CDISC Breast Cancer and Prostate Cancer Therapeutic Area User Guides – Introducing a New Approach for Broader Usage in Oncology Studies

Xiangchen (Bob) Cui

This Presentation Is An Encore of A Presentation during Pharma SUG 2023 in May 2023.

Leverage and Enhance CDISC TAUGs to Build More Traceability for and Streamline Development of Efficacy ADaM in Oncology Studies

Outlines-Introduction

- FDA Guidelines for Progression-free Survival (PFS) Analysis Being Used in This Paper
- Dates of Events Needed for Time-to-event Analyse and BOR/DOR
- Rationale of Separating the Derivation of Dates Related to Tumor Assessments and Ones Independent of Tumor Assessments
- BOR Derivation Per RECIST 1.1
- CDISC Breast Cancer Therapeutic Area User Guide (TAUG-BrCa)-ADEVENT
- CDISC Prostate Cancer Therapeutic Area User Guide (TAUG-PrCa)-ADDATES
- Pros and Cons of ADEVENT and ADDATES from These Two CDISC Standards
- Conclusion

Outlines-Our New Data Flow

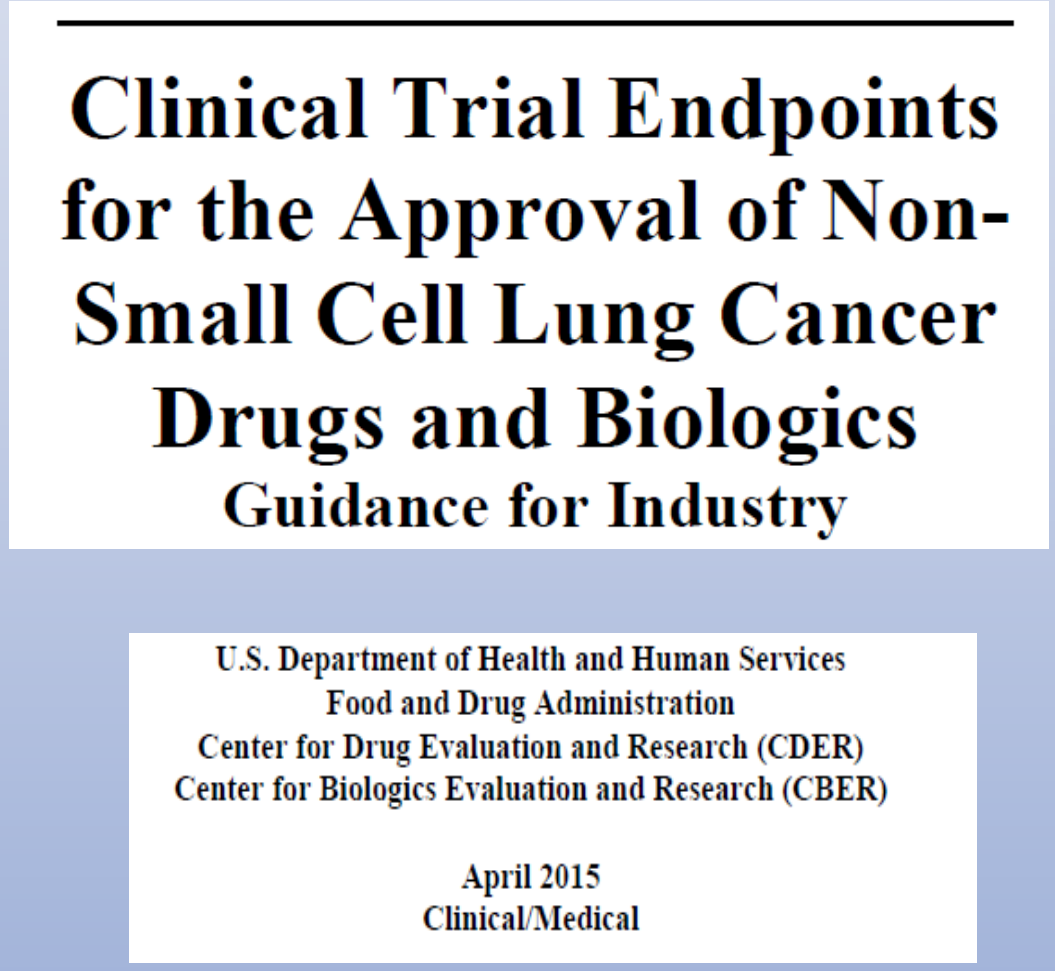
- ADEVENT Programming → ADRESP
- ADEVENT Programming -> ADDATES Programming
- ADDATES Programming -> ADTTE Programming
- ADTTE Programming for PFS
- Conveniently Build Traceability for ADTTE
- Summary & Conclusion

Quick Survey

- Who Have the Working Experience:

1. Oncology Studies
2. RECIST 1.1 or iRECIST
3. Summary of Objective Response
4. Best Overall Response (BOR) & Duration of Response (DOR)
5. ADTTE (Time-to-Event (TTE) analyses)
6. Progression-Free Survival (PFS) Related Censoring Rules
7. CDISC ADEVENT
8. CDISC ADDATES

FDA Guidelines Provides the Examples of Prespecified Censoring Schemes for Primary and Secondary Progression-free survival (PFS) Analysis.



Clinical Trial Endpoints for the Approval of Non-Small Cell Lung Cancer Drugs and Biologics

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

April 2015
Clinical/Medical

An Example for Censoring Scheme for Primary PFS Analysis from Table C1

Situation	Date of Progression or Censoring	Outcome
Incomplete or no baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: Date of progression assessment showing new lesion (if progression is based on new lesion); or Date of last progression assessment	Progressed
No progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for undocumented progression	Date of last progression assessment with no documented progression	Censored
Treatment discontinuation for toxicity or other reason	Date of last progression assessment with no documented progression	Censored
New anticancer treatment started	Date of last progression assessment with documented nonprogression before start of new treatment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last progression assessment with documented nonprogression	Censored

Dates of Events for Time-to-Event Analysis ---Needed in The Derivation of ADTTE

Dates Related to Tumor Assessment (DRTA)– From RS (**Disease Response and Clin Classification**)

1. The first date of progressive disease
2. Date of last progression assessment with no documented progression
3. Date of last progression assessment with documented nonprogression before the missed visits
4. Date of last progression assessment with documented nonprogression before start of new treatment
5. Date of First Occurrence of BOR with CR or PR
   Date of DOR Start
6. Date of DOR End

Dates Independent of Tumor Assessments (DITA)– From ADSL

1. Date of the first anticancer therapy (**NEWCTDT**)
2. Date of Randomization or the first treatment date (**RANDDT** or **TRTSDT**)
3. Date of Last Exposure to Treatment (**TRTEDT**)
4. Date of Analysis Cut-off (**CUTOFFDT**)
5. Date of death if the patient died (**DTHDT**)
6. Date Last Known Alive (**LSTALVDT**)
7. Date Lost to Follow-up (**LOSTFUDT**)
8. End of Study Date (**EOSDT**)

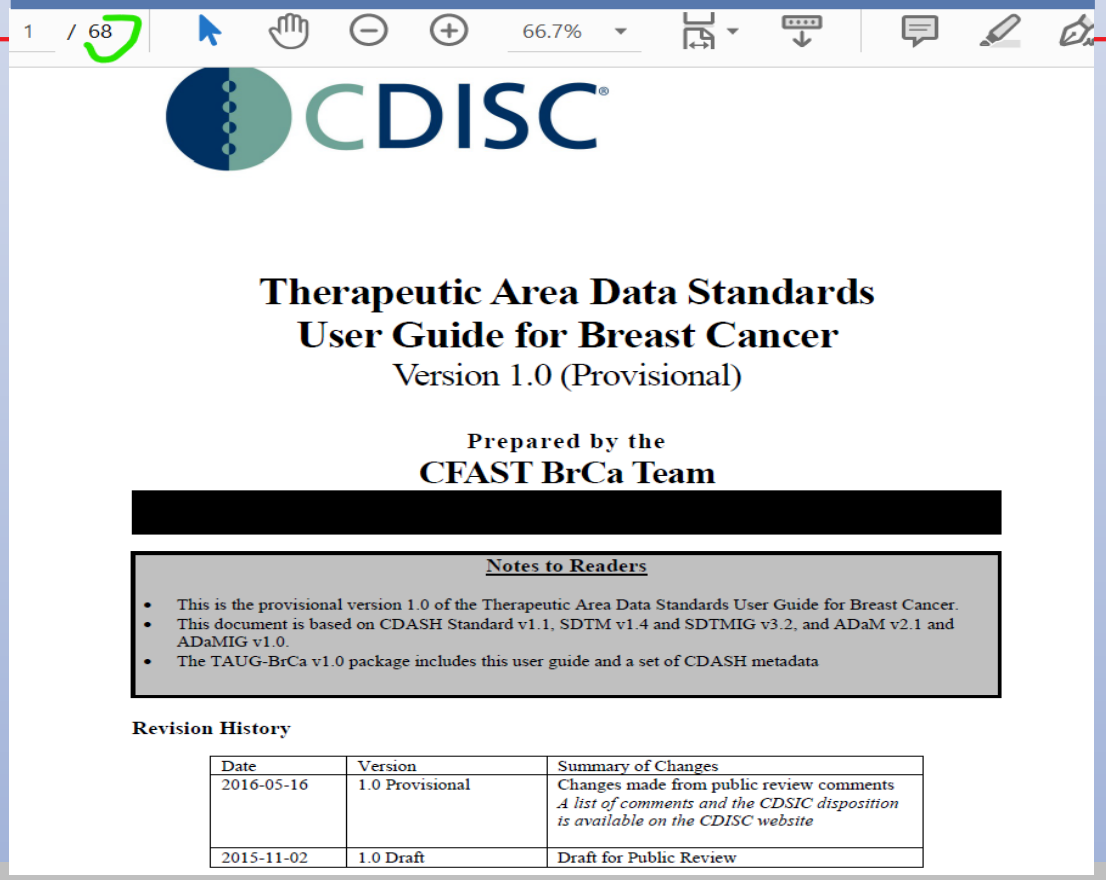
Rationale of Separating the Derivation of Dates Related to Tumor Assessments (DRTA) and Dates of Independent of Tumor Assessments (DITA)

- The Derivation for DRTA from SDTM.RS Domain Is Much More Complex than Ones of DITA, Which Is Very Similar to ADSL Programming for Demographic Variables!
- There Is Less Interdependence among DITA. However, the Programming for the Derivation of DRTA Depends on the "***Hierarchy Orders***".
- Best Programming Practice if Two Different Programming Tasks Can Be Segregated: Development of SAS Codes and Writing Specification, the Validation, and Maintenance and Updates of SAS Programming.

Introduction to CDISC Breast Cancer Therapeutic Area User Guide (TAUG-BrCa) and Prostate Cancer Therapeutic Area User Guide (TAUG-PrCa)-I

TAUG-BrCa, Published in 2016-05-16

With 68 Pages



CDISC

Therapeutic Area Data Standards User Guide for Breast Cancer

Version 1.0 (Provisional)

Prepared by the

CFAST BrCa Team

[redacted]

Notes to Readers

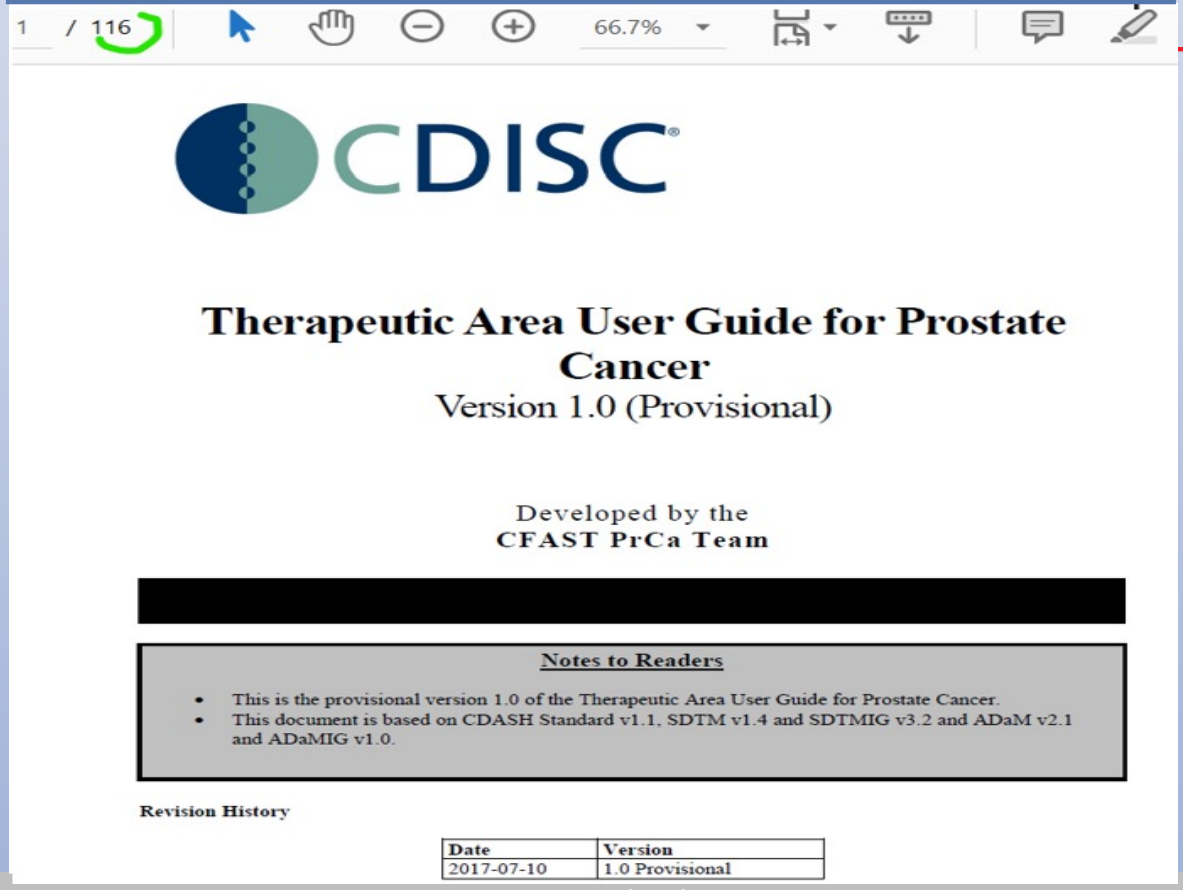
- This is the provisional version 1.0 of the Therapeutic Area Data Standards User Guide for Breast Cancer.
- This document is based on CDASH Standard v1.1, SDTM v1.4 and SDTMIG v3.2, and ADaM v2.1 and ADaMIG v1.0.
- The TAUG-BrCa v1.0 package includes this user guide and a set of CDASH metadata

Revision History

Date	Version	Summary of Changes
2016-05-16	1.0 Provisional	Changes made from public review comments *A list of comments and the CDSIC disposition is available on the CDISC website*
2015-11-02	1.0 Draft	Draft for Public Review

TAUG-PrCa, Published in 2017-07-10

With 116 Pages



CDISC

Therapeutic Area User Guide for Prostate Cancer

Version 1.0 (Provisional)

Developed by the

CFAST PrCa Team

[redacted]

Notes to Readers

- This is the provisional version 1.0 of the Therapeutic Area User Guide for Prostate Cancer.
- This document is based on CDASH Standard v1.1, SDTM v1.4 and SDTMIG v3.2 and ADaM v2.1 and ADaMIG v1.0.

