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IS Domain Scope Update for the SDTMIG v3.4 and Its Impact on the MB and LB Domains

Presented by Dr. Jordan Li;
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Meet the Speaker

Jordan Li. Ph.D.

Title: Clinical/Biomedical Information Specialist

Organization: Guidehouse; NCI-EVS

- Subject matter and terminology expert from the National Cancer Institute's Enterprise Vocabulary Services (NCI EVS).
- Over 10 years of experience creating and publishing CDISC terminology.
- Directs delivery of multiple CDISC controlled terminology teams .
- Leads the CDISC Microbiology and Immunogenicity Submission Data Standards Development (SDS) subteam.
- CDaSH and SDTM standards experts and developed standards for several CDISC disease therapeutic area projects, including Cardiovascular Imaging, Kidney Transplant, Type 1 Diabetes and multiple Traditional Chinese Medicine projects.

Jordan holds a PhD in Pharmacology and Physiology from Georgetown University.

Disclaimer and Disclosures

- *The views and opinions expressed in this presentation are those of the author(s) and do not necessarily reflect the official policy or position of CDISC.*

Reasons Behind the Scope Update for the IS Domain for the SDTMIG v3.4

LB/MB/IS Domain Scope Changes Across SDTMIG v3.2 through SDTMIG v3.4

IGv3.2

- **IS** domain scoped for study therapy-induced subject immune response.
- **LB** domain scoped to include non-host microorg tests and other subject immune response assessments.
- **MB** domain scoped to include some non-host microorg tests used for microbial identification purposes only.

