Paper SA09

The Jumpstart Traceability Assessment

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ABSTRACT

Analysis Data Model (ADaM) datasets are frequently used as primary data for U.S. Food and Drug Administration (FDA) clinical reviews. Tracing ADaM data to its Study Data Tabulation Model (SDTM) source allows FDA reviewers to assess the relationship between the original and the derived data. The SDTM to ADaM Traceability Assessment investigates SDTM Demographics, Adverse Events, Laboratory, and Vital Signs datasets and compares them to their ADaM counterparts. The JumpStart analyst uses SAS programs and various display tools such as JMP to identify and evaluate differences between SDTM and ADaM. The customized SAS programs are run at the study level and matched to the submitted variables. Similarities and differences for key variables are then summarized and presented to the clinical reviewer. This paper discusses common findings from the traceability assessments. We share these findings to inform applicants of the need for thorough documentation regarding how ADaM variables are derived and any corresponding methodology such as date imputation, thereby increasing the efficiency of the review.

INTRODUCTION

The JumpStart Traceability Assessment traces ADaM data back to its SDTM source across four key topic areas: Demographics, Adverse Events, Laboratory, and Vital Signs. Figure 1 below highlights the general flow of data from SDTM to ADaM.

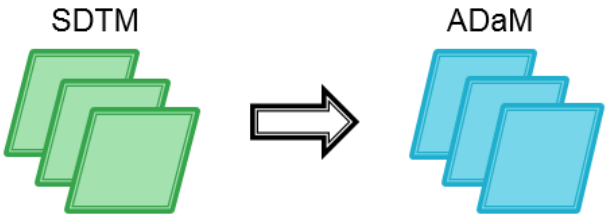

Figure 1: SDTM to ADaM Data Flow

The checks performed comparing SDTM and ADaM variables are detailed below and unique for each topic area. For findings domains, the same types of checks are performed across laboratory and vital signs datasets. Additionally, information regarding the new JumpStart assessment evaluating individual study ADaM data against Integrated Summary of Safety (ISS) ADaM data is included. In this new assessment, the same variables are checked across the four key topic areas (Demographics, Adverse Events, Laboratory, and Vital Signs), as well as an additional analysis evaluating MedDRA coding between the individual study ADaM data and the ISS ADaM data. The coding analysis assesses when differences in coding are expected due to different MedDRA versions used in the individual study and the ISS data. This analysis validates the coding used in the ISS ADAE dataset against the expected coding per the updated MedDRA version.

ANALYSIS OVERVIEW

Across all key datasets, there are two categories of checks:

1. The first is an analysis of records that exist in the SDTM dataset that were not preserved in the ADaM dataset, and derived or other records in the ADaM dataset that were not included in the original SDTM dataset. This analysis compares record counts in SDTM.DM vs. ADaM.ADSL, SDTM.AE vs. ADaM.ADAE, SDTM.LB vs. ADaM.ADLB and SDTM.VS vs. ADaM.ADVS for Demographics, Adverse Events, Laboratory and Vital Signs, respectively. Figure 2

below summarizes the scenario where record counts mismatch, and unique records exist in both the SDTM data and the ADaM data.

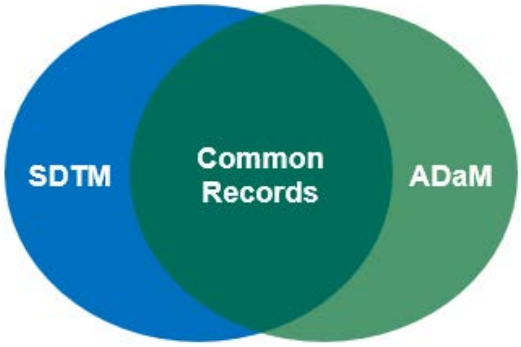

Figure 2: Venn Diagram Highlighting Common Records

Reasons that records do not exist in one dataset but exist in another are categorized, summarized, and presented to the reviewer. It is more common to see additional derived records in ADaM that do not exist in the original tabulated SDTM dataset. In this scenario, the value of this analysis allows the reviewer to filter the ADaM dataset as needed to achieve a similar tabulated view. The reviewer can then leverage additional information in this subset of the ADaM dataset, such as demographic information, analysis flags, and records that contain imputed values in ADaM that did not exist in the original SDTM dataset for their analysis.

Secondly, it may be the case that the SDTM data is a subset of the ADaM data or vice versa; if one dataset is a subset of the other, rather than the Venn Diagram in Figure 2 above, we would see a diagram like the one shown in Figure 3 below. In this scenario, all SDTM records are preserved in the ADaM dataset and the ADaM dataset contains derived records in addition to the original tabulated SDTM records.

