



INTEGO
GROUP

DS06: Mastering Pinnacle 21 for Oncology SDTM



Strasbourg 2024
PHUSE EU Connect 2024





PART I.

Introduction



Contents

- 1) Submission, what's in it
- 2) Big picture of the process
- 3) Oncology domains
- 4) Examples
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PART I. Submission



UNITED STATES

- **FDA** (Food and Drug Administration);

EUROPEAN UNION

- **EMA** (European Medicines Agency);
- **NCAs** (National Competent Authorities):
 - **MHRA** in the UK;
 - **ANSM** in France;

CANADA:

- **NCAs** (National Competent Authorities):

JAPAN

- PMDA (Pharmaceuticals and Medical Devices Agency)

AUSTRALIA

- TGA (Therapeutic Goods Administration)

INDIA

- CDSCO (Central Drugs Standard Control Organization)

BRAZIL

- ANVISA (Agência Nacional de Vigilância Sanitária)

CHINA

- NMPA (National Medical Products Administration)

SOUTH KOREA

- MFDS (Ministry of Food and Drug Safety)

- 1) FDA Business Rules [1] in July 2017, December 2017, and October 2018, respectively;
- 2) FDA Validator Rules [1] in March 2017, December 2017, and October 2018, respectively.
There are eighty-five (85) FDA business rules in total, Nonclinical with twenty-eight (28) rules, Clinical Only with twenty-one (21) rules, and Clinical and Nonclinical with thirty-six (36) rules.
- 3) “FDA business rules describe the business requirements for regulatory review to help ensure that study data is compliant and useful and supports meaningful review and analysis. The business rules are accompanied with validator rules which provide detail regarding FDA's assessment of study data for purposes of review and analysis
- 4) “Sponsors should evaluate their study data before submission against the conformance rules published by an SDO, the eCTD Technical Rejection Criteria for Study Data, and the FDA business rules.”

Types of Study Data Validation Rules [3]:

- 1) **Standards Development Organizations** (e.g., CDISC) provide rules that assess conformance to its published standards (See www.CDISC.org).
- 2) **FDA eCTD Technical Rejection Criteria** for Study Data that assess conformance to the standards listed in the FDA Data Standards Catalog (See above).
- 3) **FDA Business and Validator rules** to assess that the data support regulatory review and analysis

The whole process could be described like this:

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- 5) Adapting data for define.xml;

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- 1) eCRF;
- 2) Data Management;
- 3) define.xml;
- 4) Controlled Terminology;
- 5) Adapting data for define.xml;
- 6) Splitting into subfolders



PART II.

Big picture of the process



SDTM Package:

- SDTM SAS Transport files;
- cSDRG.pdf;
- define.xml;
- aCRF.pdf;

ADaM Package:

- ADaM datasets in xpt format;
- ADRG.pdf;
- define.xml;
- aCRF.pdf;
- Analysis Result Metadata;
- SAS programs in text formats;

In section 4.2 (Issue Summary), the explanation column allows you to justify Pinnacle 21 Community conformance issues that remain.

Issue Summary

Dataset	Diagnostic Message	Severity	Count	Explanation
LB	SD11117-Duplicate records	Warning	9	USUBJID ZJ123-1234-999-9999 was randomized twice and entered the study twice so has duplicate records.
PC	SD11117-Duplicate records	Warning	9	USUBJID ZJ123-1234-999-9999 was randomized twice and entered the study twice so has duplicate records.



PART III.

Oncology domains



ONCOLOGY DOMAINS

There are 3 oncology domains: TR, TU and RS.

1) **TU (Tumor Identification):** **the unique identification of tumors for each patient.**

- ☐ A single record is created for each distinct tumor identified.
- ☐ Tumors are typically identified only at baseline, unless a new tumor arises during a post-baseline record, necessitating its identification.
- ☐ If tumors are split or merged, additional post-baseline records are needed to clearly identify the new resultant tumors.
- ☐ The TULNKID variable serves as the key unique identifier, providing a distinct code for each identified tumor.
- ☐ According to the Findings domains within the core SDTM safety domains, controlled terminology is applied to the TUTESTCD and TUTEST variables. Examples include: TUMIDENT, TUMERGE, and TUSPLIT.