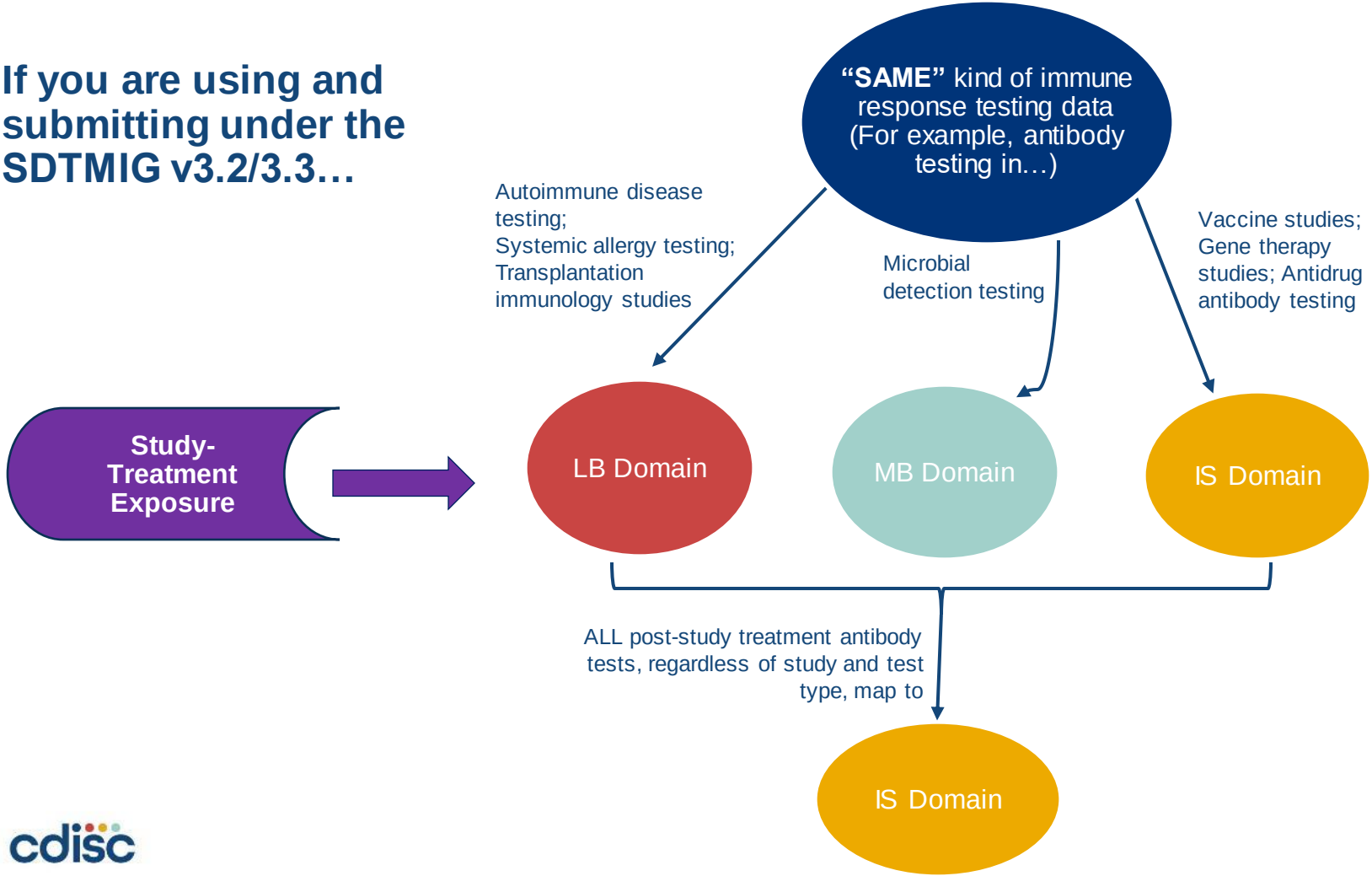
IGv3.3

- **IS** domain scoped for study therapy-induced subject immune response.
- **LB** domain scoped to include other subject immune response assessments, it no longer contains non-host microorg tests.
- **MB** domain scope broadened to include all detection, identification, quantification, and other characteristics assessments of non-host microorg, via direct detection methods and indirect, induced-host/subject immune response.

IGv3.4

- **IS** domain scoped for any antigen-induced subject immune response, not restricted to study therapy.
- **LB** domain no longer contains subject immune response assessments, or any non-host microog tests.
- **MB** domain contains “direct” detection, identification, quantification, and other characteristics assessments of non-host microorg at the time of specimen testing. It no longer contains microorg induced-subject/host immune assessments.

If you are using and submitting under the SDTMIG v3.2/3.3…



The IS Domain Scope Update for the SDTMIG v3.4

- The current IS domain in the SDTMIG v3.4 is designed to collect data pertaining to *specimen-based* assessments that measure the "presence, magnitude and scale of the immune response upon *any* ***antigen*** stimulation or encounter".
- This effectively expands the scope of the IS domain from the pervious SDTMIG versions (3.2 and 3.3) where the IS domain was limited to "assessments that describe whether a (study) ***therapy*** provoked/caused/induced an immune response."
- Per the SDTMIG 3.4, the *antigen of interest* in the above definition may be (but is not limited to), drug/test article (i.e., study/non-study therapy), allergen, microorganism (e.g. bacteria, viruses, fungi, parasites, etc.), self-antigen (autoantigen), and others, that may stimulate a host immune response.
- The current IS domain definition is also more inline with the scientific/medical definition of "immunogenicity assessment" and is well-accepted by the scientific community.
- Both humoral (antibody-mediated) immune response testing + cell-mediated immune response testing are in scope.

Rationales and the Problems that Led to the IS Domain Update for the SDTMIG v3.4

1. LB/MB/IS in the IGv3.2 and v3.3: significant overlap of domain scope and data mapping between the three domains. Scope definition and demarcation between the three domains were unclear. As a result, multiple different SDTM Findings domains were used to represent specimen-based immune response testing data.
2. Domain and variable level structure limitation for LB/MB/IS.
3. General disagreement and confusion over the prior narrow definition of the IS domain – what's considered as therapy?
4. Multiple SDTM Classes are utilized to model systemic vs. localized immune responses.

