- Faster decisions on FDA submissions
- Reduces back-and-forth with regulators

RTOR compliance *as the default* provides even more benefits.

- Updates to study specifications no longer a factor when considering whether to apply for RTOR
 - $\circ~$ Can only apply for RTOR after database lock very tight timelines
- Simplifies automation no need for "RTOR" and "non-RTOR" tools



Graphic from Friends of Cancer Research 2018 White Paper: "Real-Time Oncology Review and the Assessment Aid"



What standards guidance has the FDA provided for RTOR?

OCE/OOD Safety Team Standard Data Requests v1.3

"As part of your NDA/BLA submission, we ask that you prepare the datasets and conduct the safety analyses with [these] assumptions and dataset variables."

- Compliance not required for submission but strongly recommended
- V1.0 published in July 2019
- V1.3 published in Feb 2021
- Comments from 2021 industry review available <u>here</u>

Pilot OCE/OOD Standard Safety Data Requests v1.3

Pilot OCE/OOD Safety Team Standard Data Requests

- As part of your NDA/BLA submission, we ask that you prepare the datasets and conduct the safety analyses with the assumptions and dataset variables as below.
- Please provide define files (PDF and .xml with stylesheet) and a reviewer's guide for submitted datasets.

ADSL - Subject level Analysis Dataset (adsl.xpt):

Structure: One record per subject

In addition to the CDISC required variables for adsl and variables necessary for analyses for the submitted trials, the dataset should include the
variables listed below important for the analyses with identifiers for each trial period/drug as applicable (not an all-inclusive list):

ADSL Variable Name	Variable Label	Туре	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
USUBJID	Unique Subject Identifier	Char		Req	Req	STDM	
SUBJID	Subject Identifier for the Study	Char		Req	Req	STDM	
STUDYID	Study Identifier	Char		Req	Req	STDM	
AGE	Age	Num		Req	Req	STDM	
AGEU	Age Units	Char	(AGEU)	Req	Req	SDTM	
AGEGRy	Pooled Age Group Y	Char		Perm	Req	ADaM	Age <65 and ≥ 65 should be presented; Other groupings may also be presented as discussed with review team or deemed relevant by applicant.
AGEGRyN	Pooled Age Group y (N)	Num		Perm	Req	ADaM	
SEX	Sex	Char	(SEX)	Req	Req	SDTM	
RACE	Race	Char	(RACE)	Req	Req	SDTM	



Key Points from OCE/OOD Guidance

- Six ADaM datasets and SDTM TS domain parameters
 - ADSL, ADAE, ADEX, ADEXSUM (including value-level metadata), ADLB, ADCRSNT
- Includes a mixture of CDISC ADaM variables and new variables
 - List of variables is not exhaustive
- Was not written by standards developers
 - Provided metadata is not always aligned with CDISC
 - Derivations are (mostly) nonprescriptive
- Sponsor has freedom of implementation
 - · Comes with a responsibility to communicate choices clearly



What questions did AstraZeneca encounter while creating RTOR standards, and how did we answer them?

1. ADCRSNT

2. Other Safety ADaMs



ADCRSNT

What is ADCRSNT?

Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT)

- Subset of ADAE with additional variables
 - Prescribed structure matches ADAE (i.e., one record per adverse event per start date)
- Additional variables include type of event, maximum toxicity grade, time to resolution, etc.
 - Most new variables are subject-period level rather than record-level
- Important for studies of T-cell engaging bispecific antibodies

Pilot OCE/OOD Standard Safety Data Requests v1.3

ADCRSNT – Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) (adcrsnt.xpt) Structure: One record per subject per adverse event per start date

Dataset should include the variables listed below important for the analyses (not an all-inclusive list):

