PharmaSUG 2020 - Paper DS-329

Overcoming Pitfalls of DS: Shackling the 'Elephant in the room'

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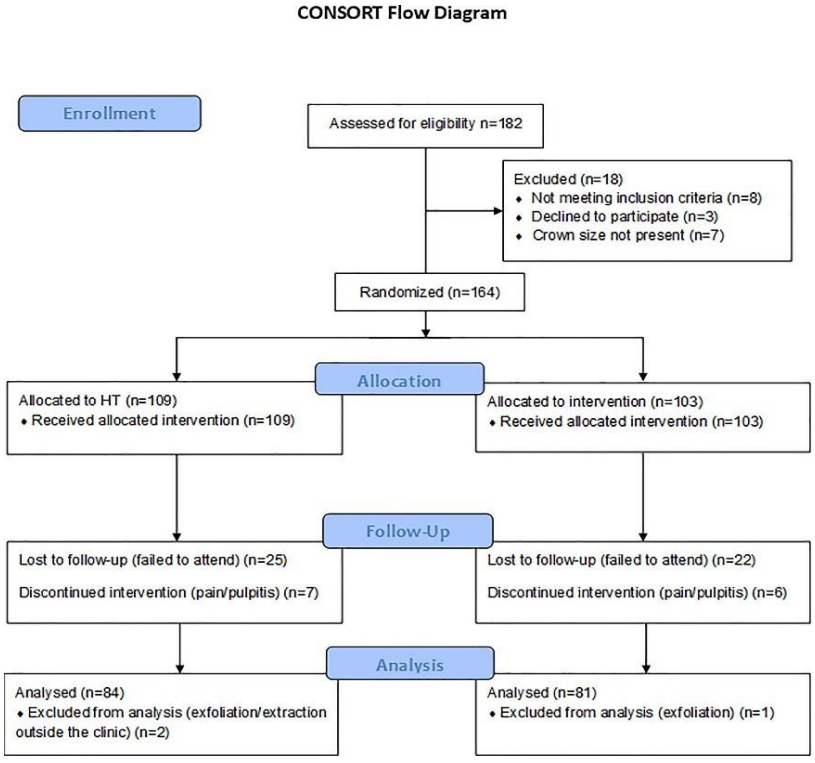
ABSTRACT

Disposition (DS) is a standard SDTM domain that has been around since the inception of SDTM. Although familiar, it has often been misinterpreted or misused. Unlike other SDTM domains, direct mapping from CRF pages presents challenges within DS. For example, CRF values may not be a perfect fit for the terms defined in controlled terminology (CT) Codelists, especially as seen in 'End of Study' or 'End of Treatment' pages. When a Codelist does not have an exact match with the CRF text, you may need to request NCI to extend the Codelist or add new terms. This, however, may create problems because not every “new term” should extend a Codelist. Also, it’s important to understand the differences between criteria so that DSCAT / DSDECOD values are assigned appropriately. From an annotation perspective, this means that if DSCAT / DSDECOD values are 'assigned', they should not be annotated on the CRF. This paper will guide you through the mapping of CRF pages to DS and illustrate how to choose appropriate CT for variables like DSCAT, DSDECOD and EPOCH. So, you should hopefully be able to overcome the pitfalls of DS and shackle that ‘elephant in the room'.

INTRODUCTION

The Disposition (DS) domain provides an account of all subjects who are enrolled in the study. It includes events such as informed consent, randomization and the completion status or reason for discontinuation (for the entire study, or each phase of the study), and follow-up. The events or verbatim --TERM’s are categorized under different criteria (DSCAT), and --DECOD’s are assigned based on CDISC Codelists for each criterion. The different DSCAT’s used include ‘Protocol Milestones’, ‘Disposition Events’ and ‘Other Events’. It’s important to understand the differences between the criteria so that the DSCAT values can be assigned appropriately. Let’s look at a few examples in the next sections to explain how DSCAT can be assigned to the right DSTERM’s/DSDECOD’s.

To begin, let us look at a typical study design from the ‘Subject Disposition’ perspective. The first step is to conceive of the study and then describe the study in detail in a protocol. We will illustrate this using a **CONSORT** (which is an organization that has produced guidelines for conducting clinical trials) flow diagram, often used to summarize the flows of a clinical study.