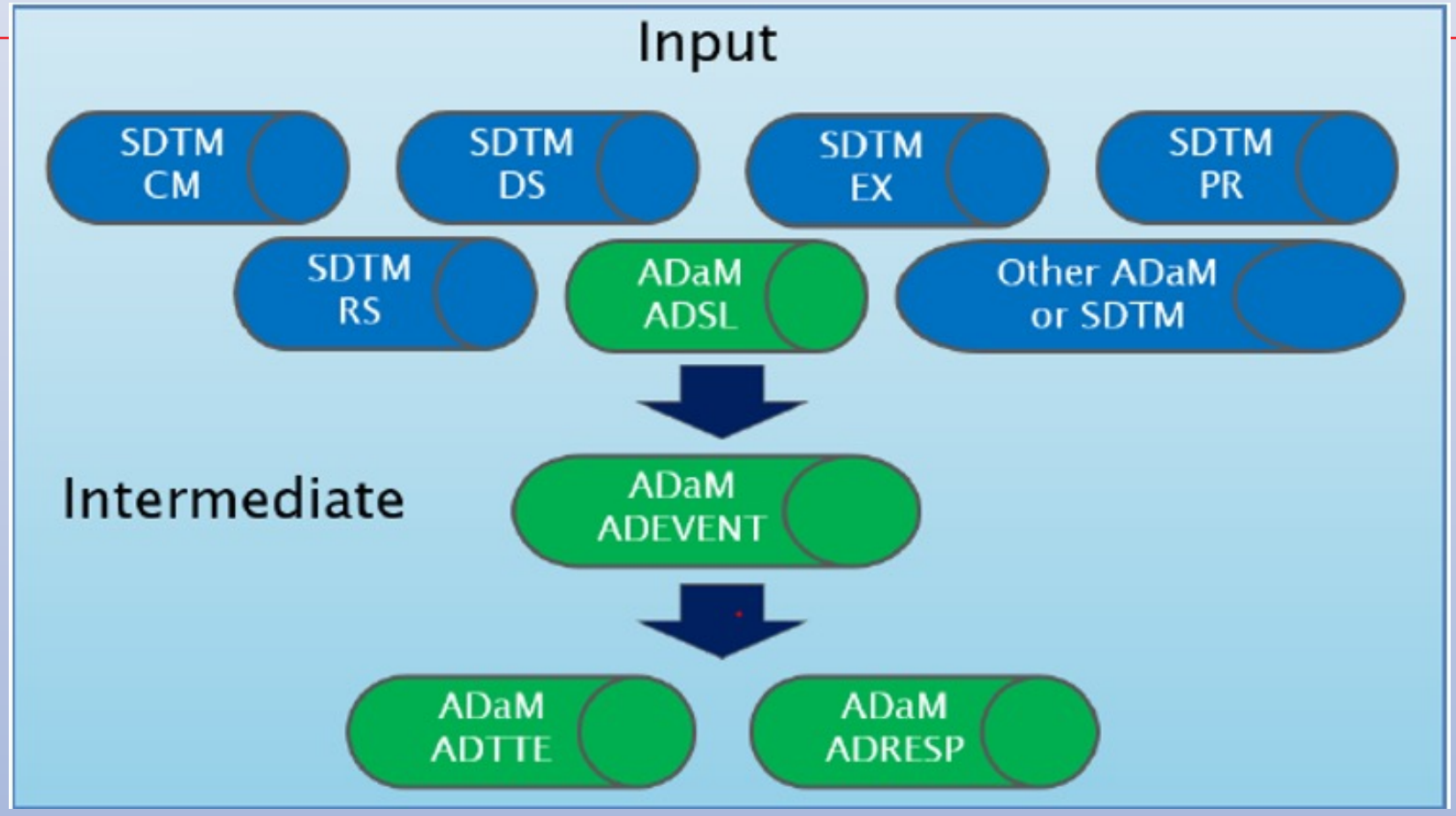
Revision History

Date	Version
2017-07-10	1.0 Provisional

Introduction to CDISC Breast Cancer Therapeutic Area User Guide (TAUG-BrCa) and Prostate Cancer Therapeutic Area User Guide (TAUG-PrCa)-II

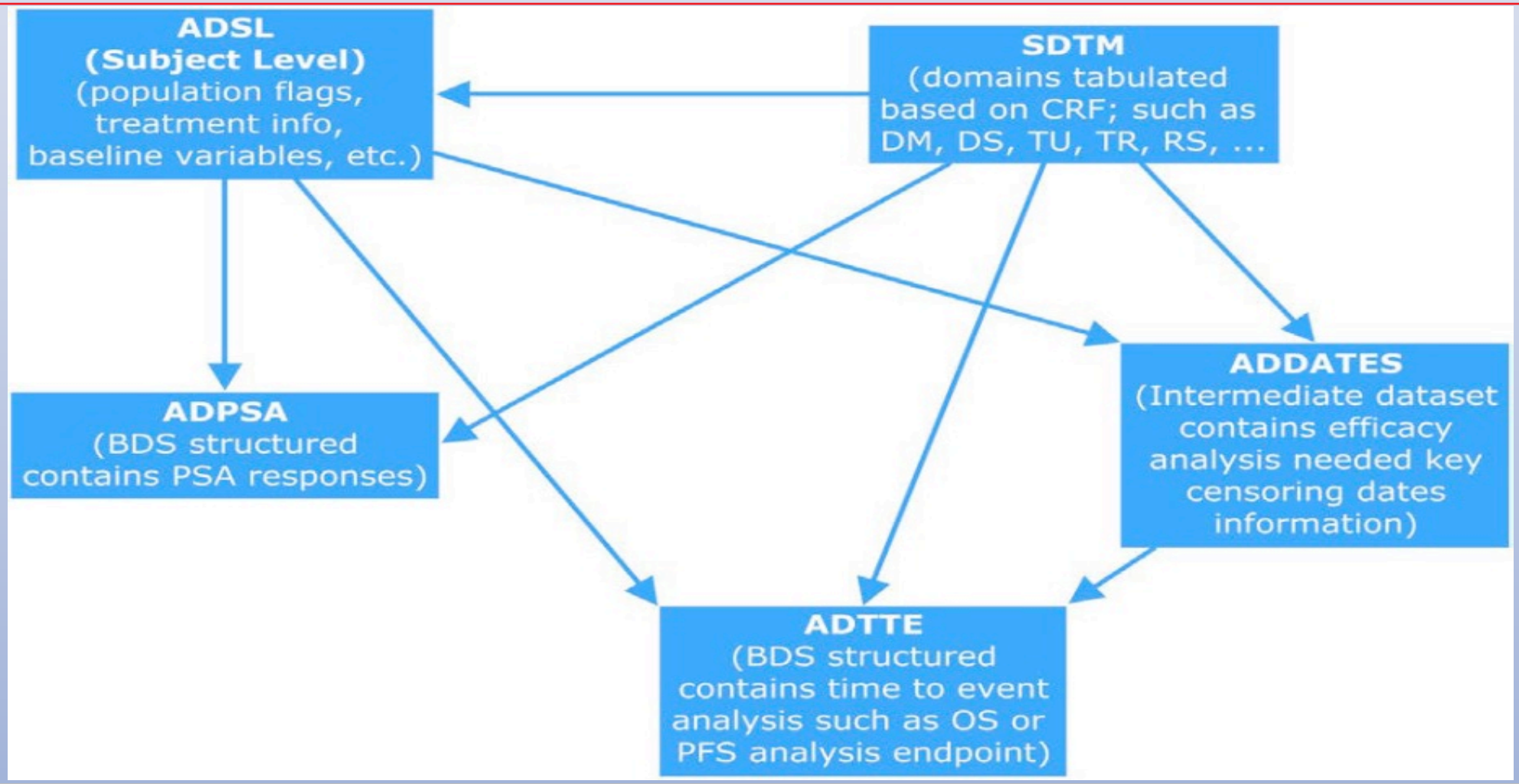
- Describe How to Use CDISC Standards to Represent Data Pertaining to Breast Cancer Studies, and Prostate Cancer Studies, Respectively.
- Provide Advice and Examples for Clinical Data Acquisition Standards Harmonization (CDASH), the Study Data Tabulation Model (SDTM), and the Analysis Data Model (ADaM), etc.
- Propose A "BDS-like" Intermediate ADaM Dataset, ADEVENT and ADDATES, Respectively.

Data Flow from Using An Intermediate Dataset ADEVENT of TAUG-BrCa



Wayne Zhong, Richann Watson, Daphne Ewing, and Jasmine Zhang, "More Traceability: Clarity in ADaM Metadata and Beyond", PharmaSUG 2019 in June 2019

Introduction to CDISC Prostate Cancer Therapeutic Area User Guide (TAUG-PrCa)



BDS-like Related Variables from ADEVENT and ADDATES

CDISC BDS Standard Variable	CDISC TAUG-BrCa/ADEVENT	CDISC TAUG-PrCa/ADDATES
PARAMCD	PARAMCD	ADTDESCD (Description of Analysis Date Code)
PARAM	PARAM	ADTDESC (Description of Analysis Date)
PARAMN	NA	NA
ADT	ASTDT (Analysis Start Date)	ADT (Analysis Date)
AVALC	AVALC	NA
ANLXXFL	ANL01FL	NA
SRCDOM	SRCDOM	SRCDOM
SRCVAR	SRCVAR	SRCVAR
SRCSEQ	SRCSEQ	SRCSEQ

- Note: Each Traceability Is Built through the Triplet of SRCDOM, SRCVAR, SRCSEQ Variables!

An Example of ADEVENT from TAUG-BrCa

Row	STUDYID	USUBJID	ASEQ	ASTDT	ASTDY	*PARQUAL*	PARAMCD	AVALC	ANL01FL
1	ABC-123	ABC-123-001	1	2013DEC29	-4	PROTOCOL	DISPOSIT	RANDOMIZED	
2	ABC-123	ABC-123-001	2	2013DEC30	-2	INVESTIGATOR	ASSESS	PD	Y
3	ABC-123	ABC-123-001	3	2013DEC31	-1	CENTRAL	ASSESS	SD	Y
4	ABC-123	ABC-123-001	4	2014JAN01	1	PROTOCOL	DISPOSIT	TREATMENT	Y
5	ABC-123	ABC-123-001	5	2014JAN21	20	INVESTIGATOR	ASSESS	SD	Y
6	ABC-123	ABC-123-001	6	2014JAN22	22	CENTRAL	ASSESS	SD	Y
7	ABC-123	ABC-123-001	7	2014FEB13	44	INVESTIGATOR	ASSESS	PR	Y
8	ABC-123	ABC-123-001	8	2014FEB14	45	CENTRAL	ASSESS	PR	Y
9	ABC-123	ABC-123-001	9	2014MAR06	65	INVESTIGATOR	ASSESS	PR	Y
10	ABC-123	ABC-123-001	10	2014MAR07	66	CENTRAL	ASSESS	PR	Y
11	ABC-123	ABC-123-001	11	2014MAR28	87	INVESTIGATOR	ASSESS	PD	Y
12	ABC-123	ABC-123-001	12	2014MAR29	88	CENTRAL	ASSESS	PD	Y
13	ABC-123	ABC-123-001	13	2014MAR30	89	PROTOCOL	DISPOSIT	TREATMENT	Y
14	ABC-123	ABC-123-001	14	2014MAR31	90	PROTOCOL	EVENT	PROHIB MED	
15	ABC-123	ABC-123-002	1	2013NOV10	-3	PROTOCOL	DISPOSIT	RANDOMIZED	
16	ABC-123	ABC-123-002	2	2013NOV11	-2	INVESTIGATOR	ASSESS	PD	Y
17	ABC-123	ABC-123-002	3	2013NOV12	-1	CENTRAL	ASSESS	PD	Y
18	ABC-123	ABC-123-002	4	2013NOV13	1	PROTOCOL	DISPOSIT	TREATMENT	Y
19	ABC-123	ABC-123-002	5	2013DEC01	19	INVESTIGATOR	ASSESS	SD	Y
20	ABC-123	ABC-123-002	6	2013DEC02	20	CENTRAL	ASSESS	SD	Y
21	ABC-123	ABC-123-002	7	2013DEC14	32	PROTOCOL	EVENT	MED PROCEED	
22	ABC-123	ABC-123-002	8	2013DEC27	45	INVESTIGATOR	ASSESS	PR	
23	ABC-123	ABC-123-002	9	2013DEC28	46	CENTRAL	ASSESS	PR	
24	ABC-123	ABC-123-002	10	2013DEC29	47	PROTOCOL	DISPOSIT	TREATMENT	

An Example of ADDATES from TAUG-PrCa

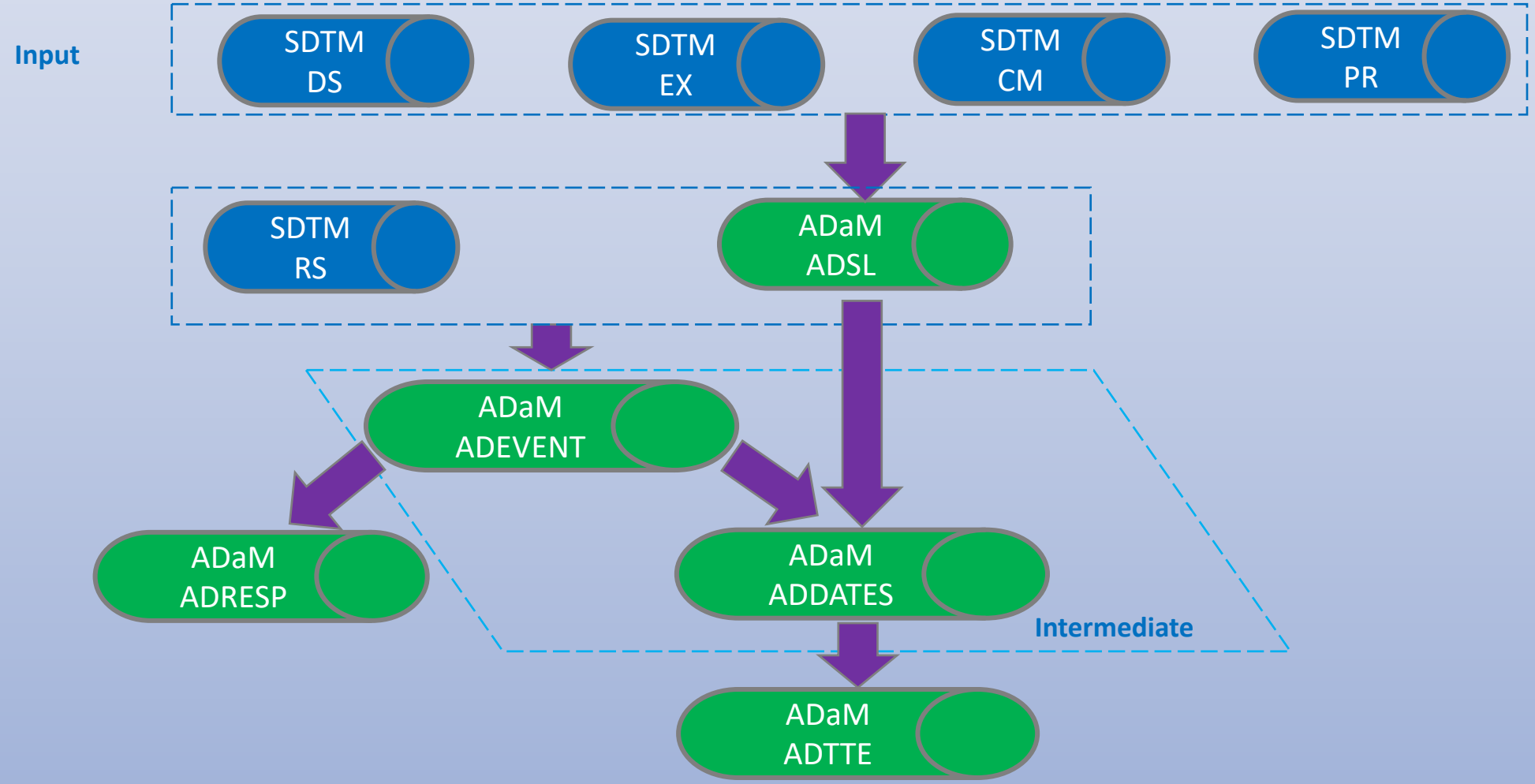
Row	USUBJID	ASEQ	ADT	ADTDESC	ADTDESCD	ADY
1	ABC-123-001	1	03MAR2014	Date of Randomization	RANDDT	1
2	ABC-123-001	2	15OCT2014	Change in Anti-Cancer Therapy	RXCHGDT	227
3	ABC-123-001	3	15SEP2014	Date of Last Tumor Assessment with No PD	LNOPDDT	197
4	ABC-123-001	4	03DEC2014	Date Last Known Alive	LSTALVDT	276
5	ABC-123-001	5	01NOV2014	Date of Analysis Cut-off	CUTOFFDT	244