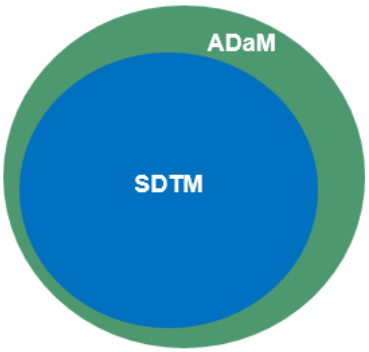

Figure 3: Venn Diagram Subset

Throughout our multiple assessments of records that exist in SDTM but are not preserved in the ADaM dataset, notable findings are summarized to the reviewer, though some are not as concerning as others. For example, it is common to see screen failure subjects who exist in the SDTM data dropped from the ADaM data which likely has a minimal impact on the review with the exception of analysis assessing for bias in patient selection. Similarly, 'Not Done' records in findings domains such as laboratory and vital signs excluded from ADaM are common and may be preferred by the reviewer to reduce 'noise' in the ADaM dataset. However, other findings such as unexplained truncation of treated subjects due to data transmittance errors are of higher concern, and in the past have led to Information Requests (IRs) being filed. For example, in one submission, records for treated subjects denoting results of key laboratory tests relevant to the indication were provided in the ADLB dataset but not submitted in the LB domain. After investigation, it was determined that the LB domain was truncated in error due to the large number of records present in the LB domain. Note that this finding is more common in large datasets where there is a higher likelihood of this error occurring, such as the laboratory domain.

2. The second category of checks is to assess values of key variables within the joined SDTM and ADaM dataset. After completing the first check, it is understood which records exist in both SDTM and ADaM datasets, and the datasets can be joined using Unique Subject Identifier (USUBJID) for Demographics, and Unique Subject Identifier and Sequence Number (xxSEQ) for Adverse Events, Laboratory, and Vital Signs. Within each topic area, specific variables are checked for consistency between SDTM and ADaM, and differences are summarized for the reviewer. For both categories of checks, the JumpStart analyst uses SAS programs and JMP to identify and evaluate

differences between SDTM and ADaM. The customized SAS programs are run at the study level and matched to the submitted variables. Each subsequent section below details the comparisons performed for each topic area.

DEMOGRAPHICS

The processes for the record count reconciliation and subsequent variable comparison for Demographics are described below.

Record Count Reconciliation

It is common to see the same subject count between the SDTM.DM domain and the ADaM.ADSL dataset. There are instances when subject counts don't match, which is primarily due to Screen Failure and/or Not Assigned subjects that exist in the DM domain but are dropped in the ADSL dataset. In this scenario, the reviewer should use the SDTM data to assess the screen failure or not assigned subjects. This is useful when evaluating potential bias in patient selection. In rare cases, treated subjects found in the DM domain that did not exist in the ADSL dataset were identified, but no explanation was provided. Scenarios like this may call into question the data practices of the applicant.

Variable Comparison

Matching records in SDTM.DM and ADaM.ADSL are joined on the Unique Subject Identifier (USUBJID) variable. Once records are joined, the SAS program completes a multitude of checks listed in Table 1 below.

Table 1: Demographics Variable Checks

DM Variable Name	DM Variable Label	ADSL Variable Name	ADSL Variable Label
AGE	Age	AGE	Age
AGEU	Age Units	AGEU	Age Units
SEX	Sex	SEX	Sex
RACE	Race	RACE	Race
ETHNIC	Ethnicity	ETHNIC	Ethnicity
RFXSTDTC	Date/Time of First Study Treatment	TRTSDT/ TRTSTM	Date of First Exposure to Treatment/ Time of First Exposure to Treatment
RFXENDTC	Date/Time of Last Study Treatment	TRTEDT/ TRTETM	Date of Last Exposure to Treatment/ Time of Last Exposure to Treatment
ARM	Description of Planned Arm	TRTxxP	Planned Treatment for Period xx
ACTARM	Description of Actual Arm	TRTxxA	Planned Treatment for Period xx
ACTARM*	Description of Actual Arm	Subject Population Flags* (e.g., RANDFL, ITTFL, SAFFL)	Randomization Flag, Intent-To-Treat Flag, Safety Flag

**The last row encompasses the population consistency checks between SDTM and ADaM which compares Description of Actual Arm (ACTARM) in SDTM against population flags submitted in the ADSL dataset. The population flags selected for comparison most often include Randomized Flag (RANDFL), Intent-To-Treat Flag (ITTFL), and Safety Flag (SAFFL); however, the SAS program is customizable to update flag variables based on the naming convention and flags submitted by the applicant. The utility of this check allows the analyst to validate if treatment arm variables in SDTM align with population flags submitted in ADaM and vice versa.*