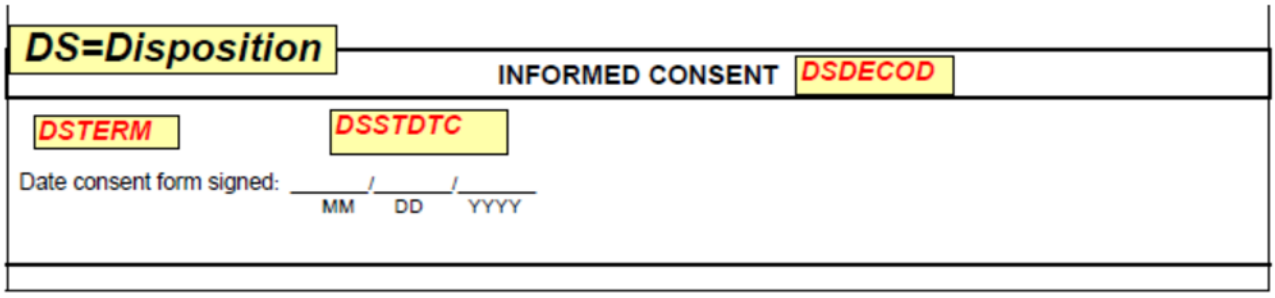
The calendar within the protocol provides the schedule for the timing of all phases of the study. Each subject has a unique path through the study that is captured within the Subject Disposition (DS) domain.

The '**Schedule of Assessments**' table below highlights the schedule of visits within each phase of the trial detailed within the protocol. The CONSORT flow diagram graphically summarizes the stages of the trial. Each subject is involved from 'Enrollment' through 'Follow-up', and 'Analysis' takes place once the subject ends participation and all data are available. Enrollment encompasses the protocol milestone of 'Signing Informed Consent' {which must take place to being the screening process} to 'Randomization' {which must take place to allow 'Allocation'}. The subject's disposition represents their state at various points in the study including End of Study. The next sections will look at how this would play out through various examples.

Assessment	**Screening**	**Treatment Period**			**EOS / Follow-up**
Visit / Day	**1**	**2**	**3**	**4**	**5**
Relative Study Day	**-16**	**1**	**14**	**21**	**25**
Informed Consent	X				
Demographics	X				
Inclusion/Exclusion	X				
Medical History	X				
Physical Exam	X				X
Vital Signs	X				X
Labs	X				X
Randomization	X				
Study Drug Administration		X	X	X	
Concomitant Meds / Procedures		X	X	X	X
AE Collection		X	X	X	X

EXAMPLE 1: PROTOCOL MILESTONES AND RELATED DISPOSITION EVENT:

The first step for any trial is having subjects read a consent form and sign it; then begins the screening process. These events are categorized as '**Protocol Milestone**' (or protocol-specified point-in-time) in SDTM. Below is the example of one subject going through the consent form and the signing it - date of their signature is captured on the (CRF):



Then the subjects are assessed for Inclusion / Exclusion criteria and may subsequently get 'Randomized' to active treatment or placebo groups (if they meet criteria); or (If they don't meet criteria) termed as "Screen Failure" and discontinue from the study. The DSTERM 'Screen Failure' gets mapped to a DSCAT of 'Disposition Event' and EPOCH of 'Screening' (Note: when DSCAT = 'Protocol Milestone' then EPOCH is not used, as per assumption no. 3d of the DS domain in the SDTM IG v3.2 – pg. 141):