PROS and CONS of ADVENT & ADDATES from CDISC Standards

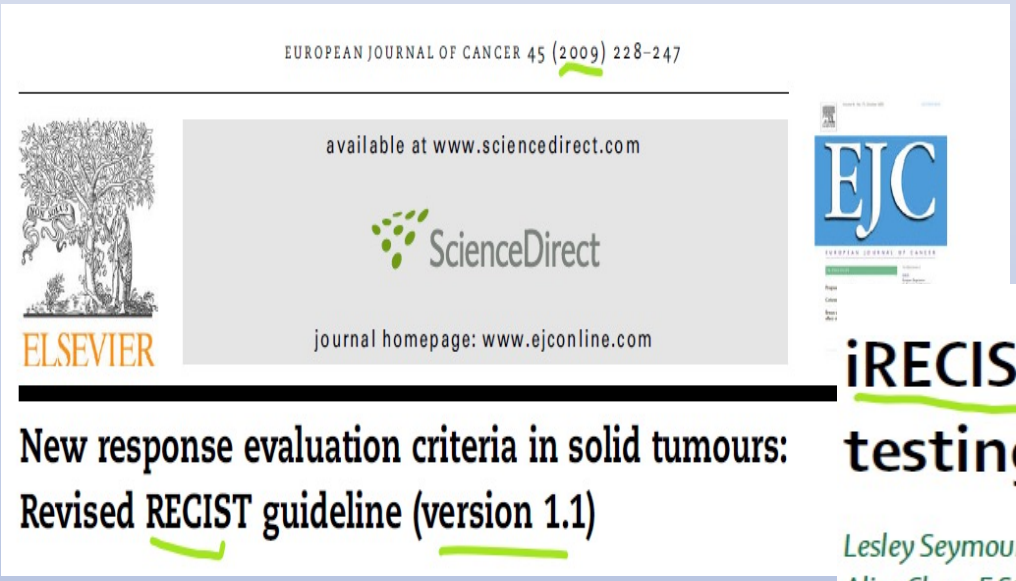
Order	Feature/Benefit	ADEVENT	ADDATES
1	Support ADTTE	Yes	Yes
2	Support BOR and DOR when no confirmation of CR and PR is required	Yes	No
3	Support BOR and DOR when the confirmation of CR and PR is required	No	No
4	Traceability of the Derivation of the Dates of Independent of Tumor Assessments (DITA)	Yes	Yes
5	Traceability of the Derivation of the Dates Related Tumor Assessments (DRTA)	Not Sufficient (RECIST 1.1/ iRECIST)	"Totally Lost" from both the dataset and metadata
6	The meaning of the event (ADEVENT.AVALC)/date (ADDATES.ADTDESCD) can be carried over to the subsequent programming.	AVALC does not store the description of event.	ADTDESC provides the description of ADTDESCD.
7	Sorting Keys to Sort the Data	No	No
8	Best Programming Practice	Does not follow	Does not follow

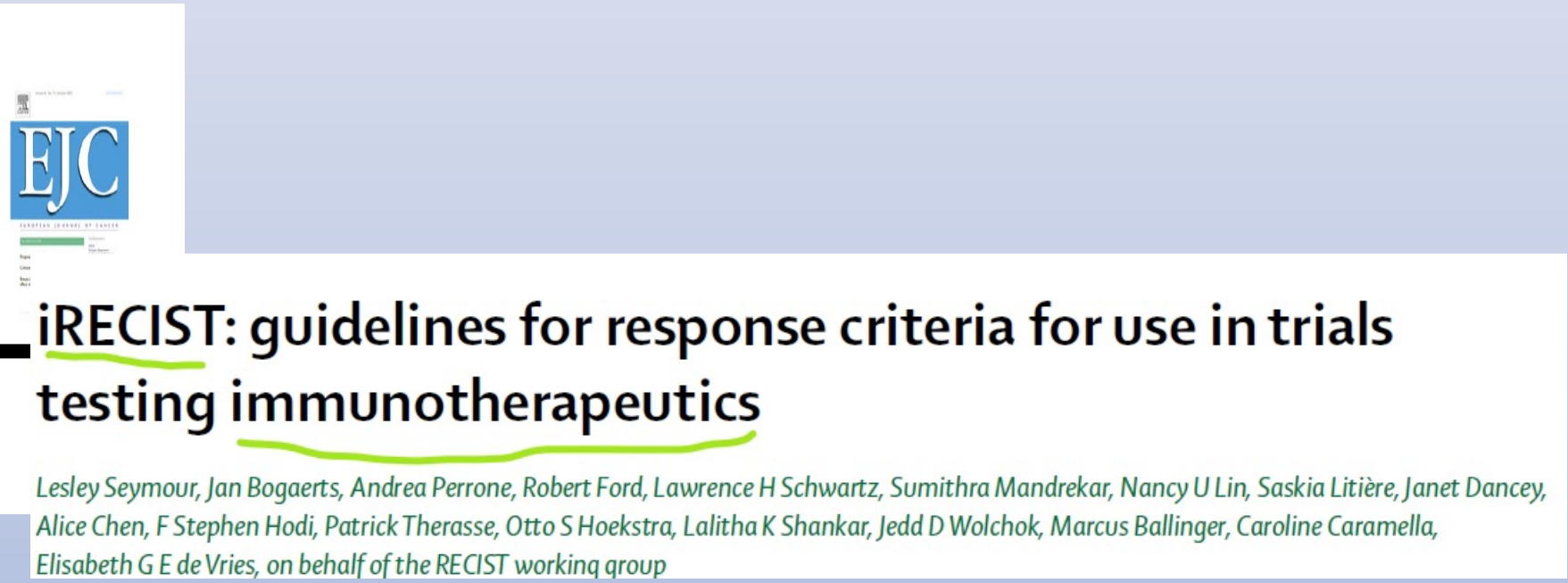
Introduction to Our New Approach

New Approach Flowchart of the Overall Logic and Data Flow



RECIST 1.1 and iRECIST Are Commonly Used in Oncology Studies!





We Will Use RECIST 1.1 in the Following Examples for the Illustration Throughout This Presentation/Paper, Which Is the Most Complex and Challenging Situation for Efficacy ADaM Programming in Oncology Studies.

PharmaSUG 2020 - Paper DV-66

Simplifying the Derivation of Best Overall Response per RECIST 1.1 and iRECIST in Solid Tumor Clinical Studies

Xiangchen (Bob) Cui, and Sri Pavan Vemuri, Alkermes Inc., Waltham, MA

CRISPR THERAPEUTICS

- Per RECIST 1.1, ANL01FL Is Used to Flag the Confirmation of CR and PR!
- If Not Confirmed, A Temporary Variable **TP_BOR** ('Derived Overall Evaluation') Is Used to Store the Possible Values among SD, PD, and NE.

ADaM Standard Variable: ANLxxFL

- In General, Analysis Flags (ANLxxFL) Enhance the Readability of A Data. If These Flags Have Certain Level of ***Interdependency***, They also Provide the Traceability of the Derivation and Its Logic Flow.

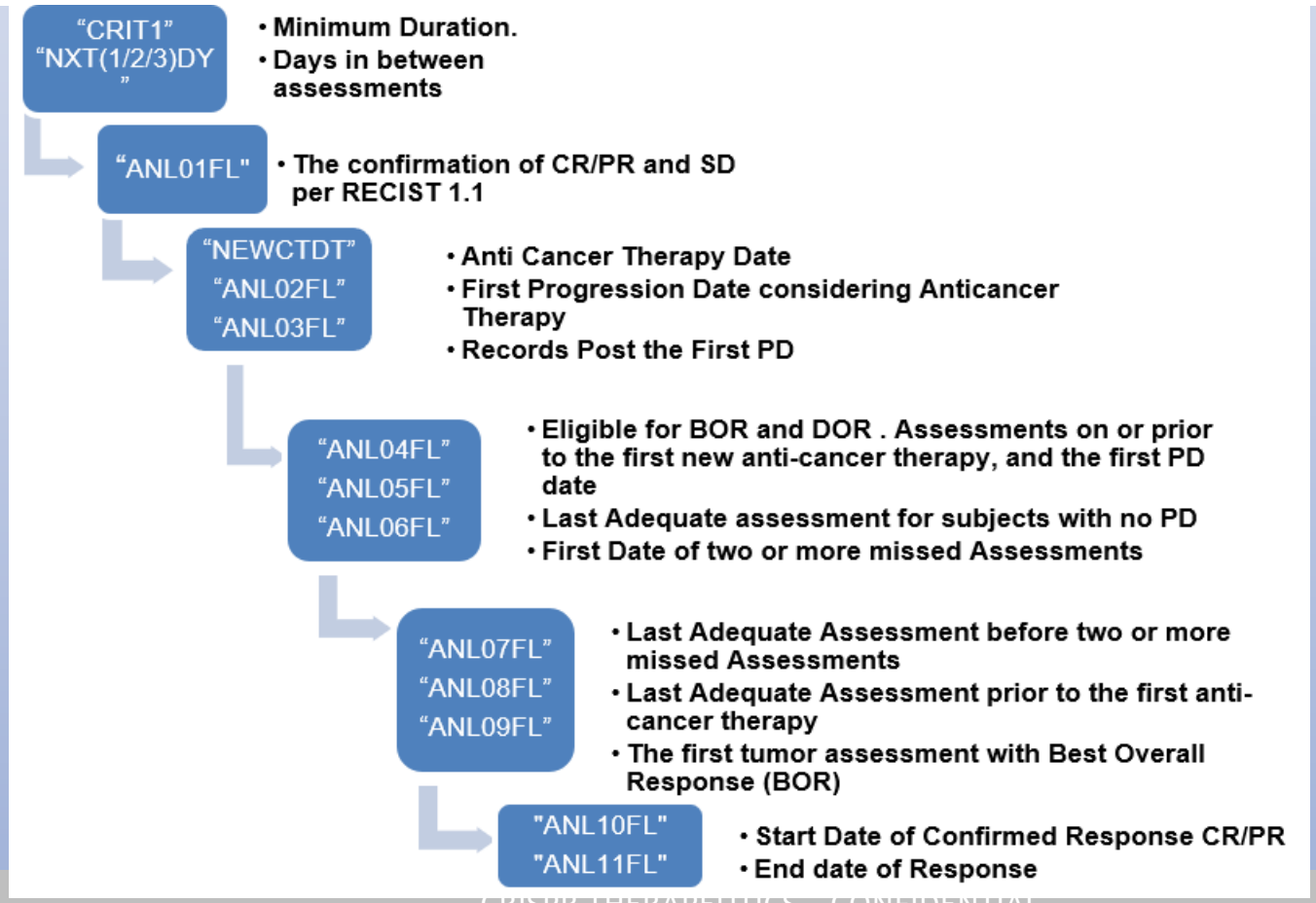
- ***Furthermore***, Ten (10) Analysis Flags (ANL01FL - ANL10FL) and CRIT1/ CRIT1FL Are Derived and Added to the Records of Tumor Assessments to Build ***More Traceability*** of the Derivation of the Dates of Progression or Censoring Related Variables for Time-to-Event Analysis, for Example PFS, as well as BOR/DOR.