If variable modifications are needed in either SDTM or ADaM, they are updated in the SAS program and the modified comparison is performed. For example, if the applicant only submitted Subject Reference Start Date/Time (RFSTDTC) and Subject Reference End Date/Time (RFENDTC) and did not submit Subject Reference Start Date/Time (RFXSTDTC) and Subject Reference End Date/Time (RFXENDTC) in the SDTM domain, the program is modified to perform checks on the submitted SDTM variables. In all cases, the variables compared are checked against the Define.xml file to ensure that the variable selection is appropriate for the study. Similarly, depending on the number of periods within the study and the structure of the ADSL dataset, it may be necessary to assess the RFXSTDTC and RFXENDTC in SDTM against Date of First Exposure in Period 01 (TR01SDT) and Date of Last Exposure in Period 01 (TR01EDT) in ADaM rather than TRTSDT and TRTEDT.

Table 2 provides additional context to the population consistency check and highlights areas of concern where the ACTARM value does not align with the subject population flags in the ADSL as expected.

Table 2: Demographics Treatment Arm Example*

DM domain			ADSL dataset		
USUBJID	ACTARM	TRT01A	RANDFL	ITTFL	SAFFL
Subject A	Treatment 1	Treatment 1	Y	Y	N
Subject B	Not Treated	Not Treated	Y	Y	Y
Subject C	Not Assigned	Not Assigned	Y	N	N

** Highlighted cells in the table indicate where discrepancies exist.*

A summary of most commonly observed demographics findings between the SDTM.DM and ADaM.ADSL datasets is provided in Table 3 below:

Table 3: Observed Demographics Findings

Category	Description
Demographic Characteristic Excluded	Variable is submitted in the DM domain but dropped from the ADSL dataset which may prevent demographic subgroup analysis. Note: If the reviewer is interested in breaking out a safety endpoint (e.g., a clinical adverse event of interest) by the desired demographic characteristic, the ADSL dataset must either be updated to include this variable from the DM domain, or the DM domain must be used instead.
Age Difference	Recalculation of Age (DM.AGE) between the DM domain and the ADSL dataset, yielding a difference in values for subjects
Race Difference	Race (DM.RACE) differences due to a more granular value submitted in the ADSL dataset than the DM domain
Treatment Start/End Date Difference	Observed reasons for differences include: • Partial dates in the DM domain that are imputed in the ADSL dataset. • Differences in the source of the date in SDTM vs. in ADaM, given the derivations in the Define.xml file, SDRG, and ADRG. For example, different sources may include Disposition (DS) or Exposure (EX). If the study includes a run-in period, it may be the case the date in one dataset (DM or ADSL) aligns with the first date of exposure to the run-in medication whereas the date in the other dataset aligns with the first date of exposure to the investigational treatment. • Mismatching dates that don't align with the derivation which may have higher impact to the review as the dates populated are unclear. An example of a questionable value is one where there exists an exposure date in the Exposure (SDTM.EX) domain that occurs after the reference end date in the DM, calling into question the DM date value and causing a mismatch between SDTM.DM and ADaM.ADSL end dates.
Treatment Arm Difference	Observed reasons for differences include: • Untreated subjects, including screen failure subjects, not assigned subjects, or not treated subjects have DM.ARM and DM.ACTARM values that list 'Screen Failure', 'Not Assigned', or 'Not Treated', respectively. In ADSL, the TRTxxP and TRTxxA variables often contain null values for these subjects as expected. • Arm variable not submitted in ADaM. For example, even though both ARM and ACTARM may have been submitted in the DM domain, if the applicant did not use actual treatment arm in their analysis, it may be possible that only the TRT01P variable exists in the ADSL dataset and therefore the comparison was only performed for ARM vs. TRT01P. • Extraneous arm variables submitted in ADaM. For example, it may be possible that the actual arm value in ADaM has an unexpected variable name (e.g., TRT30A to align with arm values assigned for the first 30-day treatment period), even though the a TRT01A variable may also exist in the ADSL dataset. • Granular description of TRTxxP and/or TRTxxA values submitted in ADaM. For example, values in ADaM may further break arm value out by dosage or frequency, whereas the value is aggregated to a higher level in the SDTM domain. Similarly, if there are multiple periods in the study, the ACTARM variable in the DM domain may append all periods together, which are then broken out in ADaM across multiple variables (e.g., TRT01A, TRT02A). Depending on the type of analysis the reviewer wishes to perform, the reviewer may need to aggregate similar arm values together for analyses if the breakout in ADaM is too granular.

Tables 4a and 4b below detail an illustrative example of treatment end date differences in SDTM.DM vs. ADaM.ADSL due to derivation differences. In Table 4a, assume that RFXENDTC is sourced from the last date of exposure, whereas TRTEDT is equal to the last disposition event for the double-blind period, indicating the subject is continuing participation in the extension study. Table 4b displays the latest date in the Exposure (EX) domain and latest disposition event in the Disposition (DS) domain for Subject A.