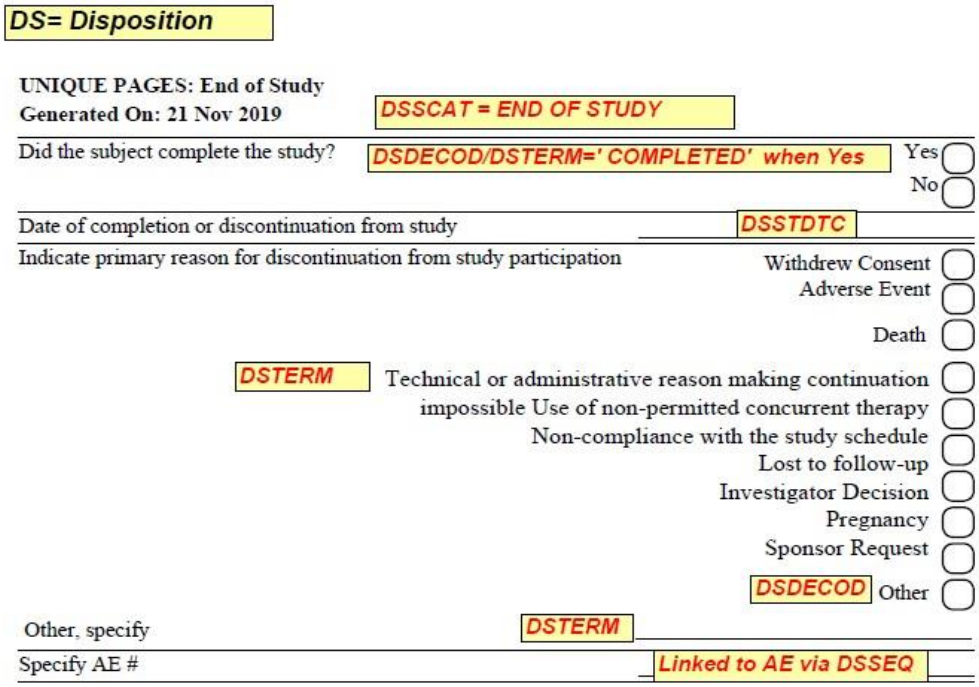
USUBJID	DSCAT	DSTERM	DSDECOD	DSSTDTC	EPOCH
0001	PROTOCOL MILESTONE	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	2019-09-03	
0001	PROTOCOL MILESTONE	ELIGIBILITY CRITERIA MET	ELIGIBILITY CRITERIA MET	2019-09-03	
0001	PROTOCOL MILESTONE	RANDOMIZED	RANDOMIZED	2019-09-19	
0002	PROTOCOL MILESTONE	INFORMED CONSENT	INFORMEDCONSENT	2019-09-02	
0002	DISPOSITION EVENT	SCREEN FAILURE	SCREEN FAILURE	2019-09-18	SCREENING

Here is a snapshot of the extensible codelist, PROTMLST (Protocol Milestone) within the SDTM CT package:

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C114118		Yes	Protocol Milestone	PROTMLST	Protocol Milestone	A terminology Codelist relevant to protocol-specified, point-in-time events during a study.
C132447	C114118		Protocol Milestone	ELIGIBILITY CRITERIA MET		The subject has fulfilled the criteria needed to enter or continue in the study.
C161417	C114118		Protocol Milestone	ENTERED INTO TRIAL		The subject has met eligibility criteria and is enrolled in the study. The subject may or may not subsequently be randomized.
C161418	C114118		Protocol Milestone	INFORMED ASSENT OBTAINED		Assent given by a minor or adult who is unable to give informed consent on their own behalf, to participate in a clinical trial. Assent must be accompanied by consent from a parent or legal guardian for full participation in the study.
C16735	C114118		Protocol Milestone	INFORMED CONSENT OBTAINED		Consent given by a subject, or in the case of an individual that can only give assent, by a parent or legal guardian, for the participation in a clinical study only after having achieved an understanding of both the relevant medical facts and the relevant risks involved.
C114209	C114118		Protocol Milestone	RANDOMIZED		Participants are assigned to arms of a clinical trial by chance.