Flowchart Depicting the Overall Logic Flow of the Programming Approach for The Best Overall Response (BOR)

PharmaSUG 2020 - Paper DV-66

Simplifying the Derivation of Best Overall Response per RECIST 1.1 and iRECIST in Solid Tumor Clinical Studies

Xiangchen (Bob) Cui, and Sri Pavan Vemuri, Alkermes Inc., Waltham, MA



Introduction to Our ADEVENT

Recall: An Example of ADEVENT from CDISC Breast Cancer Therapeutic Area User Guide (TAUG-BrCa)

PARAMCD in ('DISPOSIT', 'ASSESS', 'EVENT')

Row	STUDYID	USUBJID	ASEQ	ASTDT	ASTDY	*PARQUAL*	PARAMCD	AVALC	ANL01FL
1	ABC-123	ABC-123-001	1	2013DEC29	-4	PROTOCOL	DISPOSIT	RANDOMIZED	
2	ABC-123	ABC-123-001	2	2013DEC30	-2	INVESTIGATOR	ASSESS	PD	Y
3	ABC-123	ABC-123-001	3	2013DEC31	-1	CENTRAL	ASSESS	SD	Y
4	ABC-123	ABC-123-001	4	2014JAN01	1	PROTOCOL	DISPOSIT	TREATMENT	Y
5	ABC-123	ABC-123-001	5	2014JAN21	20	INVESTIGATOR	ASSESS	SD	Y
6	ABC-123	ABC-123-001	6	2014JAN22	22	CENTRAL	ASSESS	SD	Y
7	ABC-123	ABC-123-001	7	2014FEB13	44	INVESTIGATOR	ASSESS	PR	Y
8	ABC-123	ABC-123-001	8	2014FEB14	45	CENTRAL	ASSESS	PR	Y
9	ABC-123	ABC-123-001	9	2014MAR06	65	INVESTIGATOR	ASSESS	PR	Y
10	ABC-123	ABC-123-001	10	2014MAR07	66	CENTRAL	ASSESS	PR	Y
11	ABC-123	ABC-123-001	11	2014MAR28	87	INVESTIGATOR	ASSESS	PD	Y
12	ABC-123	ABC-123-001	12	2014MAR29	88	CENTRAL	ASSESS	PD	Y
13	ABC-123	ABC-123-001	13	2014MAR30	89	PROTOCOL	DISPOSIT	TREATMENT	Y
14	ABC-123	ABC-123-001	14	2014MAR31	90	PROTOCOL	EVENT	PROHIB MED	
15	ABC-123	ABC-123-002	1	2013NOV10	-3	PROTOCOL	DISPOSIT	RANDOMIZED	
16	ABC-123	ABC-123-002	2	2013NOV11	-2	INVESTIGATOR	ASSESS	PD	Y
17	ABC-123	ABC-123-002	3	2013NOV12	-1	CENTRAL	ASSESS	PD	Y
18	ABC-123	ABC-123-002	4	2013NOV13	1	PROTOCOL	DISPOSIT	TREATMENT	Y
19	ABC-123	ABC-123-002	5	2013DEC01	19	INVESTIGATOR	ASSESS	SD	Y
20	ABC-123	ABC-123-002	6	2013DEC02	20	CENTRAL	ASSESS	SD	Y
21	ABC-123	ABC-123-002	7	2013DEC14	32	PROTOCOL	EVENT	MED PROCEED	
22	ABC-123	ABC-123-002	8	2013DEC27	45	INVESTIGATOR	ASSESS	PR	
23	ABC-123	ABC-123-002	9	2013DEC28	46	CENTRAL	ASSESS	PR	
24	ABC-123	ABC-123-002	10	2013DEC29	47	PROTOCOL	DISPOSIT	TREATMENT	

All Possible Values of PARAMCD, PARAM, and PARAMN with One-to-one Mapping from Our ADEVENT Dataset

PARAMCD	PARAM	Comments
OVERALLR	Overall Evaluation	PARAMN=1, original RS records to maintain the traceability of the derivation of TP_BOR and EVENT
TP_BOR	Derived Overall Evaluation	PARAMN=2, Derived One Per RECIST 1.1 or iRECIST
EVENT	Event Date	PARAMN=3. Of Note, SRCDOM='RS', SRCVAR='RSDTC', and SRCSEQ is set to RSSEQ where the respective ANLxxFL has the value of 'Y'.

Two Notes

- Note 1: ADEVENT Only Keeps 'Overall Response' FROM SDTM.RS!

RSTESTCD/Assessment Short Name	RSTEST/Assessment Name
BONMARAS	Bone Marrow Biopsy Assessment
CLINIMPT	Clinical Data Impact
CTRESP	CT/MRI Response
LIVRRESP	Liver Assessment
LPHYSEXM	Lesions by Physical Exam Assessment
LUGRESP	Lugano Overall Response
NEWLPROG	New Lesion Progression
NLPHYSEX	New Lesions by Physical Exam Assessment
NTRGRESP	Non-Target Response
ONSTUTM	On Study Tumor Biopsy/Cytology/Pathology
OVRLRESP	Overall Response
PNLPHYEX	Previous New Lesions by Physical Exam
SPLNRESP	Spleen Assessment
TRGRESP	Target Response

- Note 2: **PARAMCD in ('DISPOSIT', 'ASSESS', 'EVENT') from TAUG-BrCa vs.**

  PARAMCD in ('OVERALLR', 'TP_BOR', 'EVENT') from Our New Approach!

Example 1 of ADEVENT From A Simulated Subject - I

- Tumor Assessments from RS Domain (OVERALLR)

+ Derived Record for BOR (TP_BOR) By Following RECIST 1.1

USUBJID	ASEQ	PARAMN	PARAMCD	PARAM	VISIT	ASTDT	ASTDY	AVALC	CRIT1	CRIT1FL	RSSEQ
simu_097	1	1	OVERALLR	Overall Evaluation	Cycle 2	2018-06-23	69	PR	Meets Minimum Duration (49 Days)	Y	33
simu_097	2	1	OVERALLR	Overall Evaluation	Cycle 4	2018-08-02	109	PR	Meets Minimum Duration (49 Days)	Y	34
simu_097	**2.5** (+0.5)	**2**	**TP_BOR**	**Derived Overall Evaluation**	**Cycle 4**	**2018-08-02**	**109**	**SD**			**34**
simu_097	3	1	OVERALLR	Overall Evaluation	Cycle 6	2018-09-11	149	NE	Meets Minimum Duration (49 Days)	Y	35
simu_097	4	1	OVERALLR	Overall Evaluation	Cycle 8	2018-10-21	189	NE	Meets Minimum Duration (49 Days)	Y	36
simu_097	5	1	OVERALLR	Overall Evaluation	Cycle 10	2018-11-30	229	PD	Meets Minimum Duration (49 Days)	Y	37

PR->NE with CRIT1FL='Y' Downgrade to SD per RECIST 1.1

All Possible Values of AVALC from Our ADEVENT with PARAMCD='EVENT'

ASEQ	PARAMN	PARAMCD	PARAM	AVALC
100	3	EVENT	Event Date	1:PDDT (Date of Documented Progression (PD))
200	3	EVENT	Event Date	2:LANOPDDT (Date of Last Adequate T. Asses. of No PD)
300	3	EVENT	Event Date	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)
400	3	EVENT	Event Date	4:LAPNCTDT (Date Last Tumor Asses. Pri. to New CT)
500	3	EVENT	Event Date	5:BORDT (Date of First Occurrence of BOR)
600	3	EVENT	Event Date	6:DORSTDT (Date of DOR Start)
700	3	EVENT	Event Date	7:DORENDT (Date of DOR End)
800	3	EVENT	Event Date	8:NEWCTDT (First Date of New Anticancer Therapy)

- Each Subject Can Have up to Seven (7) Records, for "1:PDDT (Date of Documented Progression (PD))" and "4:LANOPDDT (Date of Last Adequate T. Asses. of No PD)" Are Exclusive.
- Note: 'First Date of New Anticancer Therapy' Is Added Due to the Fact It Is Needed to Derive Other Variables, Even though It Is Independent of Tumor Assessment.

The Metadata for ASEQ as the Sorting Key for ADEVENT

Variable Name	Variable Label	Type	Source/Derivation/Comment
RSSEQ	Sequence Number	integer	RS.RSSEQ
ASEQ	Analysis Sequence Number	integer	Derived: For the records with PARAMCD = 'OVERALLR', Sort by STUDYID, USUBJID, ASTDT, and PARAMCD then assign value. Start at 1 for each subject. No duplicates allowed within a subject; For the records with PARAMCD = 'TP_BOR', increment ASEQ by 0.5; For the records with PARAMCD ='EVENT', ASEQ=100*input(scan(AVALC,1,':'), 1.). Note: For the records with PARAMCD = 'OVERALLR', ASEQ ranges from 1 to the largest number of tumor assessments; For the records with PARAMCD = 'TP_BOR', ASEQ ranges from 1.5 to the largest number of tumor assessments+0.5; For the records with PARAMCD ='EVENT', ASEQ ranges from 100 to 800.

Define Ten (10) Analysis Flags (ANL01FL - ANL10FL) and CRIT1/ CRIT1FL – I

Note: Hierarchy Orders and Interdependency

Variable Name	Derivation/Comments
CRIT1FL	CRIT1FL= 'Y' if RSDTC-TRTSDT +1 >= 49
CRIT1	For adequate assessment of SD, CRIT1='Meets Minimum Duration (49 Days)' if CRIT1FL= 'Y'
ANL01FL	ANL01FL='Y', if CR/PR was confirmed or SD met minimum duration (CRIT1FL= 'Y') Note: For the records with PD or NE, ANL01FL is set to 'Y' to facilitate the derivation and its programming. Of note, the derivation does not consider the anti-cancer therapy.
ANL02FL	ANL02FL='Y', if the record was the first progression disease (PD) assessment, on or prior to the first anti-cancer therapy for the derivation of BOR and DOR per RECIST 1.1
ANL03FL	ANL03FL='Y' if the record posted the first PD record
ANL04FL	ANL04FL='Y', if tumor assessments "eligible" for the derivation of BOR and DOR, which satisfied the conditions: on or prior to the first new anti-cancer therapy and the first PD date for RECIST 1.1
ANL05FL	ANL05FL='Y', if the record with ANL04FL='Y' was the last adequate tumor assessment (CR, PR, SD) for no PD subjects, and it was used for the derivation of DOR and PFS

Define Ten (10) Analysis Flags (ANL01FL - ANL10FL) and CRIT1/ CRIT1FL – II

Note: Hierarchy Orders and Interdependency

Variable Name	Derivation/Comments
ANL06FL	ANL06FL='Y', if the record with ANL04FL='Y' was the last adequate tumor assessment (CR, PR, SD) prior to the first record of more than one missed visit prior to the first PD
ANL07FL	ANL07FL='Y', if the record with ANL04FL='Y' was last adequate tumor assessment (CR, PR, SD) prior to the first new anti-cancer therapy, and prior to the first PD. It is for primary analysis of PFS.
ANL08FL	ANL08FL='Y', if the record with ANL04FL='Y' was the first tumor assessment with Best Overall Response
ANL09FL	ANL09FL='Y', if the record with ANL04FL='Y' was the start date of response of the subjects whose Best Overall Response was either CR or PR
ANL10FL	ANL10FL='Y', if the record with ANL04FL='Y' was the end date of response of the subjects whose Best Overall Response was either CR or PR.

One-to-one Relationship between Each Flag among ANL02FL, ANL05FL - ANL10FL and Its Respective Event (Date), i.e., ANLxxFL and AVALC for PARAMCD='EVENT'

- A "Bidirectional" Relationship Between ANLxxFL and AVALC for ADEVENT.PARAMCD='EVENT'
- One Can Easily Use Its Respective ANLxxFL to Locate the Record, Where the Event Occurred Per the One-to-one Relationship.

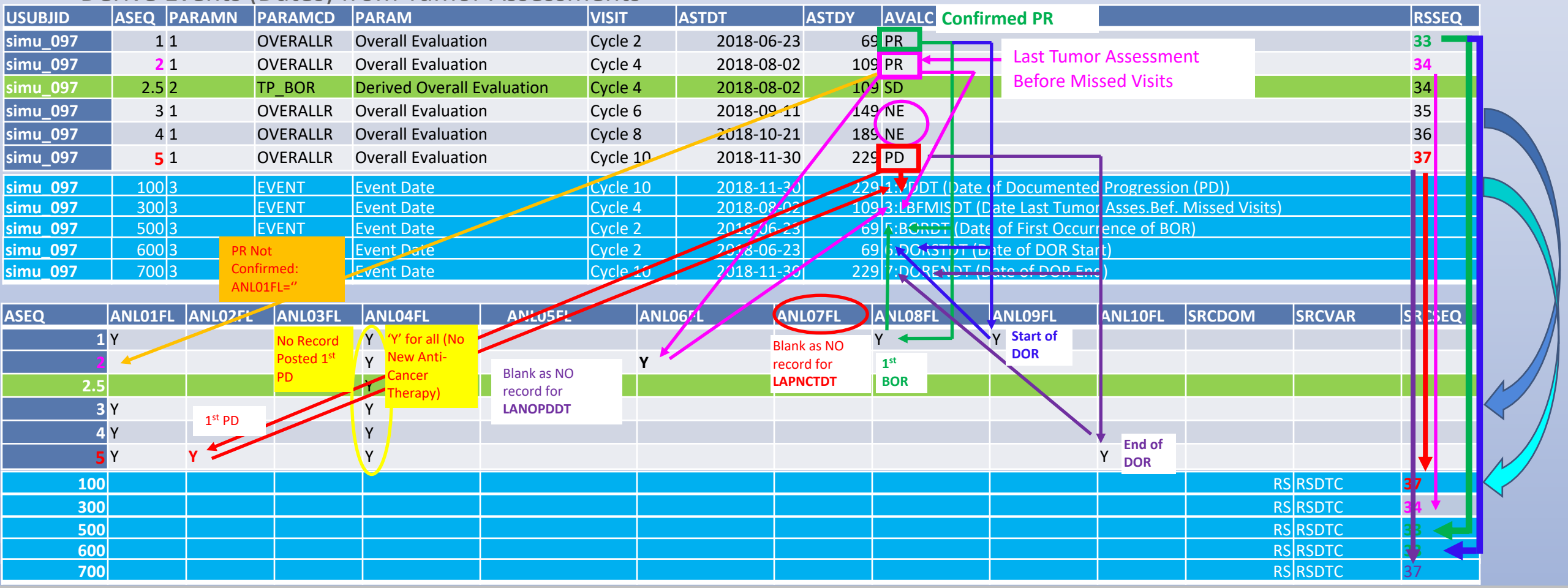
ADEVENT Flags	ADEVENT.AVALC
ANL02FL	1:PDDT (Date of Documented Progression (PD))
ANL05FL	2:LANOPDDT (Date of Last Adequate T. Asses. of No PD)
ANL06FL	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)
ANL07FL	4:LAPNCTDT (Date Last Tumor Asses. Pri. to New CT)
ANL08FL	5:BORDT (Date of First Occurrence of BOR)
ANL09FL	6:DORSTDT (Date of DOR Start)
ANL10FL	7:DORENDT (Date of DOR End)

Example 1 of ADEVENT From A Simulated Subject - II

- Derive Events (Dates) from Tumor Assessments

USUBJID	ASEQ	PARAMN	PARAMCD	PARAM	VISIT	ASTDT	ASTDY	AVALC	RSSEQ
simu_097	1	1	OVERALLR	Overall Evaluation	Cycle 2	2018-06-23	69	PR	33
simu_097	2	1	OVERALLR	Overall Evaluation	Cycle 4	2018-08-02	109	PR	34
simu_097	2.5	2	TP_BOR	Derived Overall Evaluation	Cycle 4	2018-08-02	109	SD	34
simu_097	3	1	OVERALLR	Overall Evaluation	Cycle 6	2018-09-11	149	NE	35
simu_097	4	1	OVERALLR	Overall Evaluation	Cycle 8	2018-10-21	189	NE	36
simu_097	5	1	OVERALLR	Overall Evaluation	Cycle 10	2018-11-30	229	PD	37
simu_097	100	3	EVENT	Event Date	Cycle 10	2018-11-30	229	1:PDDT (Date of Documented Progression (PD))	
simu_097	300	3	EVENT	Event Date	Cycle 4	2018-08-02	109	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)	
simu_097	500	3	EVENT	Event Date	Cycle 2	2018-06-23	69	5:BORDT (Date of First Occurrence of BOR)	
simu_097	600	3	EVENT	Event Date	Cycle 2	2018-06-23	69	6:DORSTDT (Date of DOR Start)	
simu_097	700	3	EVENT	Event Date	Cycle 10	2018-11-30	229	7:DORENDT (Date of DOR End)	

ASEQ	ANL01FL	ANL02FL	ANL03FL	ANL04FL	ANL05FL	ANL06FL	ANL07FL	ANL08FL	ANL09FL	ANL10FL	SRCDOM	SRCVAR	SRCSEQ
1	Y			Y				Y	Y				
2				Y		Y							
2.5				Y									
3	Y			Y									
4	Y			Y									
5	Y	Y		Y						Y			
100											RS	RSDTC	37
300											RS	RSDTC	34
500											RS	RSDTC	33
600											RS	RSDTC	36
700											RS	RSDTC	37



Comparison of ANLxxFL with the Triplet of SRCDOM, SRCVAR, and SRCSEQ regarding the Traceability of the Events (Dates) in ADEVENT - I

- By Using the SRCSEQ of the Triplet, One Has to Search Each Record Starting from the First Record until the Target Sequentially, the Worst-case Scenario: Going through All the Values of RSSEQ until the Last Record!