Table 4a: Demographics Treatment End Date Example

DM domain				ADSL dataset		
USUBJID	RFXSTDTC	RFXENDTC	ACTARM	TRTSDT	TRTEDT	SAFFL
Subject A	2019-06-01	2019-12-01	Treatment1	2019-06-01	2019-12-31	Y

Table 4b: Demographics Treatment End Date Example

EX domain				DS domain		
EXTRT	EXDOSE	EXDOSU	EXSTDTC	DSTERM	DSDECOD	DSSTDTC
Treatment1	100	mg	2019-12-01	Double-blind period complete; Continuing into extension study	Completed	2019-12-31

ADVERSE EVENTS

The processes for the record count reconciliation and subsequent variable comparison for Adverse Events are described below.

Record Count Reconciliation

Though it is common to see the same record count between the SDTM.AE and ADaM.ADAE datasets, the JumpStart team has observed discrepancies in record count between SDTM and ADaM datasets. Reasons for record count discrepancies include:

- Events that occurred prior to the screening period captured in the Adverse Events (AE) domain that were not included in the ADAE dataset.
    - It is expected that events captured prior to the screening period are included in the Medical History (MH) domain.
    - The reviewer may choose to subset the AE domain to exclude pre-screening events or to assess the ADAE. This may be also done by leveraging the treatment emergent flag in the SUPPAE domain or the ADAE dataset to only include treatment emergent adverse events in the analysis.
- Events observed in Screen Failure, Not Assigned, or Not Treated subjects during the screening period that were captured in the AE domain but were not included in the ADAE dataset.
- Events captured in the AE domain that occurred after the ADAE-defined TEAE cutoff date and were not included in the ADAE dataset.
- Events for derived records captured in the ADAE dataset that did not exist in the original AE domain, such as those categorizing records as 'Date Adverse Event Worsened'.
- Events for treated subjects captured in the AE domain that were not included in the ADAE dataset without a clear explanation in the documentation as to why the records were dropped.
- Events for rescreened patients captured in the AE domain that were not included in the ADAE dataset.
    - For example, events that were recorded under the initial USUBJID value were submitted in the AE domain but dropped from the ADAE dataset; therefore, only events that were recorded under the later USUBJID value generated during rescreening period were preserved in the ADAE dataset. Scenarios like this were summarized for the reviewer to determine if the events should be considered in analysis as they are relevant to the same treated subject.

Variable Comparison

Records in SDTM.AE and ADaM.ADAE are joined using both the Unique Subject Identifier (USUBJID) variable and the Sequence Number (AESEQ) variable. Once records are joined, the SAS program checks variables between SDTM.AE and ADaM.ADAE provided in Table 5 below. Note that the comparison of either Severity/Intensity or Standard Toxicity Grade is dependent on the variable submitted by the applicant in the datasets: Severity/Intensity (i.e., AESEV) or Standard Toxicity Grade (AETOXGR). It is common to only see one of the variables submitted. The SAS program is customizable to allow for either of these variables, as well as additional modifications, such as if the ADaM variable submitted is an 'analysis' version of the original SDTM variable. In this case, the ADaM analysis version (e.g., ASEV) is compared against the SDTM variable (e.g., AESEV).

Table 5: Adverse Events Variable Checks

AE Variable Name	AE Variable Label	ADAE Variable Name	ADAE Variable Label
AEDECOD	Dictionary-Derived Term	AEDECOD	Dictionary-Derived Term
AEBODSYS	Body System or Organ Class	AEBODSYS	Body System or Organ Class
AESEV	Severity/Intensity	ASEV	Analysis Severity/Intensity
AETOXGR	Standard Toxicity Grade	ATOXGR	Analysis Standard Toxicity Grade
AESTDTC	Start Date/Time of Adverse Event	ASTDT/ASTTM	Analysis Start Date/Analysis Start Time
AEENDTC	End Date/Time of Adverse Event	AENDT/AENTM	Analysis End Date/Analysis End Time
AESER	Serious Event	ASER	Analysis Serious Event
AESHOSP	Requires or Prolongs Hospitalization	AESHOSP	Requires or Prolongs Hospitalization
AESDTH	Results in Death	AESDTH	Results in Death
AESLIFE	Is Life Threatening	AESLIFE	Is Life Threatening
AESMIE	Other Medically Important Serious Event	AESMIE	Other Medically Important Serious Event
AESCONG	Congenital Anomaly or Birth Defect	AESCONG	Congenital Anomaly or Birth Defect
AESDISAB	Persistent or Significant Disability/Incapacity	AESDISAB	Persistent or Significant Disability/Incapacity
AESCAN	Involved Cancer	AESCAN	Involved Cancer
AESOD	Occurred with Overdose	AESOD	Occurred with Overdose
AEACN	Action Taken with Study Treatment	AEACN	Action Taken with Study Treatment
AEOUT	Outcome of Adverse Event	AOUT	Analysis Outcome of Adverse Event
AEREL	Causality	AREL	Analysis Causality

