# AstraZeneca RTOR Standards Implementation

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13 October 2025


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# Meet the Speaker

## Soma Sekhar Sriadibhatla

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Organization: AstraZeneca

Soma Sekhar Sriadibhatla is currently acting as Analysis and Reporting Lead for Oncology Clinical Standards Therapeutic Area at AstraZeneca, where he manages SDTM, ADaM, and TFL standards development and implementation. He has over 10 years of experience in Statistical programming and drug development, with a strong background in SAS, R, and Python programming, as well as e-submissions of clinical trial results. Soma Sekhar has led multiple studies and projects at various organizations, including Bristol Myers Squibb, PHUSE.

# Disclaimer and Disclosures

- *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

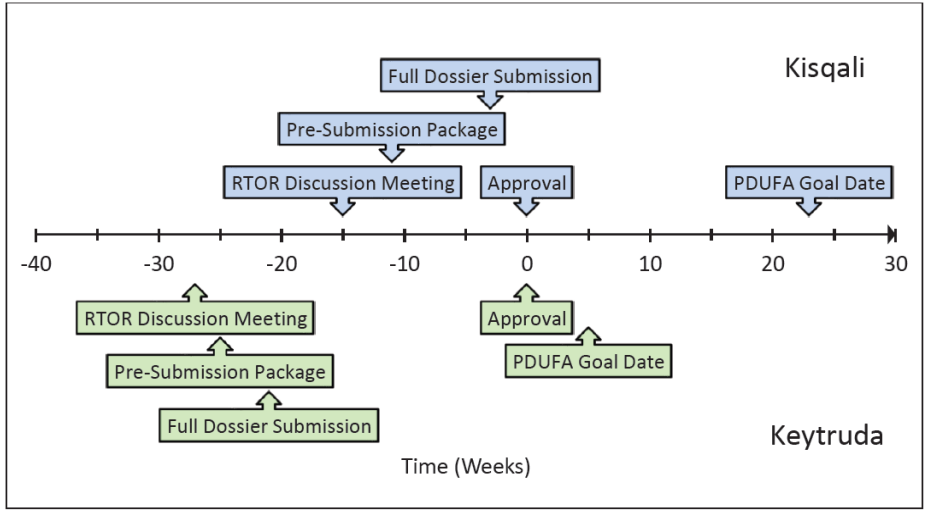
# The business case for RTOR compliance

## 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
  - Can only apply for RTOR *after* database lock – very tight timelines
- Simplifies automation – no need for "RTOR" and "non-RTOR" tools



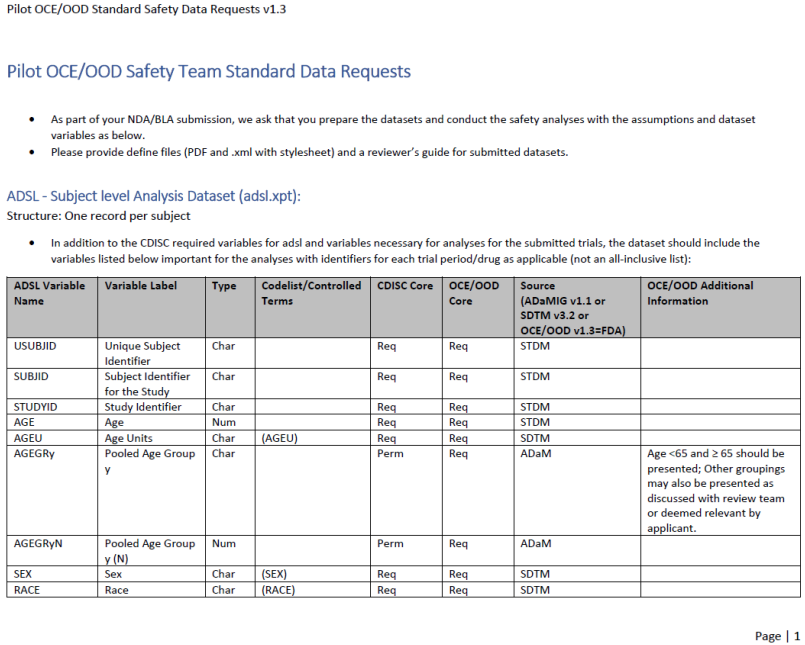

Graphic from Friends of Cancer Research 2018 White Paper: "Real-Time Oncology Review and the Assessment Aid"