- One Can Quickly and Directly Find the Unique 'Y' of Its Corresponding ANLxxFL among ANL02FL, ANL05FL - ANL10FL in RS Block. This Unique 'Y' Is Used as A "***Pointer***" to Pinpoint the Event (Record) Per One-to-one Relationship of ANLxxFL and AVALC!

- ANLxxFL Has A Hierarchy Order and Interdependency, Which ***Provide the Details re the Conditions and Logics of the Derivation in a Logical Order***, While SRCSEQ of the Triplet Does Not!

Comparison of ANLxxFL with the Triplet of SRCDOM, SRCVAR, and SRCSEQ regarding the Traceability of the Events (Dates) in ADEVENT - II

- Hence, ANLxxFL Provide More Traceability of the Derivation of Events (Dates) regarding the Complicated Rules Discussed above, for Example, RECIST 1.1/iRECIST, Compared to the Triplet.
- Both Can Be Used to Trace Back The Original RS Record, Where the Event Occurred.
- ANL08FLs Will Be Used to Subsequent Programming for ADRESP.SAS!
- ***Superior of ANLxxFL to the Triplet of SRCDOM, SRCVAR, and SRCSEQ?***

Next Step for ADRESP for **Categorical Analysis of Tumor Response ---- Skip! Please refer to the paper!**

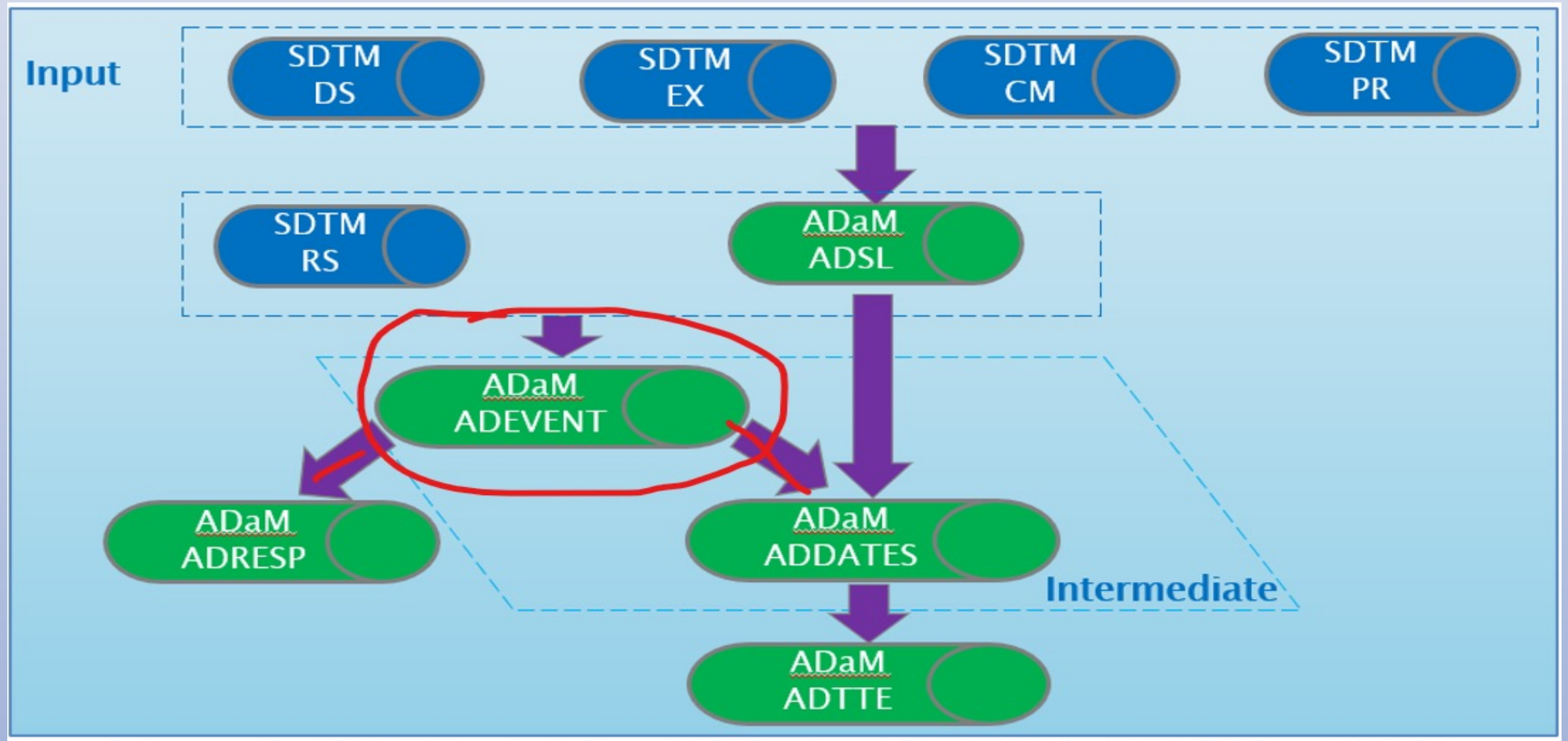


Figure 1. Leveraging CDSIC Standards from ADEVNET and ADDATES for ADRERSP and ADTTE

Next Step for ADDATES

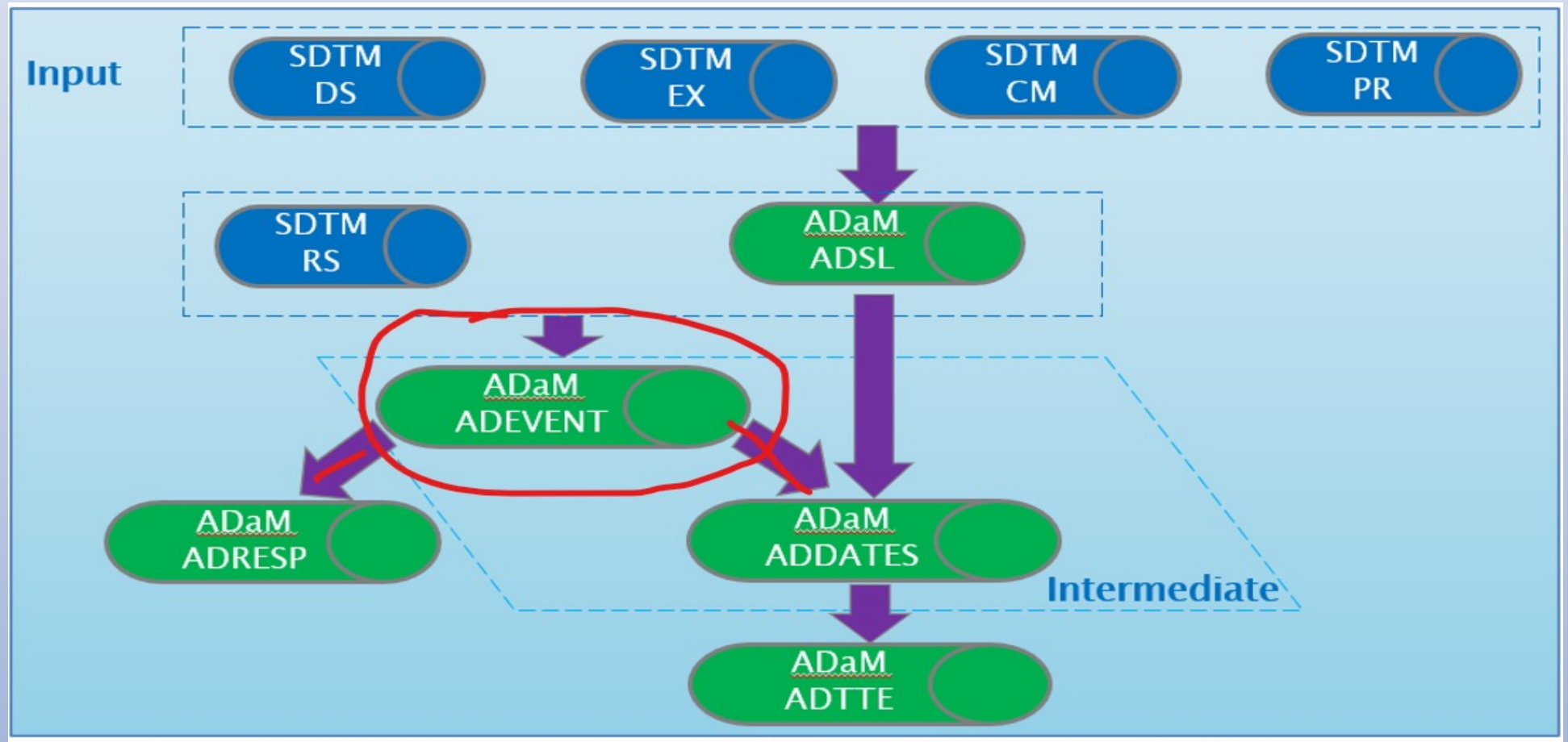


Figure 1. Leveraging CDSIC Standards from ADEVNET and ADDATES for ADRERSP and ADTTE

Dates of Events for ADDATES/Time-to-Event Analysis

Dates Related to Tumor Assessment – From ADEVENT

1. The first date of progressive disease (**PDDT**)
2. Date of last progression assessment with no documented progression (**LANOPDDT**)
3. Date of last progression assessment with documented nonprogression before the missed visits (**LBFMISDT**)
4. Date of last progression assessment with documented nonprogression before start of new treatment (**LAPNCTDT**)
5. Date of First Occurrence of BOR with CR or PR (**BORDT**)
6. Date of DOR Start (**DORSTDT**)
7. Date of DOR End (**DORENDT**)

Dates Independent of Tumor Assessments – From ADSL

1. Date of the first anticancer therapy (**NEWCTDT**)
2. Date of Randomization or the first treatment date (**RANDDT** or **TRTSDT**)
3. Date of Last Exposure to Treatment (**TRTEDT**)
4. Date of Analysis Cut-off (**CUTOFFDT**)
5. Date of death if the patient died (**DTHDT**)
6. Date Last Known Alive (**LSTALVDT**)
7. Date Lost to Follow-up (**LOSTFUDT**)
8. End of Study Date (**EOSDT**)

A New Variable: ADTDESCN Is Added to ADDATES!

It helps the sorting of ADDATES dataset. It plays the same role as BDS.PARAMN for PARAMCD and PARAM.

Variable Name	Variable Label	Type	Codelist/Controlled Terms	Source/Derivation/Comment
ADTDESCN	Description of Analysis Date (N)	integer	ADTDESCN (ADTDESC): (1) 1=Date of Documented Progression (PD) (2) 2=Date of Last Adequate T. Asses. of No PD (3) 3= Date Last Tumor Asses.Bef. Missed Visits (4) 4=Date Last Tumor Asses. Pri. to New CT (5) 5=Date of First Occurrence of BOR (6) 6=Date of DOR Start (7) 7=Date of DOR End (8) 8=New Anticancer Therapy Start Date (9) 9=Date of Randomization (10) 10=Date of First Exposure to Treatment (11) 11= Date of Last Exposure to Treatment (12) 12=Date of Analysis Cut-off (13) 13=Date of Death (14) 14=Date Last Known Alive (15) 15=Date Lost to Follow-up (16) 16=End of Study Date	Assigned: 1, if ADTDESC='Date of Documented Progression (PD)'; 2, if ADTDESC='Date of Last Adequate T. Asses. of No PD'; 3, if ADTDESC='Date Last Tumor Asses.Bef. Missed Visits'; 4, ADTDESC='Date Last Tumor Asses. Pri. to New CT'; 5, if ADTDESC='Date of First Occurrence of BOR'; 6, if ADTDESC='Date of DOR Start'; 7, if ADTDESC='Date of DOR End'; 8, if ADTDESC='New Anticancer Therapy Start Date'; 9, if ADTDESC='Date of Randomization'; 10, if ADTDESC='Date of First Exposure to Treatment'; 11, if ADTDESC='Date of Last Exposure to Treatment'; 12, if ADTDESC='Date of Analysis Cut-off'; 13, if ADTDESC='Date of Death'; 14, if ADTDESC='Date Last Known Alive'; 15, if ADTDESC='Date Lost to Follow-up'; 16, if ADTDESC= End of Study Date'

Recall All Possible Values of AVALC from ADEVENT with PARAMCD='EVENT'

ASEQ	PARAMN	PARAMCD	PARAM	AVALC
100	3	EVENT	Event Date	1:PDDT (Date of Documented Progression (PD))
200	3	EVENT	Event Date	2:LANOPDDT (Date of Last Adequate T. Asses. of No PD)
300	3	EVENT	Event Date	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)
400	3	EVENT	Event Date	4:LAPNCTDT (Date Last Tumor Asses. Pri. to New CT)
500	3	EVENT	Event Date	5:BORDT (Date of First Occurrence of BOR)
600	3	EVENT	Event Date	6:DORSTDT (Date of DOR Start)
700	3	EVENT	Event Date	7:DORENDT (Date of DOR End)
800	3	EVENT	Event Date	8:NEWCTDT (First Date of New Anticancer Therapy)

- Retrieve the number for ADTDESCN from AVALC's 'First Letter' with the Value: from 1 to 8, the Middle for ADTDESCD, the Part from Parenthesis for ADTDESC!
- Note: It Is Another Rationale to Build AVALC, In addition to the Sorting of ADEVENT, except for ASEQ.

The Snip of SAS codes in ADDATES.sas to Retrieve ADTDESCN, ADTDESCD and ADTDESC from ADEVENT.AVALC and Derive ADT directly from ADEVENT.ASTDT are shown below.

```
** Dates Related Tumor Assessment from ADEVENT where paramcd='EVENT';
data tu_events(rename=(astdt=adt astdy=ady));
     length adtdesc tmp $70. adtdescd $8. srcvar $12.;
     set adevent(drop=srcvar where=(paramcd='EVENT'));
     adtdescn=input(scan(avalc,1,':'),best.);
     tmp=translate(avalc,'',':');
     adtdescd=scan(tmp,2,'');
     len=length(strip(avalc));len1=length(strip(adtdescd))+5;len2=len-len1;
     adtdesc=substr(avalc,len1,len2);
     srcdom='ADEVENT';srcvar='AVALC$ASTDT';srcseq=aseq;
     keep usubjid avalc adtdescd adtdesc astdt astdy trtsdt adtdescn srcdom
          srcvar srcseq aseq;
run;
```

Source of ADDATES Variables from ADEVENT and ADSL

Variables in ADDATES	Dates (ASTDT) from ADEVENT	Dates (XXDT) from ADSL: TRTDT As An Example
ADTDESCN	input(scan(AVALC,1,':'),best.);	10
ADTDESCD	scan(translate(AVALC,'',':'),2,'');	TRTSDT
ADTDESC	substr(AVALC,len1,len2);	Date of First Exposure to Treatment
ADT	ASTDT	TRTSDT
SRCDOM	ADEVENT	ADSL
SRCVAR	AVALC$ASTDT	TRTSDT
SRCSEQ	ASEQ	1

Tabulation of ADTDESCN, ADTDESCD and ADTDESC from ADDATES: One-to-one Mapping!