ONCOLOGY DOMAINS

2) TR (Tumor Results):

Quantitative measurements and qualitative assessments of the tumors identified in the TU domain.

- ☐ The TRLNKID variable links back to the TU domain.
- ☐ The TRLNKGRP variable connects the records in TR that correspond to a response assessment record in the RS domain. RELREC relationships should support this connection.
- ☐ In accordance with the Findings domains within the core SDTM safety domains, controlled terminology is applied to the TRTESTCD and TRTEST variables. Examples include: AREA, DIAMETER, and VOLUME.

ONCOLOGY DOMAINS

3) RS (Disease Response):

Clinical response evaluations derived from TR data and other SDTM domains.

- ☐ The RSLNKID variable links back to the TU domain.
- ☐ The RSLNKGRP variable connects the records in TR that support a response assessment record in the RS domain. RELREC relationships should reinforce this connection.
- ☐ In line with the Findings domains within the core SDTM safety domains, controlled terminology is applied to the RSTESTCD and RSTEST variables. Examples include: BESTRESP, OVRLRESP, and TRGRESP.
- ☐ Any data contributing to the response assessment should be linked to the RS record through RELREC, even if the supportive data is located outside the SDTM Oncology domains (e.g., lab results in LB).

Dataset to dataset relationship (using RELREC)

- TU, TR, RS and PR

Another example can be provided in the TU domain, where the TUGRPID can be used to identify the 'parent' tumor of split tumors and the 'parents' of merged tumors:

DOMAIN	USUBJID	TUGRPID	TULNKID	TUTESTCD	TUTEST	TUORRES
TU	40004		T04	TUMIDENT	Tumor Identification	TARGET
TU	40004		NT01	TUMIDENT	Tumor Identification	NON-TARGET
TU	40004	T04	T04.1	TUSPLIT	Tumor Split	TARGET
TU	40004	T04	T04.2	TUSPLIT	Tumor Split	TARGET
TU	40004	T02/T03	T02/T03	TUMERGE	Tumor Merged	TARGET
TU	40004		NEW01	TUMIDENT	Tumor Identification	NEW

FDA Validator Rule ID	FDA Validator Rule Description
FDAB003	Reported Term for the Adverse Event (AETERM) is expected to be coded using the Medical Dictionary for Regulatory Affairs (MedDRA). Sponsors should code each term to the MedDRA-specified hierarchy of terms. These terms/codes are represented in SDTM variables that are subject to MedDRA: AELLT, AELLTCD, AEDECOD, AEPTCD, AEHLT, AEHLTCD, AEHLGT, AEHLGTCD, AEBODSYS, AEBDSYCD, AESOC, AESOCCD.
FDAB004	Adverse Events (AE) dataset should be included in every submission. Lab Test Results (LB) dataset should be included in every submission. Vital Signs (VS) dataset should be included in every submission. Subject Elements (SE) dataset should be included in every submission. Exposure (EX) dataset should be included in every submission. Disposition (DS) dataset should be included in every submission.
FDAB006	All death information should be populated for subjects that died during the study including any post treatment follow-up.
FDAB007	All deaths should be an independent row in the adverse event dataset.
FDAB010	All serious adverse events should be flagged.
FDAB028	Screen Failure subjects should have records in Inclusion/Exclusion dataset.
FDAB055	Trial participants should self-report race and ethnicity and they should not be assigned by the study team.

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB026	Multiple BASELINE records for the same test	By its definition clinical baseline flags (e.g., last non-missing value prior to first dose) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Baseline Flag (--BLFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Method (--METHOD), Specimen (--SPEC), Location (--LOC), Laterality (--LAT) and Directionality (--DIR).	Baseline

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB030	Inconsistent value for Standard Units	Standard Units (--STRESU) must be consistent for all records with the same Short Name of Measurement, Test or Examination (--TESTCD), Object of the Observation (--OBJ), Measurement,Test, or Examination Detail (--TSTDTL), Category (--CAT), Subcategory (--SCAT), Specimen Type (--SPEC) and Method of Test or Examination (--METHOD).	CT