A treatment emergent flag check is also completed. Currently, there is no variable in the Adverse Events (AE) domain that indicates if an adverse event is treatment-emergent. Per the FDA's *Study Data Technical Conformance Guide*[1], the AE

domain should include all adverse events that were recorded in the subjects' case report forms, regardless of whether the sponsor determined that events were or were not treatment-emergent. Since the treatment emergent flag is not required in SDTM as it is a derived record, this check is not consistently performed across applications. The SAS program is customizable to use different flag variables based on the naming convention used by the applicant, such as if the applicant used 'TRTEMFL' in SUPPAE rather than the common 'AETRTEM' variable. When submitted, the SDTM treatment emergent flag is often housed in the Supplemental Adverse Events (SUPPAE) domain. Table 6 provided below contains the variable checked.

Table 6: Adverse Events Treatment Emergent Flag Check

SUPPAE Variable Name	SUPPAE Variable Label	ADAE Variable Name	ADAE Variable Label
AETRTEM	Treatment Emergent Flag	TRTEMFL	Treatment Emergent Flag

Table 7 summarizes the most commonly observed adverse events findings between the SDTM.AE and ADaM.ADAE datasets, provided below:

Table 7: Observed Adverse Events Findings

Category	Description
MedDRA Coding Mismatch	Uncoded events in the AE domain that are coded in ADAE; Difference in wording for unknown events (e.g., 'UNKNOWN' in the AE domain vs. 'U' in the ADAE dataset).
Severity/Intensity Mismatch	Severity/Intensity (AESEV) value is missing in the SDTM.AE domain but is imputed as maximum severity in the ADaM.ADAE dataset (i.e. 'Severe').
Start Date of Adverse Event Mismatch	Observed reasons for differences include: • Missing or partial dates in SDTM.AE are imputed in ADaM.ADAE as defined in the documentation such as the ADRG or the SAP. Partial dates in the SDTM.AE domain may be missing either day, day and month, or day, month, and year (i.e., missing), and the full date is often imputed in the ADaM ADAE dataset. • Mismatching nonpartial date values sourced from different locations that don't align with the derivation in the Define.xml file, which is likely more concerning to the reviewer. In both cases, the impact of the differences in date may affect duration analysis.
Treatment Emergent Flag Mismatch	Observed reasons for differences include: • Derivation differences between SDTM and ADaM as defined in the SDTM and ADaM Define.xml file, SDRG and ADRG, or SAP documentation. • Mismatching records that don't align with the derivation which may have higher impact to the review as the differences are unclear.

Table 8 provides an illustrative example of start date differences due to a partial date value in AE.AESTDTC that was imputed in ADAE.ASTDT. For this example, assume the imputation methodology for adverse events dates is defined in the SAP, and lists that for missing day, impute day in ADaM to be the later of 1) the first day of the month and 2) Date of First Exposure to Treatment.

Table 8: Adverse Events Start Date Example

ADSL dataset		ADAE dataset				
USUBJID	TRTSDT	AEDECOD	AESTDTC	EPOCH	ASTDT	TRTEMFL
Subject A	11-01-2019T08:00:00	Headache	12-2019	Treatment	12-01-2019	Y

Below are three illustrative examples of treatment emergent flags differing due to derivation differences.

- Subject A has SUPPAE.AETRTEM = 'Y' but ADAE.TRTEMFL is null. In this case, the derivation of SUPPAE.AETRTEM only takes the date component of AESTDTC into account, ignoring the time component. Since the derivation of ADAE.TRTEMFL takes both date and time into account, the treatment emergent flag is null in ADAE.
- Subject B has SUPPAE.AETRTEM = 'N' but ADAE.TRTEMFL = 'Y'. In this case, a partial date in AESTDTC results in AETRTEM set equal to 'N'. However, after imputing start and end date in the ADAE dataset, the adverse event now falls within the treatment emergent window in ADAE and is set equal to 'Y'.
- Subject C has SUPPAE.AETRTEM = 'Y' but ADAE.TRTEMFL is null. In this case, the cutoff date within the treatment emergent flag derivations differ between SUPPAE.AETRTEM and ADAE.TRTEMFL. Here, assume the SDTM Define.xml lists a derivation for SUPPAE.AETRTEMFL as 'on or after start of first exposure to treatment', whereas the ADaM Define.xml lists a derivation for ADAE.TRTEMFL as 'on or after start of first exposure to treatment, up to 30 days past the last exposure to treatment'. Derivation differences are a common reason as to why treatment emergent flags do not match.