Tabulation of ADTDESCN, ADTDESCD and ADTDESC from ADEVENT

ADTDESCN (Description of Analysis Date (N))	ADTDESCD (Description of Analysis Date Code)	ADTDESC (Description of Analysis Date)
1	PDDT	Date of Documented Progression (PD)
2	LANOPDDT	Date of Last Adequate T. Asses. of No PD
3	LBFMISDT	Date Last Tumor Asses.Bef. Missed Visits
4	LAPNCTDT	Date Last Tumor Asses. Pri. to. New CT
5	BORDT	Date of First Occurrence of BOR
6	DORSTDT	Date of DOR Start
7	DORENDT	Date of DOR End
8	NEWCTDT	First Date of New Anticancer Therapy

Tabulation of ADTDESCN, ADTDESCD and ADTDESC for Other Dates of Independent of Tumor Assessments (ADSL)

ADTDESCN (Description of Analysis Date (N))	ADTDESCD (Description of Analysis Date Code)	ADTDESC (Description of Analysis Date)
9	RANDDT	Date of Randomization
10	TRTSDT	Date of First Exposure to Treatment
11	TRTEDT	Date of Last Exposure to Treatment
12	CUTOFFDT	Date of Analysis Cut-off
13	DTHDT	Date of Death
14	LSTALVDT	Date Last Known Alive
15	LOSTFUDT	Date Lost to Follow-up
16	EOSDT	End of Study Date

An Example of ADDATES from Example 1:

Highlighted in Green from ADEVENT, Others from ADSL Note: "the Vertical Structure of a BDS Dataset"

USUBJID	ASEQ	ADTDESCN	ADTDESCD	ADTDESC	ADT	ADY	SRCDOM	SRCVAR	SRCSEQ
simu_097	1	1	PDDT	Date of Documented Progression (PD)	2018-11-30	229	ADEVENT	AVALC$ASTDT	100
simu_097	2	3	LBFMISDT	Date Last Tumor Asses.Bef. Missed Visits	2018-08-02	109	ADEVENT	AVALC$ASTDT	300
simu_097	3	5	BORDT	Date of First Occurrence of BOR	2018-06-23	69	ADEVENT	AVALC$ASTDT	500
simu_097	4	6	DORSTDT	Date of DOR Start	2018-06-23	69	ADEVENT	AVALC$ASTDT	600
simu_097	5	7	DORENDT	Date of DOR End	2018-11-30	229	ADEVENT	AVALC$ASTDT	700
simu_097	6	9	RANDDT	Date of Randomization	2018-04-16	1	ADSL	RANDDT	1
simu_097	7	10	TRTSDT	Date of First Exposure to Treatment	2018-04-16	1	ADSL	TRTSDT	1
simu_097	8	11	TRTEDT	Date of Last Exposure to Treatment	2018-12-18	247	ADSL	TRTEDT	1
simu_097	9	12	CUTOFFDT	Date of Analysis Cut-off	2020-03-31	716	ADSL	CUTOFFDT	1
simu_097	10	14	LSTALVDT	Date Last Known Alive	2020-02-07	663	ADSL	LSTALVDT	1
simu_097	11	15	LOSTFUDT	Date Lost to Follow-up	2019-03-04	323	ADSL	EOSDT	1
simu_097	12	16	EOSDT	End of Study Date	2019-03-04	323	ADSL	EOSDT	1

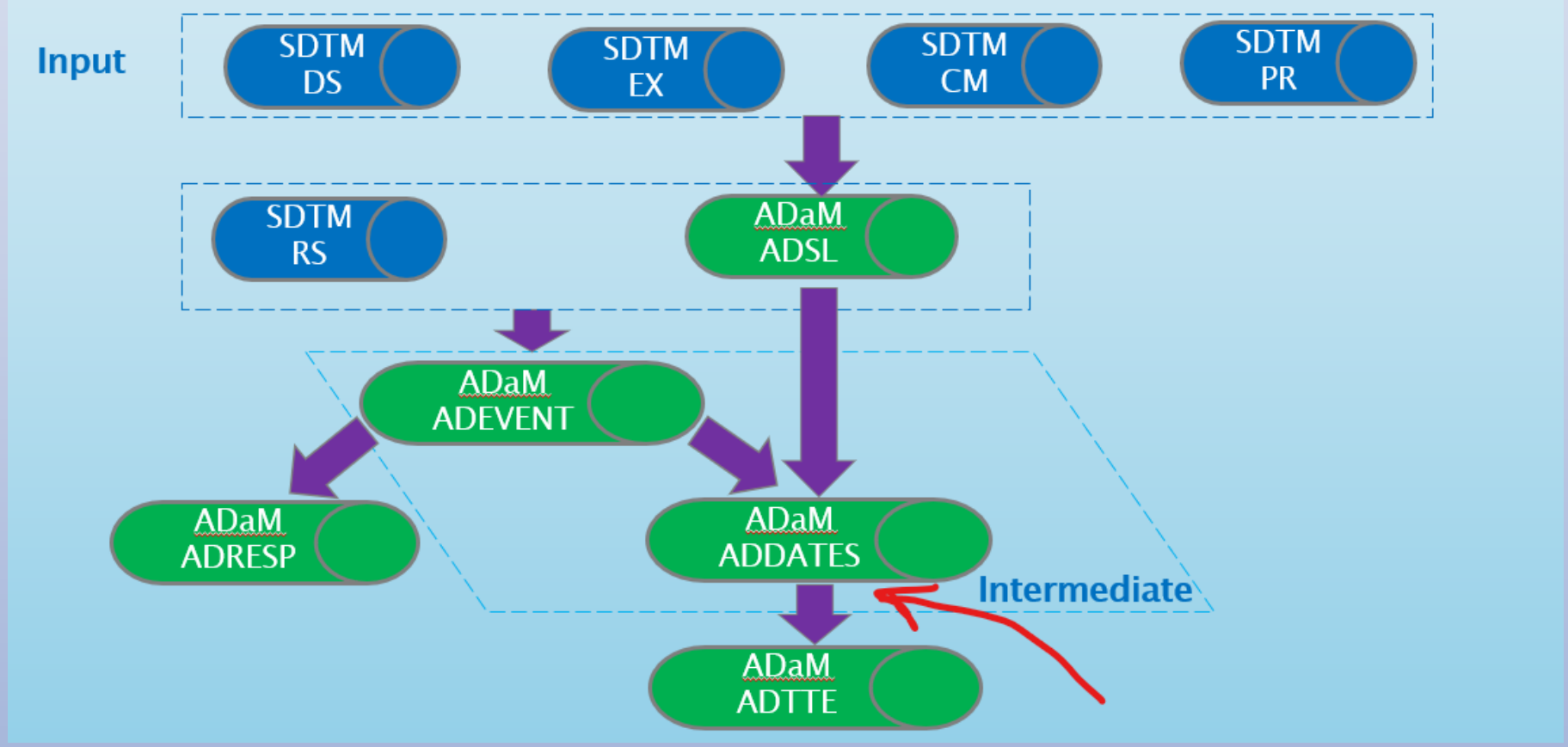
The Traceability in ADDATES Is Built by the Triplet of SRCDOM, SRCVAR, and SRCSEQ.

Triplet of SRCDOM, SRCVAR, and SRCSEQ in ADDATES	Dates from ADEVENT	Dates (XXDT) from ADSL: TRTSDT As An Example
SRCDOM	ADEVENT	ADSL
SRCVAR	AVALC$ASTDT	TRTSDT
SRCSEQ	ASEQ	1

Comparison of BDS-like PARAMCD, PARAM, and PARAMN

CDISC BDS Standard Variable	ADEVENT		ADDATES	
	CDISC TAUG-BrCa	Our New Approach	CDISC TAUG-PrCa	Our New Approach
PARAMCD	PARAMCD	PARAMCD	ADTDESCD	ADTDESCD
PARAM	PARAM	PARAM	ADTDESC	ADTDESC
PARAMN	NA	PARAMN	NA	ADTDESCN
ADT	ASTDT	ASTDT	ADT	ADT
AVALC	AVALC	AVALC	NA	NA
ANLXXFL	ANL01FL	ANL01FL-ANL10FL	NA	NA

New Approach Flowchart of the Overall Logic and Data Flow: ADTTE (Data for the Time to Event Analyses)



Step 1: Simply Use SAS Proc Transpose Procedure-I

- SAS Proc Transpose Procedure Is Used to Convert the Vertical Structure of ADDATES into the Horizontal One to Support the Derivation of ADTTE!

```
*** get all dates for PFS and OS, ect.;
proc sort data=addates;by usubjid adtdescn;run;
proc transpose data=addates out=addates2(drop=_name_ _label_);
     by usubjid;
     id adtdescd;
     idlabel adtdesc;
     var adt;
run;
```

- Note: IDLABEL Statement: Carry-over ADTDESC into The Label of Each Column!

USUBJID	TRTSDT	PDDT	DTHDT	LANOPDDT	LBFMISDT	LAPNCTDT	NEWCTDT	EOSDT	LSTALVDT	CUTOFFDT
simu_091	2018-04-16			2018-08-02		2018-08-02	2018-08-03	2019-04-25	2020-03-30	2020-03-31
simu_094	2018-04-16	2018-06-23					2018-08-22	2019-02-20	2020-01-26	2020-03-31
simu_097	2018-04-16	2018-11-30			2018-08-02			2019-03-04	2020-02-07	2020-03-31

Unique Subject Identifier	Date of First Exposure to Treatment	Date of Documented Progression (PD)	Date of Death	Date of Last Adequate T. Asses. of No PD	Date Last Tumor Asses.Bef. Missed Visits	Date of Last Tumor Asses. Pri. to New CT	New Anticancer Therapy Start Date	End of Study Date	Date Last Known Alive	Date of Analysis Cut-off
simu_091	2018-04-16			2018-08-02		2018-08-02	2018-08-15	2019-04-25	2020-03-30	2020-03-31
simu_094	2018-04-16	2018-06-23					2018-08-22	2019-02-20	2020-01-26	2020-03-31
simu_097	2018-04-16	2018-11-30			2018-08-02			2019-03-04	2020-02-07	2020-03-31

Step 1: Simply Use SAS Proc Transpose Procedure-II: Example Transposed ADDATES with ADTDESC as Labels

USUBJID	TRTSDT	PDDT	DTHDT	LANOPDDT	LBFMISDT	LAPNCTDT	NEWCTDT	EOSDT	LSTALVDT	CUTOFFDT
simu_091	2018-04-16			2018-08-02		2018-08-02	2018-08-03	2019-04-25	2020-03-30	2020-03-31
simu_094	2018-04-16	2018-06-23					2018-08-22	2019-02-20	2020-01-26	2020-03-31
simu_097	2018-04-16	2018-11-30			2018-08-02			2019-03-04	2020-02-07	2020-03-31

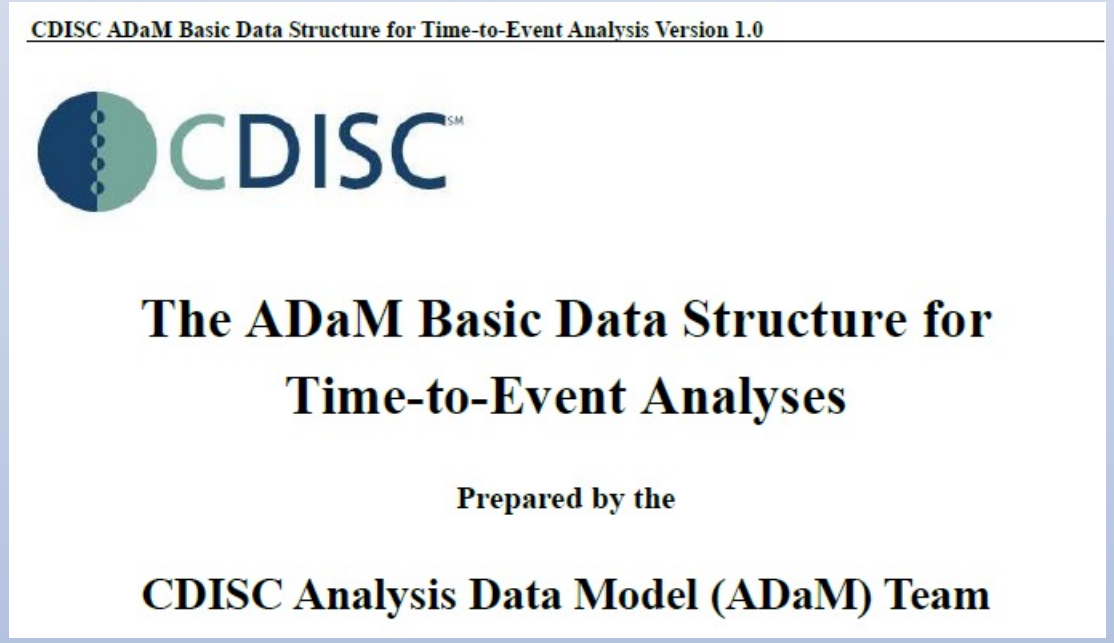
Unique Subject Identifier	Date of First Exposure to Treatment	Date of Documented Progression (PD)	Date of Death	Date of Last Adequate T. Asses. of No PD	Date Last Tumor Asses.Bef. Missed Visits	Date of Last Tumor Asses. Pri. to New CT	New Anticancer Therapy Start Date	End of Study Date	Date Last Known Alive	Date of Analysis Cut-off
simu_091	2018-04-16			2018-08-02		2018-08-02	2018-08-15	2019-04-25	2020-03-30	2020-03-31
simu_094	2018-04-16	2018-06-23					2018-08-22	2019-02-20	2020-01-26	2020-03-31
simu_097	2018-04-16	2018-11-30			2018-08-02			2019-03-04	2020-02-07	2020-03-31

- Each Label Can Help the Users to Better Understand Each Variable for Use to Facilitate the Downstream Programming for ADTTE.
- It Shows the Benefit of ADDATES.ADTDESC, Designed by CDISC TAUG-PrCa!

Introduction to ADTTE for Progression-Free Survival (PFS)

- PFS is the Mostly Used Primary/Co-primary Endpoint in Oncology Studies, in addition to OS, and Its More Complexity of the Derivation of ADTTE Compared to One for OS.
- As the Explanation in Introduction Section, the Censoring Scheme for PFS Primary Analysis in Table 1 from FDA's Guideline Is Used to Derive ADTTE.
- The Readers Could Apply This New Approach to Other TTE Endpoints Based on the Specific Context of Use, Which Would Be Specified in Study Statistical Analysis Plan (SAP).

CDISC Provides the ADaM Standards for Time-to-event (TTE) Endpoints, Named as ADTTE!



