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Strategic Approaches to the Use of SEND Controlled Terminology

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Abstract

Starting in December 2016, SEND (Standard for Exchange of Nonclinical Data) will become mandatory for nonclinical FDA submissions. One requirement of SEND is the mapping of specified study terms to CDISC SEND controlled terms (CT). However, the SEND model itself also requires inclusion of original terms recorded by pathologists and other scientists, in addition to the mapping of these terms to SEND CT. This dual representation provides sponsors with strategic options. For example, it is possible to create glossaries within LIMS (Laboratory Information Management Systems) using SEND controlled terminology. With that option, the identical information will populate SEND variables for results as collected AND results mapped to controlled terminology. In contrast, if sponsors prefer to retain their own terminologies within their LIMS, their original results will be captured in SEND in addition to also being mapped to controlled terminology within SEND. Since SEND is a standard electronic format, it can be used to build data warehouses and repositories. The decision of which controlled terminology option to choose should therefore be driven by data analysis strategies (which terms are the most appropriate and what data to capture and use for searches).

User Defined Glossaries & Controlled Terminology

User-defined glossaries and controlled terminology (CT) equivalents pose for pathologists because pathology is primarily a descriptive discipline.

The table following, from the SEND Implementation Guide (SENDIG) v3.0, describes some of the variables that comprise the microscopic pathology (MI) domain of SEND.

- **The variables "MIORRES" and "MISTRESC" are highlighted because they refer to original results entered by the Study Pathologist, which do not require CT.** (An exception occurs when populating "MISTRESC" with tumor findings, which must conform to CT.)
- "MIORRES" includes the base microscopic pathologic process and all modifiers as collected by the pathologist.
- "MISTRESC" is the base pathologic process from "MIORRES" without modifiers. Similarly, original results recorded at necropsy are part of the macroscopic pathology (MA) domain ("MAORRES" and "MASTRESC" variables).
- While controlled terminology is an important part of SEND, SEND also requires the inclusion of original terminology as recorded by the pathologist (and by other scientists for the other SEND findings domains).

6.3.8 MICROSCOPIC FINDINGS – MI

mi.xpt, Microscopic Findings — Findings. One record per finding per specimen per subject, Tabulation.

Variable Name	Variable Label	Type	Controlled Terms, Codelist, or Format	Role	CDISC Notes	Core
STUDYID	Study Identifier	Char		Identifier	Unique identifier for a study.	Req
DOMAIN	Domain Abbreviation	Char	MI	Identifier	Two-character abbreviation for the domain.	Req
USUBJID	Unique Subject Identifier	Char		Identifier	Identifier used to uniquely identify a subject across all studies for all applications or submissions involving the product.	Req
MISEQ	Sequence Number	Num		Identifier	Sequence number given to ensure uniqueness of subject records within a domain. May be any valid number.	Req
MIGRPID	Group Identifier	Char		Identifier	Used to tie together a block of related records in a single domain for a subject. This is not the treatment group number.	Perm
MIREFID	Specimen Reference Identifier	Char		Identifier	Internal or external specimen identifier. Example: Specimen barcode number.	Perm
MISPID	Mass Identifier	Char		Identifier	Mass identifier such as MASS 1 or MASS A. Used when the mass was discovered during the in-life phase or during pathology and assigned a mass identifier. The mass identification should be unique within the subject, regardless of mass location.	Perm
MITESTCD	Microscopic Examination Short Name	Char	(MITESTCD)	Topic	Short name of the measurement, test, or examination described in MITEST. It can be used as a column name when converting a dataset from a vertical to a horizontal format. The value in MITESTCD cannot be longer than 8 characters, nor can it start with a number (e.g., "1TEST" is not valid). MITESTCD cannot contain characters other than letters, numbers, or underscores. Extensible controlled value is MIEXAM.	Req
MITEST	Microscopic Examination Name	Char	(MITEST)	Synonym Qualifier	Long name for MITESTCD. The value in MITEST cannot be longer than 40 characters. Extensible controlled value is Microscopic Examination.	Req
MIBODSYS	Body System or Organ Class	Char	(BODSYS)	Record Qualifier	Body system or organ class associated with the measurement performed.	Perm
MIORRES	Result or Findings as Collected	Char		Result Qualifier	Text description of the findings as originally received or collected, including the base pathological process and any modifiers.	Exp
MISTRESC	Standardized Result in Character Format	Char		Result Qualifier	Contains only the base pathological process (e.g., NECROSIS) from MIORRES without any modifiers such as severity, distribution, frequency, grade, etc. Or, if the examination was completed and there were no findings, the value must be NORMAL. Tumors must be populated using TFSTRESC controlled list. MISTRESC is not currently controlled for non-neoplastic/non-tumor findings.	Exp
MIRESCAT	Result Category	Char	(MIRESCAT)	Result Qualifier	Used to categorize the result of a finding. Example: MALIGNANT for tumor findings. Histopathological findings may be categorized as NON-NEOPLASTIC.	Perm
MISTAT	Completion Status	Char	(ND)	Record Qualifier	Used to indicate examination not done or result is missing. Should be null if a result exists in MIORRES.	Perm