Table 9 below provides data by domain for each of these three subjects.

Table 9: Adverse Events Treatment Emergent Flag Example

DM			AE			SUPPAE	ADAE		
USUBJID	RFXSTDTC	RFXENDTC	AEDECOD	AESTDTC	AEENDTC	AETRTEM	AESTDTM	AEENDTM	TRTEMFL
Subject A	2020-01-02 T12:00:00	2020-01-02 T12:00:00	Fatigue	2020-01-02 T10:00:00	2020-01-08 T:10:00:00	Y	2020-01-02 T10:00:00	2020-01-08 T:10:00:00	
Subject B	2020-01-02 T12:00:00	2020-03-02 T12:00:00	Nausea	2020-02	2020-02-05 T:10:00:00	N	2020-02-01 T00:00:00	2020-02-05 T:10:00:00	Y
Subject C	2020-01-02 T12:00:00	2020-03-02 T12:00:00	Dizziness	2020-06-12 T12:00:00	2020-08-15 T08:30:00	Y	2020-06-12 T12:00:00	2020-08-15 T08:30:00	

LABORATORY AND VITAL SIGNS

The processes for the record count reconciliation and subsequent variable comparison for Laboratory and Vital Signs are described below. Due to the identical checks performed across both Laboratory Results and Vital Signs domains, the processes are summarized together.

Record Count Reconciliation

It is uncommon to see the same record counts between the SDTM and ADaM datasets for findings domains such as laboratory and vital signs. It is more common to see additional records in ADaM that do not exist in the original tabulated SDTM dataset. Observed reasons for record count discrepancies include:

- Derived records in ADaM that do not exist in SDTM
- Screen Failure subjects in SDTM that were not preserved in ADaM
- 'Not Done' records in SDTM that were not preserved in ADaM (i.e., where Completion Status (LB.LBSTAT) equals 'NOT DONE' or 'ND')
- Specific tests in SDTM that were not relevant to analysis for the indication and not preserved in ADaM
- Central and local laboratory results captured in SDTM, but only central labs preserved in ADLB

The JumpStart team assesses the differences in record counts to categorize the records included in one dataset but not the other and summarizes these categories for the reviewer. While it is the ideal scenario that all differences are categorized and supplemented with clear documentation from the applicant, differences in record count without a clear reason are common. In this scenario, it is recommended that the reviewer spend additional time assessing if the records not preserved in the ADaM dataset are important for analysis. For example, as detailed on page 2, the unexplained truncation of records pertaining to treated subjects due to issues such as data transmittance errors are of higher concern and in the past have led to Information Requests (IRs) being filed.

Variable Comparison

After assessing records that exist in the SDTM dataset but are not preserved in the ADaM dataset and vice versa, like records in SDTM.LB/SDTM.VS and ADaM.ADLB/ADaM.ADVS are joined using both the Unique Subject Identifier (USUBJID) variable and the Sequence Number (LBSEQ/VSSEQ) variable. Once records are joined, the SAS program completes a multitude of checks, such as checking that values align between SDTM and ADaM across several key variables. Table 10 below provides a list of the variables checked between SDTM.LB/SDTM.VS and ADaM.ADLB/ADaM.ADVS.

Table 10: Laboratory and Vital Signs Variable Checks

SDTM Variable Name	SDTM Variable Label	ADaM Variable Name	ADaM Variable Label
xxSTRESN	Numerical Result/Finding in Standard Units	AVAL	Analysis Value
xxBLFL	Baseline Flag	ABLFL	Baseline Record Flag
xxTEST	Lab/Vital Signs Test or Examination Name	PARAM	Parameter
xxCAT	Category for Lab/Vital Signs Test	$PARCAT_y$	Parameter Category y
xxSTRESC	Character Result/Finding in Standard Format	AVALC	Analysis Value (Character)
xxSTRESU	Standard Units	AVALU	Analysis Units
VISIT	Visit Name	AVISIT	Analysis Visit
xxDTC	Date/Time of Specimen Collection/ Measurements	ADT/ADM	Analysis Date/Analysis Time

Table 11 summarizes the most commonly observed laboratory and vital signs findings between the SDTM.LB/VS and ADaM.ADLB/ADVS datasets.