CDISC ADaM Basic Data Structure for Time-to-Event Analysis Version 1.0

CDISC

The ADaM Basic Data Structure for Time-to-Event Analyses

Prepared by the

CDISC Analysis Data Model (ADaM) Team

Revision History

Date	Version	Description
May 8, 2012	1.0	Final

Step 2: ADTTE for PFS-I

- Its Key Variables Are ADT, AVAL, CNSR, EVNTDESC, and CNSDTDSC, along with the Triplet of SRCDOM, SRCVAR, and SRCSEQ as the Traceability Variables.

USUBJID	TRTSDT	PDDT	DTHDT	LANOPDDT	LBFMISDT	LAPNCTDT	NEWCTDT	EOSDT	LSTALVDT	CUTOFFDT
simu_091	2018-04-16			2018-08-02		2018-08-02	2018-08-03	2019-04-25	2020-03-30	2020-03-31
simu_094	2018-04-16	2018-06-23					2018-08-22	2019-02-20	2020-01-26	2020-03-31
simu_097	2018-04-16	2018-11-30			2018-08-02			2019-03-04	2020-02-07	2020-03-31

- The Derivation of These Key Variables Could Be Derived Through A Series of IF-THEN/ELSE-DO Statements inside ADTTE.SAS Programming by Applying the Censoring Rules, per the ***Availability*** of Transposed ADDATES Dataset in Horizontal Structure!

Recall: Tabulation of ADTDESCN, ADTDESCD and ADTDESC from ADDATES: One-one Relationship Between ADTDESCN and ADTDESCD!

Tabulation of ADTDESCN, ADTDESCD and ADTDESC from ADEVENT

ADTDESCN (Description of Analysis Date (N))	ADTDESCD (Description of Analysis Date Code)	ADTDESC (Description of Analysis Date)
1	PDDT	Date of Documented Progression (PD)
2	LANOPDDT	Date of Last Adequate T. Asses. of No PD
3	LBFMISDT	Date Last Tumor Asses.Bef. Missed Visits
4	LAPNCTDT	Date Last Tumor Asses. Pri. to. New CT
5	BORDT	Date of First Occurrence of BOR
6	DORSTDT	Date of DOR Start
7	DORENDT	Date of DOR End
8	NEWCTDT	First Date of New Anticancer Therapy

Tabulation of ADTDESCN, ADTDESCD and ADTDESC for Other Dates of Independent of Tumor Assessments (ADSL)

ADTDESCN (Description of Analysis Date (N))	ADTDESCD (Description of Analysis Date Code)	ADTDESC (Description of Analysis Date)
9	RANDDT	Date of Randomization
10	TRTSDT	Date of First Exposure to Treatment
11	TRTEDT	Date of Last Exposure to Treatment
12	CUTOFFDT	Date of Analysis Cut-off
13	DTHDT	Date of Death
14	LSTALVDT	Date Last Known Alive
15	LOSTFUDT	Date Lost to Follow-up
16	EOSDT	End of Study Date

Step 2: ADTTE for PFS-II
Below Shows the Partial of the Derivation Rules for Key ADTTE Variables per FDA Guideline for Primary PFS Analysis

IF CONDITION	EVNTDESN	EVNTDESC	CNSDTDSC	CNSR	ADT	ADTDESCN
PDDT>.Z and DTHDT>.Z	1	DOCUMENTED PROGRESSION PRIOR TO DEATH		0	PDDT	1
PDDT>.Z and DTHDT=.	2	DOCUMENTED PROGRESSION		0	PDDT	1
PDDT=. and DTHDT>.Z	3	DEATH		0	DTHDT	14
.Z<LAPNCTDT<PDDT	4	PD AFTER NEW ANTICANCER THERAPY'	LAST RADIOLOGIC ASSESSMENT PRIOR TO NEW ANTICANCER THERAPY	2	LAPNCTDT	4
.Z<LBFMISDT <PDDT	5	PD AFTER MISSING ASSESSMENTS	LAST RADIOLOGIC ASSESSMENT PRIOR TO MISSING ASSESSMENTS	3	LBFMISDT	3
.Z<LAPNCTDT< DTHDT	6	DEATH AFTER NEW ANTICANCER THERAPY'	LAST RADIOLOGIC ASSESSMENT PRIOR TO NEW ANTICANCER THERAPY	2	LLAPNCTDT	4
.Z< LBFMISDT < DTHDT	7	DEATH AFTER MISSING ASSESSMENTS	LAST RADIOLOGIC ASSESSMENT PRIOR TO MISSING ASSESSMENTS	3	LBFMISDT	3
LANOPDDT>.Z	8	NO PROGRESSION	LAST RADIOLOGIC ASSESSMENT SHOWING NO PROGRESSION	1	LANOPDDT	2

- Note: ADTDESCN Is Used as A Link Between ADTTE and ADDATES so that the Triplet of SRDDOM, SRCVAR, and SRCSEQ Can Be Built for ADTTE Based on the Source from ADDATES.

We Will Provide How to Design This Logic Above for the ***Full Scenario*** in Another Paper!

- "A New Technique to Assemble ADTTE (Data for the Time to Event Analyses) with Ease and Traceability in Oncology Studies" - under preparation
- The Emphasis of The Current Paper Is to Introduce the New Approach to Enhance These Two CDISC Standards and Another Reason Is Due to the Limitation of Paper Pages.

Conveniently Build Traceability for ADTTE Through the Triplet of SRDDOM, SRCVAR, and SRCSEQ from ADDATES

- Before the Final SAS Data Is Output for ADTTE, the Triplet of SRDDOM, SRCVAR, and SRCSEQ for ADTTE Is Derived As Follows.

```
proc sort data=addates out=addates1(keep=usubjid adtdescn srcdom srcvar
                                    srcseq);by usubjid adtdescn;run;
proc sort data=adtte_tmp;by usubjid adtdescn;run;
data adtte_tmp1;
     merge adtte_tmp(in=a)
           addates1;
     by usubjid adtdescn;
     if a;
run;
```

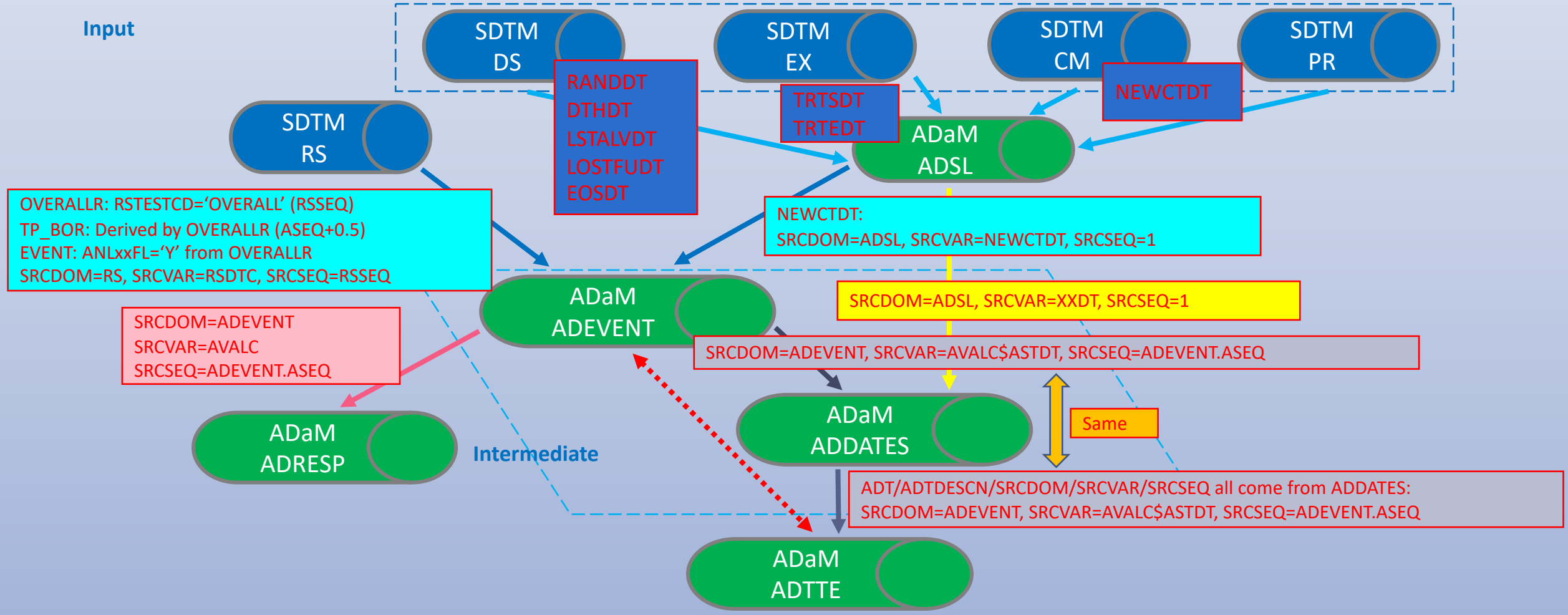
- ADDATES.ADTDESCN Plays the Key Role to Derive the Triplet for ADTTE Directly from the One of ADDATES!

An Example of ADTTE with Temporary Variable ADTDESCN & Triplet from ADDATES

- An Example of ADTTE with Temporary Variable ADTDESCN and TRIPLET (SRCDOM, SRCVAR, SRCSEQ) from ADDATES

USUBJID	PARCAT1	PARAMCD	PARAM	EVNTDESN	EVNTDESC	CNSDTDSC	ADTDESCN	CNSR	ADT	SRCDOM	SRCAR	SRCSEQ
simu_097	Primary PFS Analysis	PFS	Progression Free Survival (Days)	5	PD AFTER MISSING ASSESSMENTS	LAST RADIOLOGIC ASSESSMENT PRIOR TO MISSING ASSESSMENTS	**3**	3	2018-08-02	**ADEVENT**	**AVALC$ASTDT**	**300**

In Summary: Process to Build Traceability



Example 1: Locate the Record for the Source of ADTTE – Method 1

ADEVENT

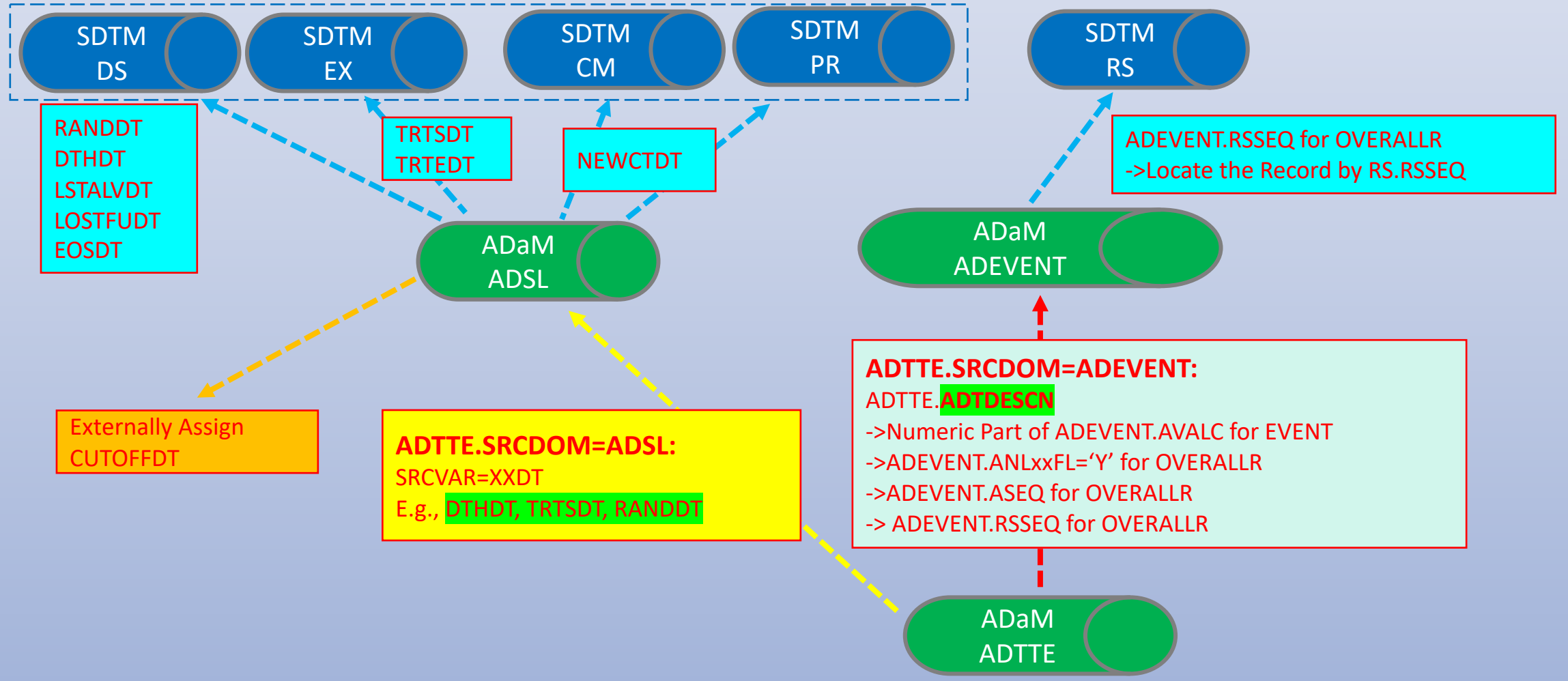
USUBJID	ASEQ	PARAMN	PARAMCD	PARAM	VISIT	ASTDT	ASTDY	AVALC	RSSEQ
simu_097	1	1	OVERALLR	Overall Evaluation	Cycle 2	2018-06-23	69	PR	33
simu_097	2	1	OVERALLR	Overall Evaluation	Cycle 4	2018-08-02	109	PR	34
simu_097	2.5	2	TP_BOR	Derived Overall Evaluation	Cycle 4	2018-08-02	109	SD	34
simu_097	3	1	OVERALLR	Overall Evaluation	Cycle 6	2018-09-11	149	NE	35
simu_097	4	1	OVERALLR	Overall Evaluation	Cycle 8	2018-10-21	189	NE	36
simu_097	5	1	OVERALLR	Overall Evaluation	Cycle 10	2018-11-30	229	PD	37
simu_097	100	3	EVENT	Event Date	Cycle 10	2018-11-30	229	1:PDDT (Date of Documented Progression (PD))	
simu_097	300	3	EVENT	Event Date	Cycle 4	2018-08-02	109	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)	
simu_097	500	3	EVENT	Event Date	Cycle 2	2018-06-23	69	5:BORDT (Date of First Occurrence of BOR)	
simu_097	600	3	EVENT	Event Date	Cycle 2	2018-06-23	69	6:DORSTDT (Date of DOR Start)	
simu_097	700	3	EVENT	Event Date	Cycle 10	2018-11-30	229	7:DORENDT (Date of DOR End)	

ASEQ	ANL01FL	ANL02FL	ANL03FL	ANL04FL	ANL05FL	ANL06FL	ANL07FL	ANL08FL	ANL09FL	ANL10FL	SRCDOM	SRCVAR	SRCSEQ
1	Y			Y				Y	Y				
2				Y		Y							
2.5				Y									
3	Y			Y									
4	Y			Y									
5	Y	Y		Y						Y			
100											RS	RSDTC	37
300											RS	RSDTC	34
500											RS	RSDTC	33
600											RS	RSDTC	33
700											RS	RSDTC	37