Pilot OCE/OOD Standard Safety Data Requests v1.3

ADCRSNT Variable Name	Variable Label	Туре	Codelist/ Controlled Terms	CDISC Core (SDTM or ADaM)	FDA Core	Source (ADaMIG v1.1 or SDTM v3.3 or FDA)	FDA Additional Information
NTFLS	TFLS Subject level NT flag by Period		Y, N			FDA	Indicates if the subject experience a NT event during treatment period specified in APERIOD
CRSONFL	Ongoing CRS flag	Char	Y, N			FDA	Indicates if CRS is ongoing at end of study or date last known alive
NTONFL	Ongoing NT flag	Char	Y, N			FDA	Indicates if NT is ongoing at end of study or date last known alive
CRSSTDY	Start day of CRS by subject and period	Char	Num			FDA	AESTDY of first CRS event for subject in APERIOD
CRSENDY	End day of CRS by subject and period	Char	Num			FDA	AEENDY of last CRS event for subject in APERIOD
NTSTDY	Start day of NT by subject and period	Char	Num			FDA	AESTDY of first NT event for subject in APERIOD
NTENDY	End day of NT by subject and period	Char	Num			FDA	AEENDY of last NT event for subject in APERIOD
CRSMAXTX	CRS max tox grade by subject-period	Char	Num			FDA	CRS max toxicity grade for subject in APERIO
NTMAXTX	NT max tox grade by subject-period	Char	Num			FDA	NT max toxicity grade for subject in APERIOD
CRSMXSDY	Time to CRS max tox grade by subject-period	Char	Num			FDA	AESTDY of first CRS event with max toxicity grade (CRSMAXTX) for subject in APERIOD
NTMXSDY	Time to NT max tox grade by subject- period	Char	Num			FDA	AESTDY of first NT event with max toxicity grade (NTMAXTX) for subject in APERIOD
CRSDUR	Time to CRS resolution by subject- period	Char	Num			FDA	CRSENDY – CRSSTDY + 1
NTDUR	Time to NT resolution by subject- period	Char	Num			FDA	NTENDY - NTSTDY + 1

ſ	CRSFLR	Record level CRS flag	Char	Y,N		FDA	Indicates if the record is a CRS event as defined in FDAGT
l	NTFLR	Record level NT flag	Char	Y, N		FDA	Indicates if the record is a NT event as defined in FDAGT
	CRSFLS	Subject level CRS flag by Period	Char	Y, N		FDA	Indicates if the subject experienced a CRS event during treatment period specified in APERIOD



Implementation Questions: Structure

Are these data represented best using OCCDS v1.0?

- OCCDS v1.1 allows for both eventlevel and summary records. Possibly more appropriate for subject-period variables.
 - FDA Technical Conformance Guide does not allow OCCDS v1.1.
- One industry reviewer suggested using BDS instead.
 - $\,\circ\,$ FDA tools may not be built to handle BDS.

AZ have decided to use OCCDS v1.0 until further FDA guidance is provided.

Pilot OCE/OOD Standard Safety Data Requests v1.3

ADCRSNT – Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT) (adcrsnt.xpt) Structure: One record per subject per adverse event per start date

Dataset should include the variables listed below important for the analyses (not an all-inclusive list):

Immediately below is a list of SDO properties that have been evaluated by CBER and CDER and are not considered to align with their current business needs. Consider referring to FDA comments that were submitted to the SDO for more details. This list may not be comprehensive of all properties and absence form this list does not indicate encouragement to use. Consult with your division for more specific instructions:

- CDISC OCCDSv1.1
- CDISC ADaM Examples of Traceability-v1.0
- CDISC ADaM Metadata Submission Guidlines-v1.0
- CDISC Document: Interim User Guide for COVID-19
- CDISC Document: Guidance for Ongoing Studies Disrupted by COVID-19
- CDISC SENDIG-DARTv1.2



Implementation Questions: Derivations

Guidance includes new variables with minimalist derivations.

- FDA Grouped Term (FDAGT)
 - Where can these groupings be found?
- Subject level [CRS/NT] flag by Period (CRSFLS/NTFLS)
 - Does "experience during treatment period" mean "start during period" or "any overlap with period"?
- End day of [CRS/NT] by subject and period (CRSENDY/NTENDY)
 - If CRS AE continues into subsequent period, should CRSENDY be missing?
 - If CRS event is unresolved, should CRSENDY be censored (e.g., at last known alive date)?

FDAGT FDA Grouped Term	Char	CRS, NT	FDA-defined composite grouping of MedDRA Preferred Terms for CRS and NT
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CRSFLS	Subject level CRS flag by Period	Char	Y, N	Indicates if the subject experienced a CRS event during treatment period specified in APERIOD
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CRSENDY End day of CRS by subject and period	Char	Num	AEENDY of last CRS event for subject in APERIOD	
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FDA Grouped Term (FDAGT)

FDA-defined composite grouping of MedDRA Preferred Terms for CRS and NT

Question: Where can these groupings be found?