User Defined Glossaries & Controlled Terminology *(cont)*

A continuation of the first table in this poster, showing additional MI variables from SENDIG 3.0, is presented below. SEND variables (modifiers) that can be derived from "MIORRES" and require CT are highlighted in yellow.

Variable Name	Variable Label	Type	Controlled Terms, Codelist, or Format	Role	CDISC Notes	Core
MIREASND	Reason Not Done	Char		Record Qualifier	Describes why MISTAT is NOT DONE, such as SAMPLE AUTOLYZED or SPECIMEN LOST.	Perm
MINAM	Laboratory Name	Char		Record Qualifier	Name or identifier of the laboratory or vendor who provides the test results if different per animal or different from Trial Summary (TS).	Perm
MISPEC	Specimen Material Type	Char	(SPEC)	Record Qualifier	Subject of the observation. Defines the type of specimen used for a measurement. Examples: LIVER, HEART, BONE MARROW.	Req
MIANTREG	Anatomical Region of Specimen	Char		Variable Qualifier	Example: Cortex, Medulla, or Femur (if the MISPEC is, for example, BONE MARROW).	Perm
MISPCOND	Specimen Condition	Char		Variable Qualifier	Free or standardized text describing the condition of the specimen. Example: AUTOLYZED	Exp
MISPCUFL	Specimen Usability for the Test	Char	(NY)	Variable Qualifier	Describes the usability of the specimen for the test. Example: N = the specimen is not usable; otherwise null.	Exp
MIMETHOD	Method of Test or Examination	Char		Record Qualifier	Method of the test or examination. This could be different types of coloring used for the slides whenever appropriate. Examples: H&E.	Perm
MILAT	Specimen Laterality within Subject	Char	(LAT)	Variable Qualifier	Qualifier for laterality of the specimen within the subject for paired specimens. Examples: LEFT, RIGHT, BILATERAL.	Perm
MIDIR	Specimen Directionality within Subject	Char	(DIR)	Variable Qualifier	Qualifier for directionality of the specimen within the subject. Examples: DORSAL, PROXIMAL.	Perm
MIEVAL	Evaluator	Char		Record Qualifier	Role of the person who provided the evaluation. Example: TOX PATHOLOGIST, PEER REVIEW, SPONSOR PATHOLOGIST.	Perm
MISEV	Severity	Char	(SEV)	Variable Qualifier	Describes the severity of a particular finding.	Exp
MIDTHREL	Relationship to Death	Char	(NY)	Record Qualifier	Describes the relationship of a particular finding to the death of a subject (Y=caused death; N=did not cause death, U=unknown). May be left null if not available.	Perm
MIDTC	Date/Time of Specimen Collection	Char	ISO 8601	Timing	Date/time of specimen collection, in ISO 8601 format.	Perm
MIDY	Study Day of Specimen Collection	Num		Timing	Study day of specimen collection, in integer days. The algorithm for calculations must be relative to the sponsor-defined RFSTDTC variable in the Demographics (DM) domain.	Perm

Strategic Approaches to Mapping CT

There are several options for how to implement CT mapping:

1. Continue using sponsor-created glossaries in LIMS / data collection systems and map CT within the SEND solution;
2. Update LIMS glossaries with CT, eliminating or greatly reducing the need for CT mapping;
3. Apply a hybrid approach.

If a pathologist (or other scientist) chooses the first option, data from LIMS will populate "MIORRES" and "MISTRESC" and the final toxicology reports. CT equivalents for modifiers (SEND 3.0) or base pathological processes and modifiers (SEND 3.1) will populate appropriate SEND variables per SENDIG.

With the second option, the same CT terms will populate "MIORRES", "MISTRESC", the SEND variables requiring CT, and the toxicology reports.