# 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 here



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 | 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 |
|---|---|---|---|---|---|---|---|
| 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 | |

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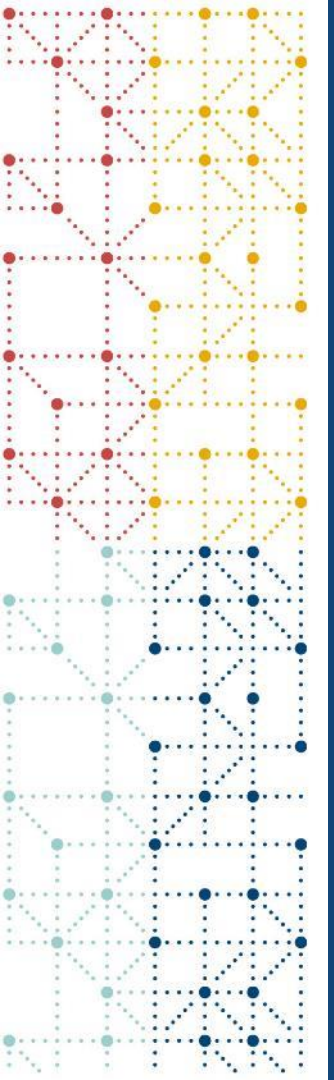
# Key Points from OCE/OOD Guidance

- 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 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 | Type | Codelist/ Controlled Terms | CDISC Core (SDTM or ADaM) | FDA Core | Source (ADaMIG v1.1 or SDTM v3.3 or FDA) | FDA Additional Information |
|---|---|---|---|---|---|---|---|
| NTFLS | Subject level NT flag by Period | Char | 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 APERIOD |
| 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 |
| CRSFLR | Record level CRS flag | Char | Y,N | | | FDA | Indicates if the record is a CRS event as defined in FDAGT |
| 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 |

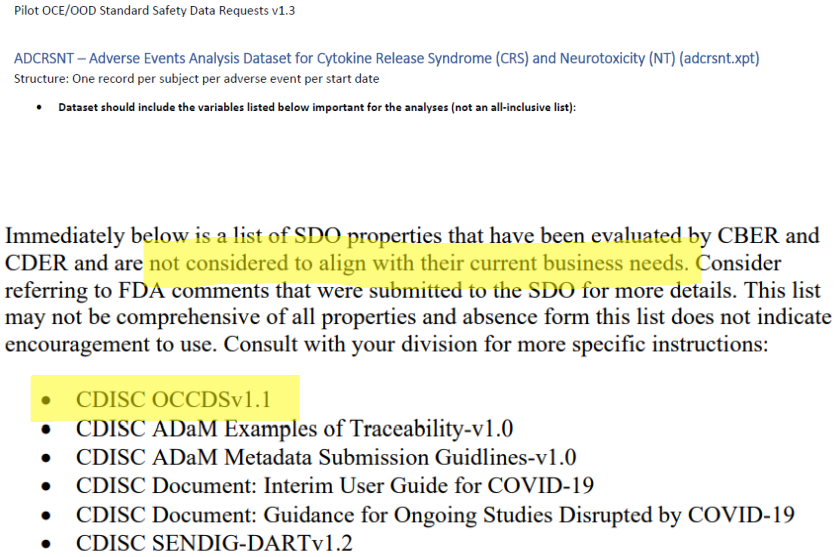
Values in parenthesis are the names of CDISC Controlled Terminology codelists