List of FDA Medical Queries was published in 2022 but does not include CRS or NT/ICANS

Resolution: Allow studies to define CRS and NT groupings until the FDA publishes definitions.

Rationale: FDAGT is essential for other derivations in ADCRSNT and cannot be left undefined.

Q: Why not define a separate variable for study-level groupings?

A: FDA reviewers are expecting FDAGT to hold grouping information. We will update our standards to use FDA groupings when they are published.



Subject level [CRS/NT] flag by Period (CRSFLS/NTFLS)

Indicates if the subject experienced a CRS event during treatment period specified in APERIOD

Question: Does "experience during treatment period" mean "start during period" or "any overlap with period"?



Resolution: Choose definition "any overlap with period".

• CRSFLS = Y for Period 3 in above example

Rationale: More conservative.



End day of [CRS/NT] by subject and period (CRSENDY/NTENDY)

AEENDY of last CRS event for subject in APERIOD

Questions: If CRS AE continues into subsequent period, should CRSENDY be missing? If CRS event is unresolved, should CRSENDY be censored (e.g., at last known alive date)?



Resolution: Interpret as "AEENDY of latest event which started in this period for this subject". No further imputation/censoring.

• CRSENDY = 23 for Period 1 and CRSENDT = . for Period 2 in above example

Rationale: OCE/OOD guidance is explicit about using AEENDY for this derivation.

Implementation Questions: Metadata

Prescribed Dataset Label exceeds 40-character limit for submission.

- "Adverse Events Analysis Dataset for Cytokine Release Syndrome (CRS) and Neurotoxicity (NT)" is 90 characters.
- Resolution: Propose Dataset Label of "CRS and Neurotoxicity AE Analysis Data" (38 chars).
- Rationale: Conformance to Study Data Technical Conformance Guide more important than conformance to guidance document.

New Timing variables are prescribed to be Character rather than Numeric.

- Resolution: Leave as Character.
- $\,\circ\,$ Rationale: No CDISC requirement for these variables to be Numeric.

Flag variables end in –FLR or –FLS rather than –FL.

- $\,\circ\,$ Resolution: Leave FDA-prescribed endings.
- Rationale: Reviewers are expecting the given variable names. Adopting –FL ending would require significant renaming. For example, CRSFLR (record-level CRS flag) and CRSFLS (subject-period CRS flag) cannot both be named CRSFL.



Other Safety ADaMs

Implementation Questions

- Treated Population Flag (ADSL.TRTFL)
 - OCE/OOD guidance mentions using this variable for combination therapies but not monotherapies. Is this flag applicable to monotherapy studies?
- Sponsor assessment of relatedness (ADAE.AERELS)
- Cause of Death Sponsor (ADSL.DTHCAUSS)
 - How are these variables traceable to SDTM?
- Group ID (ADAE.GRPID)
 - Many of our studies collect all grade changes on a single logline and then create separate records for each grade change in ADAE. Is the purpose of GRPID to group these grade change records? If so, could we use an SDTM variable (e.g., AE.AESPID) instead?
- Duration of Treatment (days) (ADEX.EXDURD)
 - Should we include or exclude interruptions?
- And more...



Conclusion: So, we've created the "perfect" RTOR standards...

...or maybe we haven't

Feedback from pilot studies:

- Some studies collect both CTCAE grade and ASTCT grade for CRS/ICANS events
 - $\,\circ\,$ Decided to add variables to ADCRSNT to capture both
- Some studies collect changes in ASTCT grade for CRS/ICANS events
 - $\,\circ\,$ Decided to add variables to ADCRSNT to capture these
- Derivations are overly complex for single-period studies
 - $\circ\,$ Example: CRSFLS (Subject level CRS flag by Period)
 - Multi-period: Set to "Y" if subject has any records where CRSFLR = "Y" and at least one of the following is true: ... (then three more lines of text to check for overlap with period)
 - Single-period: Set to "Y" if this subject has any records where CRSFLR = "Y".



Standards are always evolving. No standard stays "perfect" for long. $\ensuremath{\textcircled{\odot}}$

cdise

#ClearDataClearImpact



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Thank you for your time!