For more information, refer to this Knowledge Base Article on www.cdisc.org:
https://www.cdisc.org/kb/articles/domain-scope-update-sdtmig-v3-4-development-history-and-difficulties-standardizing

1: Domain and variable level structure limitation for LB/MB/IS

Prior to the SDTMIG v3.4, most specimen-based, immune response testing data had been mapped to the MB, LB and IS domains which were not built to collect and model complicated experimental designs and biological processes, which yield complicated data. **These domains do NOT have the sufficient structure and standard variables to support the meaningful and *consistent* representation of such data.**

As a result, various supplemental qualifiers had been created and used to map key information in both LB, MB and IS. This also resulted in too much information being mapped and pre-coordinated into the --TEST/--TESTCD variables, and therefore **overloading the --TEST and --TESTCD variables**.

2: Multiple different SDTM Findings domains were used to represent specimen-based immune response testing data

The prior IS domain scope defined by the SDTMIG v3.2/v3.3 limited its use to ONLY collection of "study therapy"-induced immune response testing data, this led to "baseline" immune response testing data *prior to study treatment exposure* having to be mapped to a different domain. Compounding on this problem, the *same* pre-study treatment exposure data would have to be mapped to different domains depending on the version of the SDTMIG used and the study types.

Ex 1: Specimen-based Allergy Immune Response Testing Data are Mapped to LB and IS, Per SDTMIG v3.2/v3.3

Prior to (Study) Therapy Exposure

Post (Study) Therapy Exposure
*IS domain only reserved for (study) therapy induced immune responses

…	Domain	SEQ	GRPID	--TESTCD	--TEST	--ORRES	--ORRESU	VISIT
	LB (SDTMIG 3.2/3.3)	1	1	C130128	Dog Dander Antigen IgE Antibody	120	kU/L	SCREENING
	LB (SDTMIG 3.2/3.3)	2	1	C165932	Dog Dander IgE AB RAST Score	6		SCREENING
	IS (SDTMIG 3.2/3.3)	3	2	C130128	Dog Dander Antigen IgE Antibody	157	kU/L	VISIT 2
	IS (SDTMIG 3.2/3.3)	4	2	C165932	Dog Dander IgE AB RAST Score	6		VISIT 2
	IS (SDTMIG 3.2/3.3)	5	3	C165932	Dog Dander Antigen IgE Antibody	45	kU/L	VISIT 4
	IS (SDTMIG 3.2/3.3)	6	3	C165932	Dog Dander IgE AB RAST Score	4		VISIT 4

Note the use of the NCI C-code in place of LBTESTCD, and heavily abbreviated LBTEST due to Conformance Rules dictating <8, <40 characters for --TESTCD and --TEST. Also, It is nearly impossible to create and maintain unique and meaningful LBTESTCDs for the large amount and vastly different anti-allergen antibody tests available. The use of NCI c-codes for TESTCD and truncated TEST values renders --TESTCD and --TEST less valuable SDTM mapping assets.

Resolution to Ex 1: Specimen-based Allergy Immune Response Testing Data in IS, Per SDTMIG v3.4

Prior to (Study) Therapy Exposure

Post (Study) Therapy Exposure

* IS domain now is used for all antigen induced immune responses

…	Domain	ISSEQ	ISGRPID	ISTESTCD	ISTEST	ISBDAGNT	ISTSTDTL	ISORRES	ISORRESU	VISIT
	IS	1	1	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN		120	kU/L	SCREENING
	IS	2	1	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN	RAST SCORE	6		SCREENING
	IS	3	2	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN		157	kU/L	VISIT 2
	IS	4	2	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN	RAST SCORE	6		VISIT 2
	IS	5	3	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN		45	kU/L	VISIT 4
	IS	6	3	ARIGEAB	Allergen-induced IgE Antibody	DOG DANDER ANTIGEN	RAST SCORE	4		VISIT 4

1. IS domain is no longer restricted to a subset of immunogenicity response assessments.
2. ALL "antigen"-stimulated immune response tests are in the same domain, no distinction made for prior vs after study therapy exposure.
3. New TEST qualifier variables are introduced in the SDTMIG v3.4 to alleviate TEST/TESTCD overloading issues.
   - LBTESTCD remains human-readable.
   - --TEST, --BDAGNT (binding agent) and --TSTDTL (test detail) clearly and separately represent the "analyte being assessed", the "binding target of the analyte", and further testing details of the assessment – note all this INFO was pre-coordinated into the TEST in IGv3.2/v3.3, leading to heavy abbreviation/truncation of the test due to character limit.