# Implementation Questions: Structure

## Are these data represented best using OCCDS v1.0?

- OCCDS v1.1 allows for both event-level 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.
  - 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 |

| | | | | |
|---|---|---|---|---|
| CRSFLS | Subject level CRS flag by Period | Char | Y, N | Indicates if the subject experienced a CRS event during treatment period specified in APERIOD |

| | | | | |
|---|---|---|---|---|
| CRSENDY | End day of CRS by subject and period | Char | Num | AEENDY of last CRS event for subject in APERIOD |

# 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.

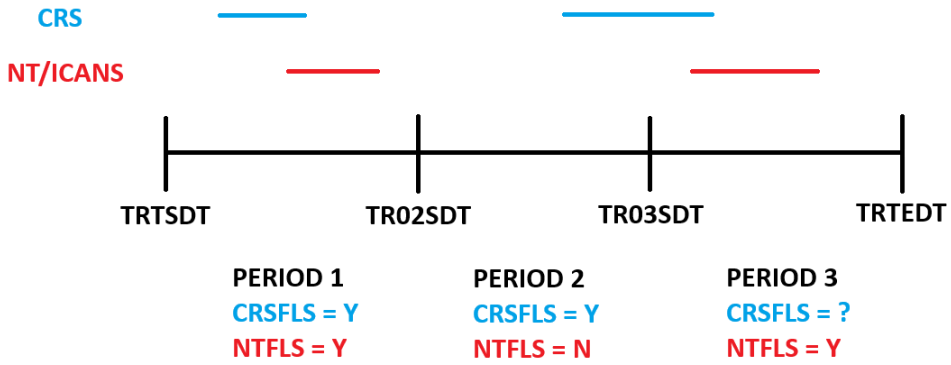
Q: Why not define a separate variable for study-level groupings?

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”.

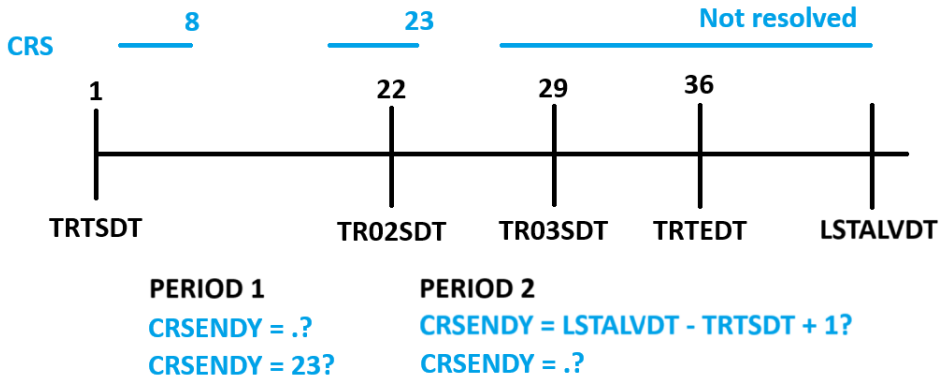
- CRSFLS = Y for Period 3 in above example

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.
- Rationale: No CDISC requirement for these variables to be Numeric.

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

- 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

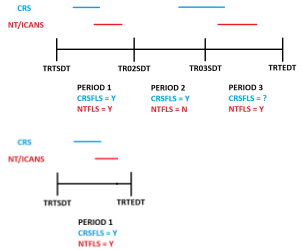
- Treated Population Flag (ADSL.TRTFL)
  - OCE/OOD guidance mentions using this variable for combination therapies but not monotherapies. Is this flag applicable to monotherapy studies?
- Sponsor assessment of relatedness (ADAE.AERELS)
- Cause of Death Sponsor (ADSL.DTHCAUSS)
  - How are these variables 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
  - Decided to add variables to ADCRSNT to capture both
- Some studies collect changes in ASTCT grade for CRS/ICANS events
  - Decided to add variables to ADCRSNT to capture these
- Derivations are overly complex for single-period studies
  - 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. ☺**

# Contact Us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Thank you for your time!