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB022	Missing EPOCH value, when a start or observation date is provided	The EPOCH variable is not populated, however either a start date or a collection date is provided. The presence of a start date or collection date for a record should allow for the EPOCH variable to be populated. Variables requested by the relevant regulatory agency in policy documents (e.g., EPOCH) should be included in the dataset and populated.	Epoch

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB026	Multiple --LOBXFL records for the same test	By its definition Last Observation Before Exposure Flag (--LOBXFL) should have only a single record for the same test for subject. Therefore, each subject (USUBJID) should have no more than one record with Last Observation Before Exposure Flag (--LOBXFL) equals 'Y' for the same assessment which is defined by Test (--TESTCD), Category (--CAT), Subcategory (--SCAT), Position of Subject During Observation (--POS), Method (--METHOD), Specimen (--SPEC), Location (--LOC) and Laterality (--LAT).	Flags

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB018	Inconsistent variable length within split datasets	Split datasets should have matching variable lengths for future merges. Datasets should be resized to the maximum length used prior to splitting.	Meta

FDA Validator Rule ID	FDA Validator Rule Message	FDA Validator Rule Description	Type
FDAB042	Missing value for --REASND, when -STAT is 'NOT DONE'	Value of Reason Not Done (--REASND) variable should be populated, when Status (--STAT) variable value is 'NOT DONE'.	Status
FDAB042	Value for --STRESC is populated, when --STAT is 'NOT DONE'	Status (--STAT) should be NULL, when Standardized Result in Character Format (--STRESC) is provided.	Status



PART IV.

Examples



- 1) Not found in CT
- 2) SDRG
- 3) Long term follow-up
- 4) LNKID (RELREC)