ADTTE

USUBJID	PARCAT1	PARAMCD	PARAM	EVNTDESN	EVNTDESC	CNSDTDSC	ADTDESCN	CNSR	ADT	SRCDOM	SRCAR	SRCSEQ
simu_097	Primary PFS Analysis	PFS	Progression Free Survival (Days)	5	PD AFTER MISSING ASSESSMENTS	LAST RADIOLOGIC ASSESSMENT PRIOR TO MISSING ASSESSMENTS	3	3	2018-08-02	ADEVENT	AVALC$A STDT	300

Locate the Record for the Source of ADTTE – Method 1



Example 1: Locate the Record for the Source of ADTTE – Method 2

ADEVENT

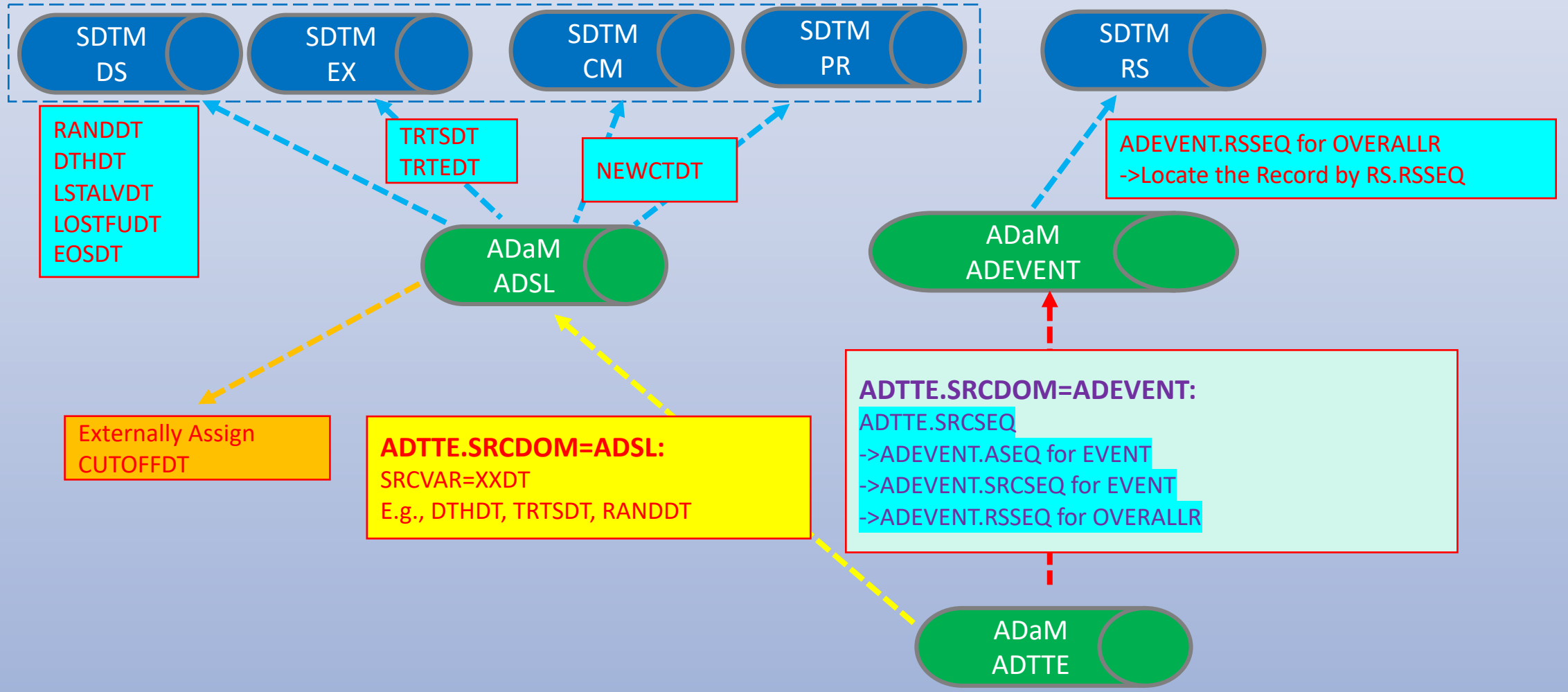
USUBJID	ASEQ	PARAMN	PARAMCD	PARAM	VISIT	ASTDT	ASTDY	AVALC	RSSEQ
simu_097	1	1	OVERALLR	Overall Evaluation	Cycle 2	2018-06-23	69	PR	33
simu_097	2	1	OVERALLR	Overall Evaluation	Cycle 4	2018-08-02	109	PR	34
simu_097	2.5	2	TP_BOR	Derived Overall Evaluation	Cycle 4	2018-08-02	109	SD	34
simu_097	3	1	OVERALLR	Overall Evaluation	Cycle 6	2018-09-11	149	NE	35
simu_097	4	1	OVERALLR	Overall Evaluation	Cycle 8	2018-10-21	189	NE	36
simu_097	5	1	OVERALLR	Overall Evaluation	Cycle 10	2018-11-30	229	PD	37
simu_097	100	3	EVENT	Event Date	Cycle 10	2018-11-30	229	1:PDDT (Date of Documented Progression (PD))	
simu_097	300	3	EVENT	Event Date	Cycle 4	2018-08-02	109	3:LBFMISDT (Date Last Tumor Asses.Bef. Missed Visits)	
simu_097	500	3	EVENT	Event Date	Cycle 2	2018-06-23	69	5:BORDT (Date of First Occurrence of BOR)	
simu_097	600	3	EVENT	Event Date	Cycle 2	2018-06-23	69	6:DORSTDT (Date of DOR Start)	
simu_097	700	3	EVENT	Event Date	Cycle 10	2018-11-30	229	7:DORENDT (Date of DOR End)	

ASEQ	ANL01FL	ANL02FL	ANL03FL	ANL04FL	ANL05FL	ANL06FL	ANL07FL	ANL08FL	ANL09FL	ANL10FL	SRCDOM	SRCVAR	SRCSEQ
1	Y			Y				Y	Y				
2				Y		Y							
2.5				Y									
3	Y			Y									
4	Y			Y									
5	Y	Y		Y						Y			
100											RS	RSDTC	37
300											RS	RSDTC	34
500											RS	RSDTC	33
600											RS	RSDTC	33
700											RS	RSDTC	37

ADTTE

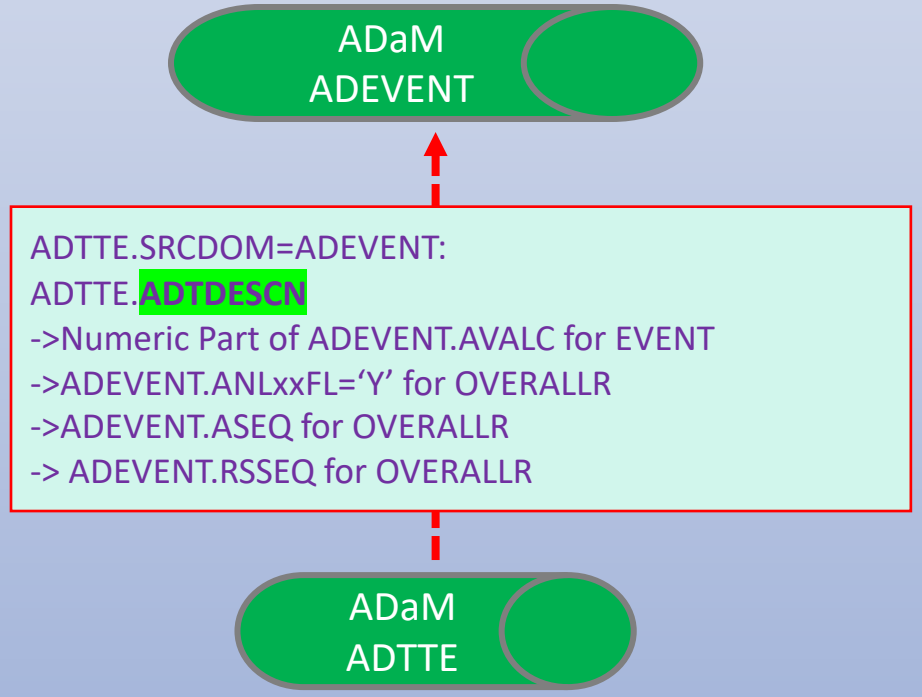
USUBJID	PARCAT1	PARAMCD	PARAM	EVNTDESN	EVNTDESC	CNSDTDSC	ADTDESCN	CNSR	ADT	SRCDOM	SRCAR	SRCSEQ
simu_097	Primary PFS Analysis	PFS	Progression Free Survival (Days)	5	PD AFTER MISSING ASSESSMENTS	LAST RADIOLOGIC ASSESSMENT PRIOR TO MISSING ASSESSMENTS	3	3	2018-08-02	ADEVENT	AVALC$A STDT	300

Locate the Record for the Source of ADTTE – Method 2

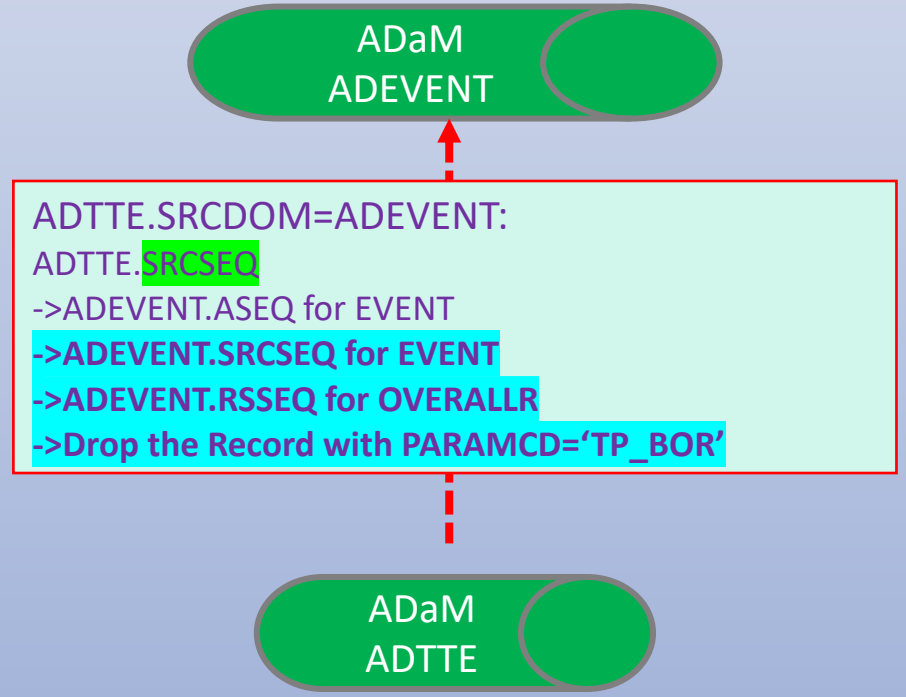


Comparison of Method 1 and Method 2

Method 1



Method 2



In Summary

Recall: PROS and CONS of ADVENT & ADDATES from CDISC Standards

Order	Feature/Benefit	ADEVENT	ADDATES
1	Support ADTTE	Yes	Yes
2	Support BOR and DOR when no confirmation of CR and PR is required	Yes	No
3	Support BOR and DOR when the confirmation of CR and PR is required	No	No
4	Traceability of the Derivation of the Dates of Independent of Tumor Assessments	Yes	Yes
5	Traceability of the Derivation of the Dates Related Tumor Assessments	Not Sufficient (RECIST 1.1/ iRECIST)	"Totally Lost" from both the dataset and metadata
6	The meaning of the event (ADEVENT.AVALC)/date (ADDATES. ADTDESCD) can be carried over to the subsequent programming.	AVALC does not store the description of event.	ADTDESC provides the description of ADTDESCD.
7	Sorting Keys to Sort the Data	No	No
8	Best Programming Practice	Does not follow	Does not follow

The Enhancement of ADEVENT

Order in Table 5	Feature/Benefit	ADEVENT Deficiency	Enhancement from This Paper
3	Support BOR and DOR when the confirmation of CR and PR is required	No	Create a new record with PARAMCD='TP_BOR' PARAM='Derived Overall Evaluation', please refer to [8] for the details
5	Traceability of the Derivation of the Dates Related Tumor Assessments	Not Sufficient (RECIST 1.1/ iRECIST)	Same as above, and add ANLxxFL flags providing more traceability, along with ASEQ
6	The meaning of the event (ADEVENT.AVALC)	AVALC does not store the description of event.	The meaning/description of the event is attached to the "original" AVALC, and the numbering (1-8) is prefixed to it for the sorting key.
8	Sorting Keys to Sort the Data	No	Same as above, along with ASEQ
7	Best Programming Practice	Does not follow	Separate the derivation of dates related to tumor assessments and dates of independent of tumor assessments into two independent programming

The Enhancement of ADDATES

Order in Table 5	Feature/Benefit	ADDATES Deficiency	Enhancement from This Paper
2	Support BOR and DOR when no confirmation of CR and PR is required	No	Following ADEVENT, ADRESP supports BOR, and ANL09FL and ANL10FL facilitate the DOR derivation in ADTTE.
3	Support BOR and DOR when the confirmation of CR and PR is required	No	Same as one for ADEVENT enhancement
5	Traceability of the Derivation of the Dates Related Tumor Assessments	"Totally Lost" from both the dataset and metadata	Being Built in ADEVENT through ANLxxFL flags, along with the triplet of SRCDOM, SRCVAR, and SRCSEQ
7	Sorting Keys to Sort the Data	No	Adding a new variable: ADTDESCN (Description of Analysis Date (N)) as the sorting key
8	Best Programming Practice	Does not follow	Same as one for ADEVENT enhancement

Conclusion-I

- This Presentation Introduces Two CDISC TAUGs Intermediate Datasets: ADEVENT and ADDATES to Support Traceability.
- It Pinpoints and Explains Their Pros and Cons, and It Leverages Their Pros, and Overcomes Their Cons. It Presents A New Process to Enhance Them.
- Traceability Provides Transparency, and further Builds/Increases Confidence in the Result or Conclusion for the FDA Reviewers.

Conclusion-II

- The New Approach Streamlines the Programming for the Generation of ADEVENT, ADRESP, ADDATES, and ADTTE.
- The Enhancement of Two CDISC TAUGs Standards from both ADEVNET and ADDATES Make Them Possible to Be Applied Broadly to Other Areas of Oncology Studies, Besides Breast Cancer Therapeutic Area and Prostate Cancer Therapeutic Area.
- The Intent of This Presentation Is to Guide Readers in Developing a CDISC ADaM Compliant Programming with Much Clearer Traceability That Is Applicable across Multiple Projects in Oncology Studies.

Contact Information

- Name: Xiangchen (Bob) Cui, Ph.D.
- Enterprise: CRISPR Therapeutics AG
- Address: 105 West 1st Street
- City, State ZIP: Boston, MA 02127
- Work Phone: 908-240-4086
- E-mail:xiangchen.cui@crisprtx.com

Thank You!