The decision of which option to implement should be driven by science (which terms are the most appropriate), data warehousing strategies (which data to capture and use for searches), what a sponsor wants to appear in a final toxicology report & SEND datasets, and the practical need to update CT as new releases are issued quarterly. Conversion of historical / legacy data to SEND is another factor when deciding which CT approach to use. *Selection of an appropriate CT mapping strategy will become even more important for SENDIG 3.1 due to the introduction of CT for non-neoplastic lesions and new pathology variables.*

In panel 3 of this poster, we present SEND 3.0 MI domains populated with the same data but utilizing different CT mapping approaches.

QUICK TIPS

Extensible Vs NonExtensible CT, MI Domain, & SDRG:

If a sponsor deems it necessary to use a term that is not included in a CDISC nonextensible codelist, the justification to do so, along with the term, should be included in the SDRG & discussed with the FDA division reviewer.

Approach 1: User Defined LIMS Glossary for MIORRES and MISTRESC

When using Approach 1, it is not necessary to update LIMS glossaries. Rather, CT is mapped outside of the LIMS, within the SEND solution. The tables in the final toxicology report will contain the LIMS terms. The SEND datasets will contain the LIMS terms in --ORRES and their controlled terminology equivalents in the appropriate SEND variables for modifiers as required and specified by SENDIG.

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MITESTCD	MITEST	MIORRES
1	123	MI	123-01	1	MIEXAM	Microscopic Examination	Brain, temporal cortex, necrosis, bilateral, focally extensive, slight
2	123	MI	123-02	2	MIEXAM	Microscopic Examination	Brain, temporal cortex, necrosis, bilateral, focally extensive, trace

Row	MISTRESC	MISPEC	MIANTREG	MISEV
1 (cont)	Necrosis	BRAIN	LEFT TEMPORAL CORTEX	MILD
2 (cont)	Inflammation	BRAIN	LEFT TEMPORAL CORTEX	MINIMAL

In this example, the pathologist recorded the brain lesion severities for USUBJIDs 123-01 and 123-02 as "slight" and "trace", and these were included in MIORRES. Because neither term is part of CDISC SEND CT, "slight" was mapped to the CT term "MILD" and entered under MISEV for USUBJID 123-01. "Trace" was mapped to the CT term MINIMAL and entered under MISEV for USUBJID 123-02. Note that the distribution modifier *focally extensive* would become part of a SUPPMI domain (supplemental qualifiers domain for microscopic findings) because a variable for distribution is not present in the MI domain in SEND 3.0.

Approach 2: LIMS Glossaries are Updated to Contain CT

With Approach 2, LIMS (data collection) glossaries will contain CDISC SEND CT. The CT will be used for data entry into LIMS, tables in the final toxicology report, the SEND variables --ORRES, --STRESC, and any associated modifiers that require CT as specified by SENDIG.

Row	STUDYID	DOMAIN	USUBJID	MISEQ	MITESTCD	MITEST	MIORRES
1	123	MI	123-01	1	MIEXAM	Microscopic Examination	Brain, temporal cortex, necrosis, bilateral, focally extensive, mild
2	123	MI	123-02	2	MIEXAM	Microscopic Examination	Brain, temporal cortex, necrosis, bilateral, focally extensive, minimal

Row	MISTRESC	MISPEC	MIANTREG	MISEV
1 (cont)	Necrosis	BRAIN	LEFT TEMPORAL CORTEX	MILD
2 (cont)	Inflammation	BRAIN	LEFT TEMPORAL CORTEX	MINIMAL

In the example above, the controlled terms for the severity modifiers "mild" and "minimal" were part of the original findings entered by the pathologist and entered under MIORRES. They were also used to populate MISEV, which requires CT.

QUICK TIPS

MI Domain: SENDIG 3.1

SENDIG 3.1 includes 2 new variables for microscopic pathology modifiers: MICHRON (chronicity) and MIDISTR (distribution). MISTRESC will be populated with terms from 2 new codelists: one for neoplastic lesions and another for non-neoplastic lesions. The new codelists for MICHRON, MIDISTR, and MISTRESC have already been released by CDISC. They all include terms derived from INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) and are extensible.

Conclusion

Whether to incorporate CDISC CT into LIMS glossaries or perform CT mapping in SEND software external to the LIMS are options that can potentially impact which terms are used in final reports and in the different SEND variables, as well as potential search strategies for data mining. Whichever approach is adopted, flexibility will be required to maintain up to date CT mapping based on the anticipated four CDISC CT releases each year.