

Detecting ADaM Traceability Discrepancies in FDA’s JumpStart Service

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Background

ADaM datasets are frequently used as a primary data source for FDA clinical reviews. Since ADaM is derived from SDTM, it is essential to be able to trace ADaM data back to their SDTM sources. The JumpStart service provides CDER review teams with an assessment of the traceability quality and identifies differences between SDTM and ADaM datasets. The Office of Computational Science (OCS) JumpStart service has expanded the suite of capabilities offered in the traceability service including advanced treatment validation, additional adverse event variable changes, and analysis visit creation. Using a combination of automated scripts and additional investigation, the JumpStart team reviews errors as well as derivation concepts that may impact the review. Since FY17, the OCS JumpStart has offered over 120 SDTM to ADaM Traceability assessments to reviewers. This poster discusses some of the common findings and analytical advancements within the JumpStart Traceability Assessment.

Datasets Evaluated

The SDTM to ADaM Traceability programs provide systematic comparisons between SDTM and ADaM data, comparing important analysis variables across key datasets. These key datasets include Demographics, Adverse Events, Laboratory, and Vital Signs. Each dataset is investigated on dataset-specific characteristics. For example, characteristics such as age, race, sex, and ethnicity for Demographics and MedDRA coding, descriptive event information such as severity/toxicity, seriousness, seriousness qualifiers, and start and end dates for Adverse Events. For Labs & Vital Signs, tests and categories, results, start dates, reference ranges, baseline, and visit values are evaluated.

**Demographics**

**Adverse Events**

**Laboratory**

**Vital Signs**



Demographic Findings

In addition to demographic characteristics, the SDTM to ADaM Traceability analysis identifies differences in treatment information between DM and ADSL datasets. These include treatment arm and timing, population flags, and exposure information sourced from SDTM.EX. Examples of contradictory values are listed below:

DM			ADSL			Exposure Record?
USUBJID	ARM	ACTARM	TRT01P	TRT01A	SAFFL	
Subject A	Treatment 1	Treatment 1	Treatment 1	Treatment 2	Y	Y
Subject B	Treatment 2	Treatment 2	Treatment 2	Treatment 2	Y	N
Subject C	Treatment 1	Not Treated	Treatment 1	Not Treated	N	Y

JumpStart: Inconsistencies in treatment information may result in discrepancies between data and information reported in the CSR. JumpStart will work with the review team to understand, in detail, why subjects may be misaligned.



Adverse Event Findings

A common critical traceability issue identified in Adverse Events is differences in treatment emergent adverse event (TEAE) flag between the SDTM supplemental dataset (SUPPAE) and the ADaM ADAE dataset. The table below highlights examples of TEAE flag differences:

DM		AE		SUPPAE	ADAE	
USUBJID	RFXSTDTC	AEDECOD	AESTDTC	AETRTEM	AESTDTM	TRTEMFL
Subject A	2020-01-02 T12:00:00	Fatigue	2020-01-02 T10:00:00	Y	2020-01-02 T10:00:00	
Subject B	2020-01-02 T12:00:00	Nausea	2020-02	N	2020-02-01 T00:00:00	Y

JumpStart: Treatment emergent flag may be in the ADAE dataset as shown by the examples above. Records differ due to incorporating timestamp in the ADAE derivation for Subject A, and imputing day and time in the ADAE dataset for Subject B. For both subjects, flag results differ between SDTM and ADaM.

Changes in Lab & Vital Sign Baselines



Analysis Labs (ADLB) and Vital Sign (ADVS) datasets derive baseline record flags for analysis purposes. Baseline records in ADaM that do not align with SDTM baseline records due to differences in derivation or other reasons may call into question the data practices of the applicant. In this example, the derivation in ADaM takes timestamp into account whereas SDTM does not, resulting in differing flag results between SDTM and ADaM:



DMs		LB						ADLB
USUBJID	RFXSTDTC	LBTEST	LBSTRESN	LBSTRESU	LB DTC	LB DY	L BBLFL	A BBLFL
Subject B	2020-01-08 T08:30:00	Bilirubin	0.15	mg/dL	2020-01-01 T12:00:00	-7	Y	
		Bilirubin	0.18	mg/dL	2020-01-08 T08:00:00	1		Y

JumpStart: Differing numerical value for baseline records may result in shift tables and other baseline vs. postbaseline analysis will return different results if using SDTM rather than ADaM.

Advanced Traceability Capabilities

ISS Traceability Assessment

JumpStart offers the individual study ADaM to ISS ADaM data traceability assessment to support a full end-to-end traceability on demographic, adverse events, laboratory, and vital signs datasets for application submissions.

STUDYID	USUBJID	ASEQ	AVAL
Study 1	USUBJID-001-234	1	10
Study 2	USUBJID-002-234	1	23
Study 2	USUBJID-002-234	2	11
Study 3	USUBJID-003-234	8	102
Study 4	USUBJID-004-234	1	1

STUDYID	USUBJID	ASEQ	AVAL
Study 2	USUBJID-002-234	1	23
Study 2	USUBJID-002-234	2	11

STUDYID	USUBJID	AEDECOD
Study 1	USUBJID-001-234	...
Study 1	USUBJID-001-234	...

STUDYID	USUBJID	AEDECOD
Study 1	USUBJID-001-234	...
Study 1	USUBJID-001-234	...

MedDRA Upcoding Quality Check

In the event that MedDRA versions differ, JumpStart offers a MedDRA Upcoding program to check MedDRA coding accuracy from the individual study ADaM to ISS ADaM datasets. The program maps levels of the MedDRA hierarchy for each adverse event in the study and validates if the events were coded correctly given the updated ISS MedDRA version.