Variable Name	Variable Label	Type	Controlled Terms, Codelist or Format ¹	Role	CDISC Notes	Core
TRTESTCD	Tumor/Lesion Assessment Short Name	Char	(TRTESTCD)	Topic	Short name of the TEST in TRTEST. TRTESTCD cannot contain characters other than letters, numbers, or underscores. Examples: "TUMSTATE", "DIAMETER", "LESSCIND", "LESRVIND". See assumption 3.	Req
TRTEST	Tumor/Lesion Assessment Test Name	Char	(TRTEST)	Synonym Qualifier	Verbatim name of the test or examination used to obtain the measurement or finding. The value in TRTEST cannot be longer than 40 characters. Examples: "Tumor State", "Diameter", "Volume", "Lesion Success Indicator", "Lesion Revascularization Indicator". See assumption 3.	Req
TORRES	Result or Finding in Original Units	Char		Result Qualifier	Result of the tumor/lesion measurement/assessment as originally received or collected.	Exp
TORRESU	Original Units	Char	(UNIT)	Variable Qualifier	Original units in which the data were collected. The unit for TORRES. Example: "mm".	Exp
TRSTRESC	Character Result/Finding in Std Format	Char	(TRPROPRS)	Result Qualifier	Contains the result value for all findings copied or derived from TORRES, in a standard format or standard units. TRSTRESC should store all results or findings in character format; if results are numeric, they should also be stored in numeric format in TRSTRESN.	Exp
TRSTRESN	Numeric Result/Finding in Standard Units	Num		Result Qualifier	Used for continuous or numeric results or findings in standard format; copied in numeric format from TRSTRESC. TRSTRESN should store all numeric test results or findings.	Exp
TRSTRESU	Standard Units	Char	(UNIT)	Variable Qualifier	Standardized unit used for TRSTRESN.	Exp
TRSTAT	Completion Status	Char	(ND)	Record Qualifier	Used to indicate a scan/image/physical exam was not performed or a tumor/lesion measurement was not taken. Should be null if a result exists in TORRES.	Perm
TRREASND	Reason Not Done	Char		Record Qualifier	Describes why a scan/image/physical exam was not performed or a tumor/lesion measurement was not taken. Examples: "SCAN NOT PERFORMED", "NOT ASSESSABLE: IMAGE OBSCURED TUMOR". Used in conjunction with TRSTAT when value is "NOT DONE".	Perm
TRNAM	Laboratory/Vendor Name	Char		Record Qualifier	The name or identifier of the vendor that performed the tumor/lesion measurement or assessment. This column can be left null when the investigator provides the complete set of data in the domain.	Perm
TRMETHOD	Method Used to Identify the Tumor/Lesion	Char	(METHOD)	Record Qualifier	Method used to measure the tumor/lesion/location of interest. Examples: "MRI", "CT SCAN", "PET SCAN", "Coronary angiography".	Exp
TRLOBXFL	Last Observation Before Exposure Flag	Char	(NY)	Record Qualifier	Operationally-derived indicator used to identify the last non-missing value prior to RFXSTDTC. Should be "Y" or null.	Exp
TRBLFL	Baseline Flag	Char	(NY)	Record Qualifier	Indicator used to identify a baseline value. Should be "Y" or null. Note that TRBLFL is retained for backward compatibility. The authoritative baseline flag for statistical analysis is in an ADaM dataset.	Perm
TREVAL	Evaluator	Char	(EVAL)	Record Qualifier	Role of the person who provided the evaluation. Used only for results that are subjective (e.g., assigned by a person or a group). Examples: "ADJUDICATION COMMITTEE", "INDEPENDENT ASSESSOR".	Exp
TREVALID	Evaluator Identifier	Char	(MEDEVAL)	Variable Qualifier	Used to distinguish multiple evaluators with the same role recorded in TREVAL. Examples: "RADIOLOGIST1", "RADIOLOGIST2". See assumption 6.	Perm
TRACPTFL	Accepted Record Flag	Char	(NY)	Record Qualifier	In cases where more than 1 independent assessor (e.g., "RADIOLOGIST 1", "RADIOLOGIST 2", "ADJUDICATION COMMITTEE") provide independent assessments at the same time point, this flag identifies the record that is considered to be the accepted assessment.	Perm
VISITNUM	Visit Number	Num		Timing	Clinical encounter number. Numeric version of VISIT, used for sorting.	Exp
VISIT	Visit Name	Char		Timing	Protocol-defined description of a clinical encounter.	Perm
VISITDY	Planned Study Day of Visit	Num		Timing	Planned study day of the visit based upon RFSTDTC in Demographics.	Perm
TAETORD	Planned Order of Element within Arm	Num		Timing	Epoch associated with the date/time at which the assessment was made.	Perm
EPOCH	Epoch	Char	(EPOCH)	Timing	Epoch associated with the element in the planned sequence of elements for the arm to which the subject was assigned.	Perm

tu.xpt

Row	STUDYID	DOMAIN	USUBJID	TUSEQ	TUGRPID	TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC	TULOC	TULAT	TUMETHOD	TUEVAL	VISITNUM	VISIT	TUDTC	TUDY
1	ABC	TU	44444	1		T01	TUMIDENT	Tumor Identification	TARGET	TARGET	LIVER		CT SCAN	INVESTIGATOR	10	SCREEN	2010-01-01	-3
2	ABC	TU	44444	2		T02	TUMIDENT	Tumor Identification	TARGET	TARGET	KIDNEY	RIGHT	CT SCAN	INVESTIGATOR	10	SCREEN	2010-01-01	-3
3	ABC	TU	44444	3		T03	TUMIDENT	Tumor Identification	TARGET	TARGET	CERVICAL LYMPH NODE	LEFT	MRI	INVESTIGATOR	10	SCREEN	2010-01-02	-2
4	ABC	TU	44444	4		T04	TUMIDENT	Tumor Identification	TARGET	TARGET	SKIN OF THE TRUNK		PHOTOGRAPHY	INVESTIGATOR	10	SCREEN	2010-01-03	-1
5	ABC	TU	44444	5		NT01	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	THYROID GLAND	RIGHT	CT SCAN	INVESTIGATOR	10	SCREEN	2010-01-01	-3
6	ABC	TU	44444	6		NT02	TUMIDENT	Tumor Identification	NON-TARGET	NON-TARGET	CEREBELLUM	RIGHT	MRI	INVESTIGATOR	10	SCREEN	2010-01-02	-2
7	ABC	TU	44444	7	T04	T04.1	TUSPLIT	Tumor Split	TARGET	TARGET	SKIN OF THE TRUNK		PHOTOGRAPHY	INVESTIGATOR	40	WEEK 6	2010-02-20	48
8	ABC	TU	44444	8	T04	T04.2	TUSPLIT	Tumor Split	TARGET	TARGET	SKIN OF THE TRUNK		PHOTOGRAPHY	INVESTIGATOR	40	WEEK 6	2010-02-20	48