EXAMPLE 2: DISPOSITION EVENTS AFTER SCREENING

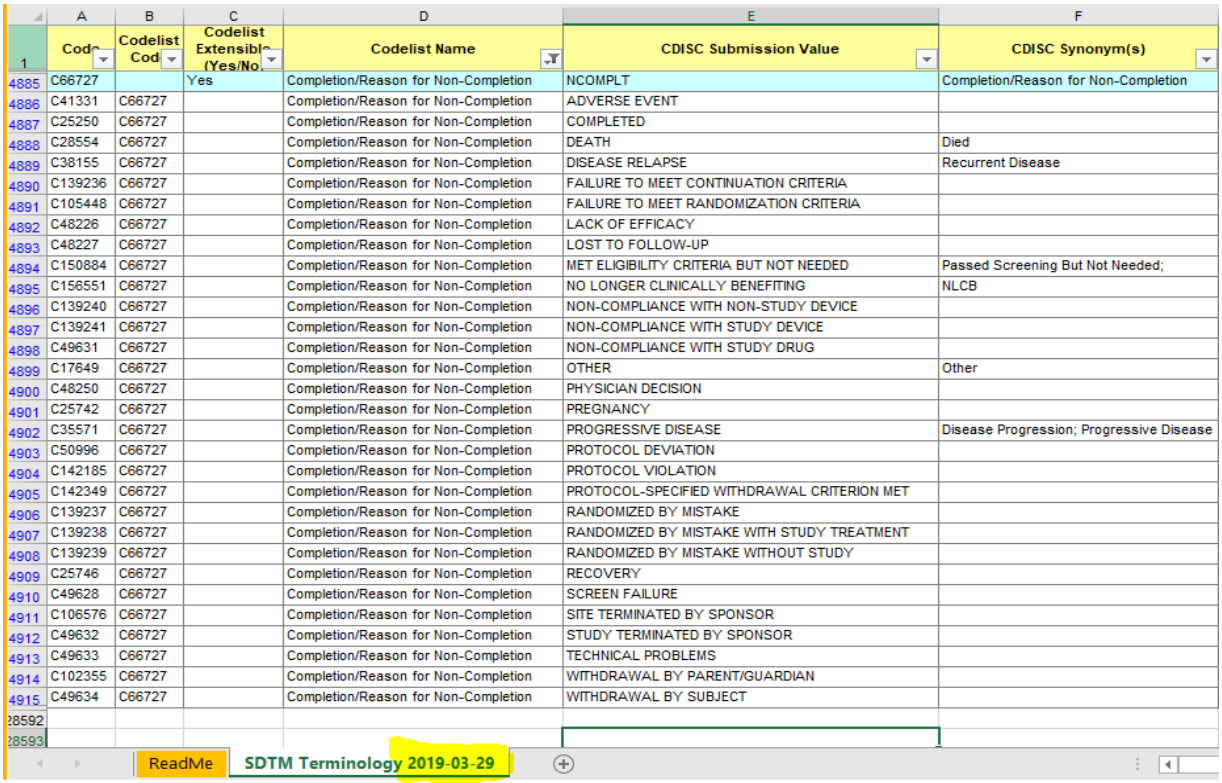
The next step for the subject is to go through 'Treatment' phase, and they either 'Complete' it or 'Discontinue from the study', and a 'reason for non-completion' is captured on the CRF as shown in the below screenshot. These events are categorized (DSCAT) as 'Disposition Event' in DS (Note: DSCAT is not annotated because it's an 'Assigned' variable as opposed to being collected on the CRF).



In Example 1 (Protocol Milestones), the values for DSTERM and DSDECOD were identical because the CRF term matched the standardized term in the PROTMLST Codelist. This may not always be the case, especially for 'Disposition Events'. Sometimes the text collected on the CRF may not directly map to a term in the NCOMPLT Codelist. The below table illustrates how the collected status – whether the subject completed (Treatment or Study) or the reasons for non-completion can be mapped using the NCOMPLT (Completion/Reason for Non-Completion) codelist:

DSCAT	DSSCAT	DSTERM	DSDECOD	
Disposition Event	End of Study	COMPLETED	COMPLETED	
Disposition Event	End of Study	Lost to follow-up	LOST TO FOLLOW-UP	
Disposition Event	End of Study	Withdrew Consent	WITHDRAWAL BY SUBJECT	
Disposition Event	End of Study	Adverse event	ADVERSE EVENT	
Disposition Event	End of Study	Death	DEATH	
Disposition Event	End of Study	Technical or administrative reason making continuation impossible	FAILURE TO MEET CONTINUATION CRITERIA	Mapped to existing codelist
Disposition Event	End of Study	Use of non-permitted concurrent therapy	PROTOCOL DEVIATION	
Disposition Event	End of Study	Non-compliance with the study schedule	NON-COMPLIANCE WITH STUDY SCHEDULE	Sent to NCI for extending the codelist
Disposition Event	End of Study	Investigator Decision	PHYSICIAN DECISION	
Disposition Event	End of Study	Pregnancy	PREGNANCY	
Disposition Event	End of Study	Sponsor request	SPONSOR REQUEST	
Disposition Event	End of Study	Unwilling to comply with the study procedures (free text for other specify)	OTHER	

In the above table, the terms: "NON-COMPLIANCE WITH STUDY SCHEDULE" and "SPONSOR REQUEST" were not in the NCOMPLT codelist of the current version of CT package (March 29th, 2019) for SDTM terms at the time that this study was mapped:



	A	B	C	D	E	F
1	Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
4885	C66727		Yes	Completion/Reason for Non-Completion	NCOMPLT	Completion/Reason for Non-Completion
4886	C41331	C66727		Completion/Reason for Non-Completion	ADVERSE EVENT	
4887	C25250	C66727		Completion/Reason for Non-Completion	COMPLETED	
4888	C28554	C66727		Completion/Reason for Non-Completion	DEATH	Died
4889	C38155	C66727		Completion/Reason for Non-Completion	DISEASE RELAPSE	Recurrent Disease
4890	C139236	C66727		Completion/Reason for Non-Completion	FAILURE TO MEET CONTINUATION CRITERIA	
4891	C105448	C66727		Completion/Reason for Non-Completion	FAILURE TO MEET RANDOMIZATION CRITERIA	
4892	C48226	C66727		Completion/Reason for Non-Completion	LACK OF EFFICACY	
4893	C48227	C66727		Completion/Reason for Non-Completion	LOST TO FOLLOW-UP	
4894	C150884	C66727		Completion/Reason for Non-Completion	MET ELIGIBILITY CRITERIA BUT NOT NEEDED	Passed Screening But Not Needed;
4895	C156551	C66727		Completion/Reason for Non-Completion	NO LONGER CLINICALLY BENEFITING	NLCB
4896	C139240	C66727		Completion/Reason for Non-Completion	NON-COMPLIANCE WITH NON-STUDY DEVICE	
4897	C139241	C66727		Completion/Reason for Non-Completion	NON-COMPLIANCE WITH STUDY DEVICE	
4898	C49631	C66727		Completion/Reason for Non-Completion	NON-COMPLIANCE WITH STUDY DRUG	
4899	C17649	C66727		Completion/Reason for Non-Completion	OTHER	Other
4900	C48250	C66727		Completion/Reason for Non-Completion	PHYSICIAN DECISION	
4901	C25742	C66727		Completion/Reason for Non-Completion	PREGNANCY	
4902	C35571	C66727		Completion/Reason for Non-Completion	PROGRESSIVE DISEASE	Disease Progression; Progressive Disease
4903	C50996	C66727		Completion/Reason for Non-Completion	PROTOCOL DEVIATION	
4904	C142185	C66727		Completion/Reason for Non-Completion	PROTOCOL VIOLATION	
4905	C142349	C66727		Completion/Reason for Non-Completion	PROTOCOL-SPECIFIED WITHDRAWAL CRITERION MET	
4906	C139237	C66727		Completion/Reason for Non-Completion	RANDOMIZED BY MISTAKE	
4907	C139238	C66727		Completion/Reason for Non-Completion	RANDOMIZED BY MISTAKE WITH STUDY TREATMENT	
4908	C139239	C66727		Completion/Reason for Non-Completion	RANDOMIZED BY MISTAKE WITHOUT STUDY	
4909	C25746	C66727		Completion/Reason for Non-Completion	RECOVERY	
4910	C49628	C66727		Completion/Reason for Non-Completion	SCREEN FAILURE	
4911	C106576	C66727		Completion/Reason for Non-Completion	SITE TERMINATED BY SPONSOR	
4912	C49632	C66727		Completion/Reason for Non-Completion	STUDY TERMINATED BY SPONSOR	
4913	C49633	C66727		Completion/Reason for Non-Completion	TECHNICAL PROBLEMS	
4914	C102355	C66727		Completion/Reason for Non-Completion	WITHDRAWAL BY PARENT/GUARDIAN	
4915	C49634	C66727		Completion/Reason for Non-Completion	WITHDRAWAL BY SUBJECT	
28592						
28593						

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Hence, they were sent to NCI to be added to the codelist through the link to the 'request form' below (and the most current one shows them added to the codelist): https://nciterm form.nci.nih.gov/nciterm form/?version=cdisc

Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)
C66727		Yes	Completion/Reason for Non-	NCOMPLT	Completion/Reason for Non-
C41331	C66727		Completion/Reason for Non-	ADVERSE EVENT	
C25250	C66727		Completion/Reason for Non-	COMPLETED	
C28554	C66727		Completion/Reason for Non-	DEATH	Died
C38155	C66727		Completion/Reason for Non-	DISEASE RELAPSE	Recurrent Disease
C13923	C66727		Completion/Reason for Non-	FAILURE TO MEET CONTINUATION CRITERIA	
C10544	C66727		Completion/Reason for Non-	FAILURE TO MEET RANDOMIZATION CRITERIA	
C48226	C66727		Completion/Reason for Non-	LACK OF EFFICACY	
C48227	C66727		Completion/Reason for Non-	LOST TO FOLLOW-UP	
C15088	C66727		Completion/Reason for Non-	MET ELIGIBILITY CRITERIA BUT NOT NEEDED	Passed Screening But Not Needed;
C15655	C66727		Completion/Reason for Non-	NO LONGER CLINICALLY BENEFITING	NLCB
C13924	C66727		Completion/Reason for Non-	NON-COMPLIANCE WITH NON-STUDY DEVICE	
C13924	C66727		Completion/Reason for Non-	NON-COMPLIANCE WITH STUDY DEVICE	
C49631	C66727		Completion/Reason for Non-	NON-COMPLIANCE WITH STUDY DRUG	
C16141	C66727		Completion/Reason for Non-	NON-COMPLIANCE WITH STUDY SCHEDULE	
C17649	C66727		Completion/Reason for Non-	OTHER	Other
C48250	C66727		Completion/Reason for Non-	PHYSICIAN DECISION	
C25742	C66727		Completion/Reason for Non-	PREGNANCY	
C35571	C66727		Completion/Reason for Non-	PROGRESSIVE DISEASE	Disease Progression; Progressive
C50996	C66727		Completion/Reason for Non-	PROTOCOL DEVIATION	
C14218	C66727		Completion/Reason for Non-	PROTOCOL VIOLATION	
C14234	C66727		Completion/Reason for Non-	PROTOCOL-SPECIFIED WITHDRAWAL	
C13923	C66727		Completion/Reason for Non-	RANDOMIZED BY MISTAKE	
C13923	C66727		Completion/Reason for Non-	RANDOMIZED BY MISTAKE WITH STUDY	
C13923	C66727		Completion/Reason for Non-	RANDOMIZED BY MISTAKE WITHOUT STUDY	
C25746	C66727		Completion/Reason for Non-	RECOVERY	
C49628	C66727		Completion/Reason for Non-	SCREEN FAILURE	
C16607	C66727		Completion/Reason for Non-	SCREENING NOT COMPLETED	
C10657	C66727		Completion/Reason for Non-	SITE TERMINATED BY SPONSOR	
C16141	C66727		Completion/Reason for Non-	SPONSOR REQUEST	
C49632	C66727		Completion/Reason for Non-	STUDY TERMINATED BY SPONSOR	
C49633	C66727		Completion/Reason for Non-	TECHNICAL PROBLEMS	
C10235	C66727		Completion/Reason for Non-	WITHDRAWAL BY PARENT/GUARDIAN	
C49634	C66727		Completion/Reason for Non-	WITHDRAWAL BY SUBJECT	

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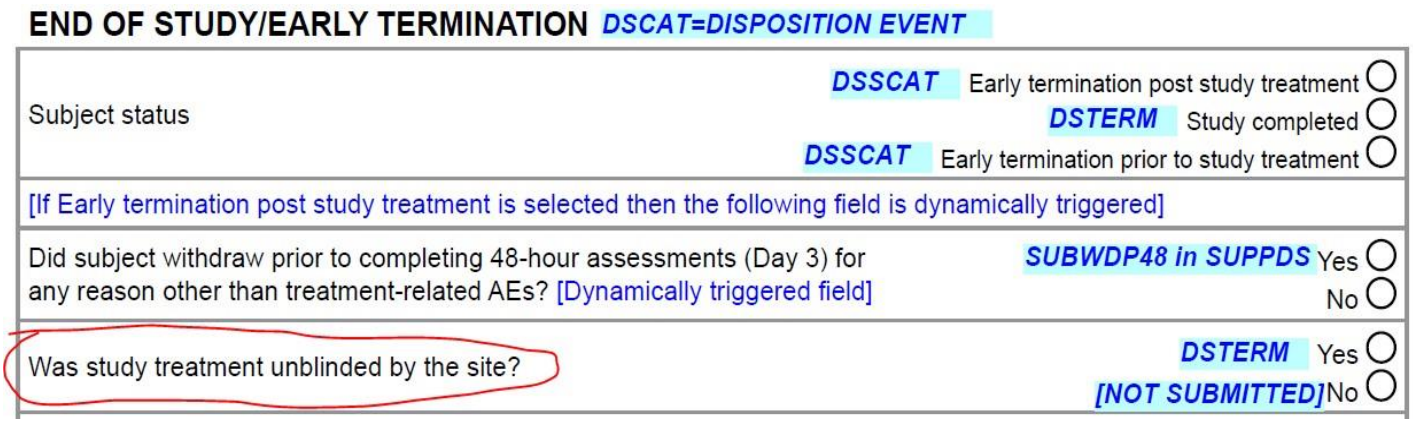
EXAMPLE 3: EPOCH FOR MULTIPLE DISPOSITION EVENTS:

In Example 1 we saw how 'Screen Failure' was a 'Disposition Event' collected at 'Screening', while example 2 demonstrated the different disposition events that may have occurred at 'Treatment' or 'Follow-up'. Some events like "Screen Failure' would only expect to occur at 'Screening'. So, the SDTM IG illustrates how we can assign EPOCH to help differentiate the timing of these events. When there are multiple disposition events and protocol milestones per subject, EPOCH is populated to show the difference in study periods for the occurrence of these events. It is especially recommended to be used when DSCAT has a value of 'DISPOSITION EVENT'. The below table will show you how subject 0003 has progressed through the different study phases and where he/she dropped out or terminated from the study:

USUBJID	DSCAT	DSSCAT	DSTERM	DSDECOD	DSSTDTC	EPOCH
0001	DISPOSITION EVENT	ELIGIBILITY CRITERIA	SCREEN FAILURE	SCREEN FAILURE	2019-09-18	SCREENING
0002	DISPOSITION EVENT	END OF TREATMENT	USE OF NON-PERMITTED CONCURRENT THERAPY	PROTOCOL DEVIATION	2019-10-01	TREATMENT
0003	PROTOCOL MILESTONE	ELIGIBILITY CRITERIA	SUBJECT MET ELIGIBILITY CRITERIA	ELIGIBILITY CRITERIA MET	2019-09-19	
0003	DISPOSITION EVENT	END OF TREATMENT	COMPLETED	COMPLETED	2019-10-02	TREATMENT
0003	DISPOSITION EVENT	END OF STUDY	MOVED OUT OF STATE	LOST TO FOLLOW-UP	2019-11-06	FOLLOW-UP

EXAMPLE 4: OTHER EVENT

OTHER EVENT is a newer value for DSCAT: Includes DSTERMs that are not previously defined in the protocol, but may not fall under 'Disposition Event' category, for example: "TREATMENT UNBLINDED". This Codelist is also extensible.



This is an unusual situation but it does happen and is not a 'Disposition Event'. Suppose that due to uncertainty about the dispensed drug for subject 0001, he and the principal investigator where unblinded. This unique situation has its own DSCAT value (Event Other). The values for this event are maintained within the NCI 'Other Disposition Event Response extensible Codelist:

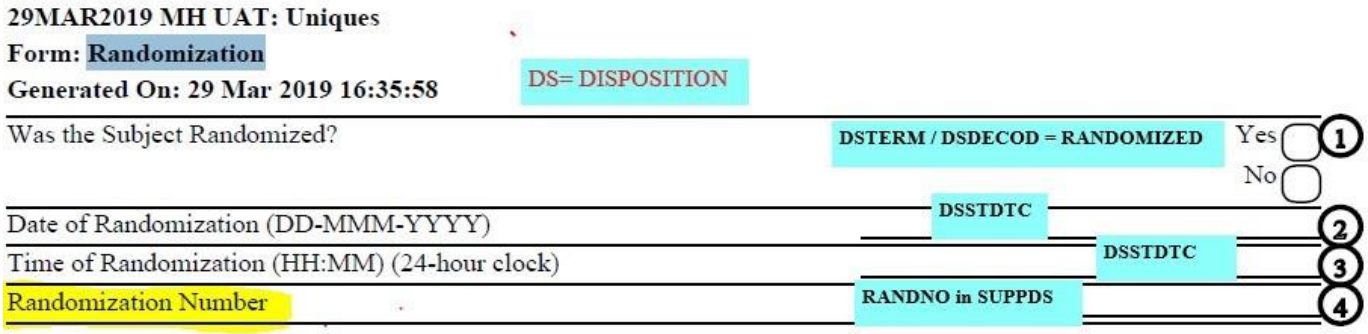
Code	Codelist Code	Codelist Extensible (Yes/No)	Codelist Name	CDISC Submission Value	CDISC Synonym(s)	CDISC Definition
C150811		Yes	Other Disposition Event Response	OTHEVENT	Other Disposition Event Response	A terminology codelist relevant to other important events that occur during a trial but are not driven by protocol requirements.
C142742	C150811		Other Disposition Event Response	TREATMENT UNBLINDED		A study event during which the treatment assignment is made known to the subject, investigator, and/or other trial personnel.

Within the DS domain, this is how the unblinding would be represented:

USUBJID	DSCAT	DSTERM	DSDECOD	DSSTDTC	EPOCH
0003	PROTOCOL MILESTONE	SUBJECT MET ELIGIBILITY CRITERIA	ELIGIBILITY CRITERIA MET	2019-09-19	
0003	OTHER EVENT	TREATMENT UNBLINDED	TREATMENT UNBLINDED	2019-11-19	TREATMENT

EXAMPLE 5: SUPPLEMENTAL QUALIFIER FOR DS:

Sometimes the CRF collects fields or variables that are not part of the standard DS structure or domain model. For example, below is a CRF that collects the 'Randomization Number' that is attached to the lead questions "Was the subject randomized?". In this example, we would map the date and time of randomization to DSSTDTC for this 'Protocol Milestone' but would have to use SUPPDS for 'Randomization Number'.