Table 11: Observed Laboratory and Vital Signs Findings

Observed Laboratory/Vital Signs Findings	
Category	**Description**
Numerical Value Differences	Common differences are due to either value imputation in the ADaM dataset or difference in values due to unit conversion or rounding.
Baseline Flag Differences	Observed reasons for differences include: • Derivation differences between the baseline flag in SDTM vs. the baseline flag in ADaM, given the derivations in the Define.xml file, SDRG, ADRG, and/or SAP documentation. • Baseline flag value being dropped in ADaM for select tests, such as a pregnancy test records in the laboratory dataset. • Multiple baseline flags assigned in SDTM may be removed in ADaM, so that each subject and test only have a maximum of one baseline record. Conversely, a subject and test may have multiple baseline flags in ADaM due to assigning multiple flags for both local and central laboratory results to unique subject and tests, to account for all safety and efficacy analysis needs. • Baseline flags that were not derived in SDTM may be derived in ADaM. • Contradictions between records marked as baseline in either SDTM or ADaM and the metadata have been observed, where the records marked as baseline has been unclear.
Visit Differences	Common differences are due to derivation differences in SDTM vs. ADaM, sourced from different variables such as study day, baseline flags, or time windows. Note that differences in visit are expected; per the ADaMIG v1.1, *'AVISIT is a derived field and does not have to map to VISIT from the SDTM.'* However, providing a frequency table of the VISIT to AVISIT mapping to highlight differences may help the reviewer in assessing which variable they may want to use in their analysis.

Table 12 highlights illustrative examples of numerical value differences due to null value in LB.LBSTRESN that were updated in ADLB.AVAL. In the example below for Subject A, AVAL was populated with the numerical component of LBSTRESC. For Subject B, AVAL was imputed as 'x/2' where x equals the numerical component of LBSTRESC – this uncommon imputation methodology has been observed in prior submissions.

Table 12: Laboratory Value Example

LB domain						ADLB		
USUBJID	**LBTEST**	**LBSTRESC**	**LBSTRESN**	**LBSTRESU**	**EPOCH**	**AVALC**	**AVAL**	**AVALU**
Subject A	Bilirubin	<0.2		mg/dL	TREATMENT	<0.2	0.2	mg/dL
Subject B	Bilirubin	<0.3		mg/dL	TREATMENT	<0.3	0.15	mg/dL

Table 13 provides an illustrative example of baseline flags that differ due to derivation differences. In this example, the original baseline flag in the LB domain is assigned to the screening record that took place a week before treatment began whereas the baseline flag in the ADLB dataset aligns with the record that occurred on the same day but at a time prior to the beginning of treatment. In this case below, the values differ between baseline records. Therefore, shift tables and other baseline vs. postbaseline analysis will return different results if using SDTM rather than ADaM datasets.

Table 13: Laboratory Baseline Record Flag Example

DM		LB						ADLB	
USUBJID	**RFXSTDTC**	**LBTEST**	**LBSTRESN**	**LBSTRESU**	**LBDTC**	**LBDY**	**LBBLFL**	**AVAL**	**ABLFL**
Subject B	2020-01-08 T08:30:00	Bilirubin	0.15	mg/dL	2020-01-01 T12:00:00	-7	Y	0.15	
		Bilirubin	0.18	mg/dL	2020-01-08 T08:00:00	1		0.18	Y

INDIVIDUAL STUDY ADAM TO ISS ADAM TRACEABILITY

In the ISS Traceability Assessment, the individual study ADaM data is joined with and compared against the ISS ADaM data. This assessment allows for a more complete assessment on the traceability of data as it flows from the tabulated SDTM datasets to the analysis ADaM datasets to the integrated ADaM datasets as illustrated by Figure 3 below.

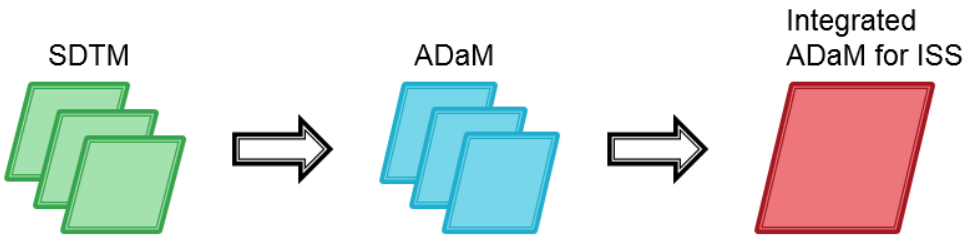

Figure 3: Individual SDTM to Individual ADaM to ISS ADaM Data Flow

This assessment is useful for reviewers who plan to use the integrated summary of safety (ISS) data in their analysis that was submitted for their application. The two categories of checks are similar to those detailed above in the SDTM to ADaM Traceability Assessment. The first category includes checking records that exist in the individual study ADaM dataset that were not included in the ISS ADaM dataset, as well as records that exist in the ISS ADaM dataset that were not contained within the individual study ADaM dataset. This analysis is completed for all four topic areas: Demographics (individual study ADaM.ADSL vs. ISS ADaM.ADSL), Adverse Events (individual study ADaM.ADAE vs. ISS ADaM.ADAE), Laboratory (individual study ADaM.ADLB vs. ISS ADaM.ADLB), and Vital Signs (individual study ADaM.ADVS vs. ISS ADaM.ADVS).