Example target tumor T04, identified at the screening visit, splits into 2 at week 16. Two new records are created with TUTEST = "Tumor Split"; TULNKID reflects the split by adding 0.1 and 0.2 to the original TULNKID value.

TULNKID	TUTESTCD	TUTEST	TUORRES	VISIT
T01	TUMIDENT	Tumor Identification	TARGET	SCREEN
T02	TUMIDENT	Tumor Identification	TARGET	SCREEN
T03	TUMIDENT	Tumor Identification	TARGET	SCREEN
T04	TUMIDENT	Tumor Identification	TARGET	SCREEN
NT01	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
NT02	TUMIDENT	Tumor Identification	NON-TARGET	SCREEN
T04.1	TUSPLIT	Tumor Split	TARGET	WEEK 16
T04.2	TUSPLIT	Tumor Split	TARGET	WEEK 16
NEW01	TUMIDENT	Tumor Identification	NEW	WEEK 32

STUDYID	DOMAIN	USUBJID	TULNKID	TUTESTCD	TUTEST	TUORRES	TUSTRESC	VISIT
NNNNNN	TU	10101010	T01	TUSPLIT	Tumor Split	NO MEASUREMENTS	NOT MEASURED	SCREENING
NNNNNN	TU	10101011	T02	TUSPLIT	Tumor Split	DISTANT	DISTANT	SCREENING
NNNNNN	TU	10101012	T03	TUSPLIT	Tumor Split	MEASURED	MEASURED	SCREENING
NNNNNN	TU	10101013	T04	TUSPLIT	Tumor Split	NOT A TARGET	NON-TARGET	SCREENING

STUDYID	RDOMAIN	USUBJID	IDVAR	IDVARVAL	RELTYPE	RELID
ABC12345	TU		TULNKID		ONE	TUTR-I
ABC12345	TR		TRLNKID		MANY	TUTR-I
ABC12345	TR		TRLNKGRP		MANY	TRRS-II
ABC12345	RS		RSLNKGRP		ONE	TRRS-II
ABC12345	PR		PRREFID		ONE	PRTU-I
ABC12345	TU		TUREFID		MANY	PRTU-I
ABC12345	PR		PRLNKGRP		MANY	PRRS-III
ABC12345	RS		RSLNKGRP		ONE	PRRS-III

Table 11. Oncology domains linked among themselves and with PR which captures the Procedure methods



PART V.

Conclusion



GENERAL APPROACH TO REVIEW PINNACLE 21 REPORTS:

The general approach to review Pinnacle 21 reports are as follows.

1. Review errors and warnings carefully. Understanding P21C findings can be difficult and it is the responsibility of the programmer to discern which issues can or cannot be resolved. It is common to have issues come from multiple sources such as dirty data, incorrect mapping, and programming errors. Additionally, some issues are present simply because the study is ongoing (this is especially true with issues related to the Disposition domain). Before the programmer can communicate issues to Data Management, the programmer must discern which issues are suspected to be data related.

2. Notify data management (DM) about any data related and try to fix any programming errors, mapping, and CT related issues. But, strictly avoid any workaround programming to get rid of errors and warnings e.g. no date imputation on SDTM level to avoid any warning related to date. General perspective, Errors always have High severity; whereas Warnings have either Low or Medium severity. Errors must be corrected; however, Warnings should be corrected in order to assist with the submission, even though some warning and errors may be acceptable depending on the study.
3. Give special attention to notices it might be related to configuration issue.
4. If the issue is irresolvable then provide a proper justification in reviewer's guide. Issue explanations should be detailed and study specific. Unfortunately, there are many cases when provided explanations are generic and invalid.



QUESTIONS?





THANK YOU FOR ATTENTION

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