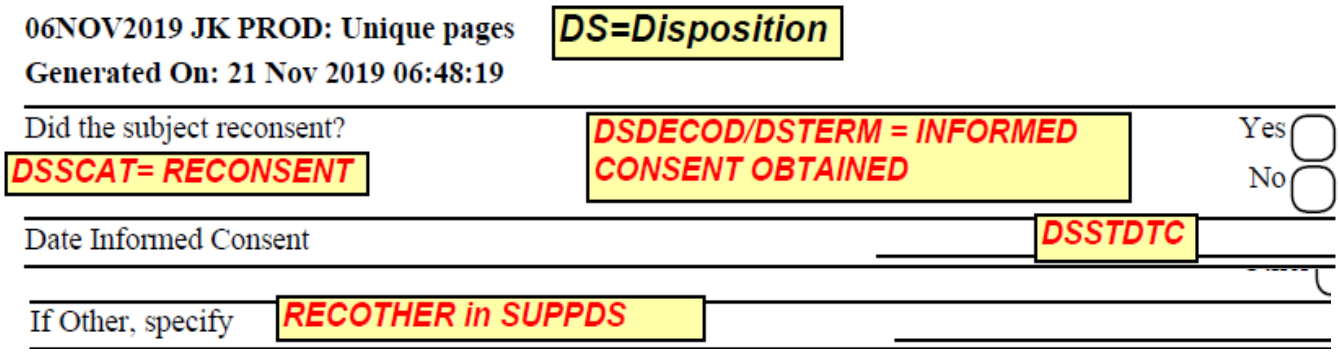
DS

USUBJID	DSSEQ	DSCAT	DSTERM	DSDECOD	DSSTDTC	EPOCH
0001	3	PROTOCOL MILESTONE	RANDOMIZATION	RANDOMIZATION	2019-11-19	SCREENING

SUPPDS

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
0001	DSSEQ	3	RANDNUM	Randomization Number	134549	CRF

SUPPDS Example 2: "Reason for reconsent": In this example, we would map the "Other, Specify" free text field to SUPPDS.QVAL and relate it to the DSTERM "Informed Consent Obtained" by DSSEQ. Note how DSSCAT is being used to indicate that this is "Re-consent" which is different from the original Consent.



DS

USUBJID	DSSEQ	DSCAT	DSSCAT	DSTERM	DSDECOD	DSSTDTC	EPOCH
0002	2	PROTOCOL MILESTONE	RECONSENT	INFORMED CONSENT OBTAINED	INFORMED CONSENT OBTAINED	2019-11-19	SCREENING

SUPPDS

USUBJID	IDVAR	IDVARVAL	QNAM	QLABEL	QVAL	QORIG
0002	DSSEQ	2	RECOTHER	Re-consent Other, Specify	PROTOCOL WAS AMENDED WITH ADDITIONAL CRITERIA	CRF

CONCLUSION:

- To summarize, this paper should give you a good idea of how to map the appropriate CRF values to DSTERM / DSDECOD and associate the right DSCAT values to them.
- Not every value on the CRF may be a perfect fit for the terms defined in the CDISC Codelist – so don't be afraid of requesting the NCI to 'extend' the Codelist, if it needs to be done.
- However be cautious to not add to a Codelist if the existing terms already imply or represent what the CRF is collecting.
- EPOCH can be really useful to help determine the study periods when the different disposition events occurred.
- When there are fields on the CRF that don't fit within the standard DS structure, they can be mapped to SUPPDS as a non-standard variable / value.

REFERENCES:

- Consolidated Standards of Reporting Trials (CONSORT): http://www.consort-statement.org/
- NCI Codelist Extension Request Form: https://nciterm form.nci.nih.gov/ncitermform/?version=cdisc
- NCI SDTM CT Codelist (Excel) (We have referenced versions of CT from March 2019 and Dec 2019): https://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.xls
- NCI SDTM CT Codelist (PDF): https://evs.nci.nih.gov/ftp1/CDISC/SDTM/SDTM%20Terminology.pdf
- CDISC SDTM IG v3.2: https://www.cdisc.org/system/files/members/standard/foundational/sdtmig/sdtmig_20v3.2_20noportfolio.pdf

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