The second category of checks is to assess values for key variables within the joined individual study ADaM dataset and the ISS ADaM dataset. After completing the first check, it is understood which records exist in both the individual study ADaM and ISS ADaM datasets. The process for joining records to check these variables is similar to the process for SDTM to ADaM Traceability; however, Study Identifier (STUDYID) is leveraged in the join. Like records are joined using the STUDYID variable and the Unique Subject Identifier (USUBJID) variable for Demographics. For Adverse Events, Laboratory, and Vital Signs, like records are joined using STUDYID, USUBJID, and Sequence Number (e.g., AESEQ, LBSEQ, and VSSEQ, respectively). To aid in this assessment, SAS programs were designed to perform the same variable checks that are performed in the SDTM to ADaM traceability assessment and updated to match the data types of the variables submitted in the ADaM datasets. For example, instead of comparing character date in SDTM against numerical date in ADaM, the check was updated to check numerical date in the individual study ADaM dataset against numerical date in the ISS ADaM dataset.

Note that common findings identified in the tables above for each topic area are also relevant to the ISS data; however, reasons behind the differences vary when assessing ISS data. For example, differences in date values are a common finding in both the SDTM to ADaM Traceability and the Individual Study ADaM to ISS ADaM Traceability. Consider the comparison of adverse event end date: In the SDTM to ADaM Traceability Assessment, differences in adverse events dates are often due to partial dates in SDTM that are imputed in ADaM as described in the adverse events table above. When completing similar checks in the individual study ADaM ADAE vs. ISS ADaM ADAE datasets, end dates were different due to different imputation methodologies implemented across the ADAE datasets. Different imputation methodologies are acceptable; however, these cases are useful to show the reviewer as it may affect the results of adverse events duration analysis depending on the dataset used.

MEDDRA UPCODING

Checking the consistency of MedDRA coding (i.e., Dictionary-Derived Term (AEDECOD) and the Body System or Organ Class (AEBODSYS) variables) within the Adverse Events domain is an additional evaluation in the individual study ADaM to ISS ADaM traceability assessment. The additional complexity of different MedDRA versions is considered when the individual study ADaM ADAE dataset leverages MedDRA coding from an earlier MedDRA version than the version used in the ISS ADaM ADAE dataset. A SAS program designed to check for MedDRA coding differences due to the use of different versions is implemented to assess the severity of coding differences. The program reports any differences in AEDECOD and AEBODSYS values between the individual ADaM ADAE dataset and the ISS ADaM ADAE dataset. Furthermore, it validates differences in coding against the MedDRA version used in the ISS dataset to ensure the upcoding matches to the correct version. Though it is recommended that all MedDRA coding is thoroughly reviewed for accuracy, the utility of this program helps reviewers pinpoint areas to review where differences exist between ADAE datasets. Figure 4 below provides a conceptual example as to the differences that may exist between ADAE datasets. In the example, different MedDRA versions are leveraged; Event A is 'upcoded' to Event C, and Event B is 'upcoded' to Event D.

Study 1: MedDRA v19.1

STUDYID	USUBJID	AESEQ	AEDECOD
Study 1	123-ABC	1	Event A
Study 1	123-ABC	2	Event B

ISS: MedDRA v21.0

STUDYID	USUBJID	AESEQ	AEDECOD
Study 1	123-ABC	1	Event C
Study 1	123-ABC	2	Event D

Figure 4: Conceptual MedDRA Upcoding Example

CONCLUSION

Traceability is a key area of analysis. When records are similar across SDTM and ADaM, the reviewers can confidently use both SDTM and ADaM data throughout the review of their application. The JumpStart Traceability Assessment has assessed the SDTM to ADaM datasets for over 75 applications since 2017, and recently incorporated individual study ADaM to ISS ADaM traceability checks in FY20, having completed two assessments to date. The JumpStart program aims to aid the FDA in end-to-end traceability assessment services and works toward tracking and reporting differences observed across topic areas, including Demographics, Adverse Events, Laboratory, and Vital Signs. In addition, the purpose of the JumpStart assessment is to help the reviewer assess the impact of the differences in data observed for their application. As detailed above, the impact of the data differences depends on the finding, the number of records affected, and the documentation and reasoning provided by the applicant. Over the years, differences in datasets where reasoning is unclear due to an error may call into question the data practices of the applicant and result in an Information Request (IR) being filed. The JumpStart team reports these examples of a wider range of traceability findings in order to inform applicants of the need for thorough data and documentation in order to increase the efficiency and timeliness of the review.

REFERENCES

[1]*Study Data Technical Conformance Guide* (March 2018): https://www.fda.gov/media/88173/download

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