Ex 2: Antimicrobial Host Humoral Immune Response Testing Data are mapped to LB, MB and IS, Per SDTMIG v3.2/v3.3

	Domain	SEQ	--TESTCD	--TEST	--ORRES	--ORRESU	VISIT	Supplemental Qualifier Variable
Prior to (Study) Vaccine Exposure	MB (v3.3) or LB (v3.2)	1	NRSVIGG or C-code	MB: Neut. Respirat. Syncytial Virus IgG or LB: Neut. Respirat. Syncytial Virus IgG NT50*	10	titer	Baseline	suppMB: 50% NEUTRALIZATION TITER
Post (Study) Vaccine Exposure	IS (v3.2/3.3)	2	NRSVIGG	IS: Neut. Respirat. Syncytial Virus IgG	60	titer	Visit 1	suppIS: 50% NEUTRALIZATION TITER
	IS (v3.2/3.3)	3	NRSVIGG	IS: Neut. Respirat. Syncytial Virus IgG	90	titer	Visit 2	suppIS: 50% NEUTRALIZATION TITER

*TEST = Neutralizing Respiratory Syncytial Virus IgG Antibody 50% Neutralization Titer

1. Baseline data are triaged into LB if submitting under IGv3.2 and MB if submitting under IGv3.3.
2. MB is used to model non-host microorganism detection, identification and quantification type of data. In this case, the RSV antibody levels at baseline are collected to compare with the RSV vaccine-induced protective antibody levels after study vaccine administration – the baseline measurement is not meant for microbial identification/detection purpose, using MB is a stretch on its domain scope.
3. Baseline data indicates presence of antimicrobial subject antibody response which may be the result of a *previous, non-study* vaccination and/or infection, which is undistinguishable from a scientific perspective - this makes deciding IS vs MB even more difficult, and the use of either domain is incorrect.
4. Again, heavy abbreviation to the TEST due to <40 character limit – rendering the TEST variable a less meaningful SDTM mapping asset.
5. Inconsistent modeling and use of supplemental qualifiers between LB, MB and IS for the exact SAME test. (Row 1 red text is how this test would appear in LB, all values are pre-coordinated into the TEST variable, no suppLB qualifiers used).

Resolution to Ex 2: Antimicrobial Host Humoral Immune Response Testing Data are mapped to IS ONLY, Per SDTMIG v3.4

Prior to (Study) Vaccine Exposure

Post (Study) Vaccine Exposure

…	Domain	ISSEQ	ISTESTCD	ISTEST	ISBDAGNT	ISTSTDTL	ISORRES	ISORRESU	VISIT
	IS (v3.4)	1	MBIGGNAB	Neutralizing Microbial-induced IgG Antibody	Respiratory Syncytial Virus	50% NEUTRALIZATION TITER	10	titer	Baseline
	IS (v3.4)	2	MBIGGNAB	Neutralizing Microbial-induced IgG Antibody	Respiratory Syncytial Virus	50% NEUTRALIZATION TITER	60	titer	Visit 1
	IS (v3.4)	3	MBIGGNAB	Neutralizing Microbial-induced IgG Antibody	Respiratory Syncytial Virus	50% NEUTRALIZATION TITER	90	titer	Visit 2

*ISTSTDTL could also be: NT80, NT90, PRNT50-90, FRNT50-90, IC50-90, etc. (see CT codelist).

1. All antigen-stimulated immune response tests are in the same (IS) domain
   - no distinction made for prior vs after study treatment exposure.
   - no need to decide whether the baseline measurement should be mapped to IS vs MB.
2. Consistent data modeling using the same set of IS standard variables with clear variable scope definitions
3. Controlled terminology codelists supporting ISTEST-CD, ISBDAGNT and ISTSTDTL. This helps to set boundaries on variable scope and shows what values should go into these standard variables.

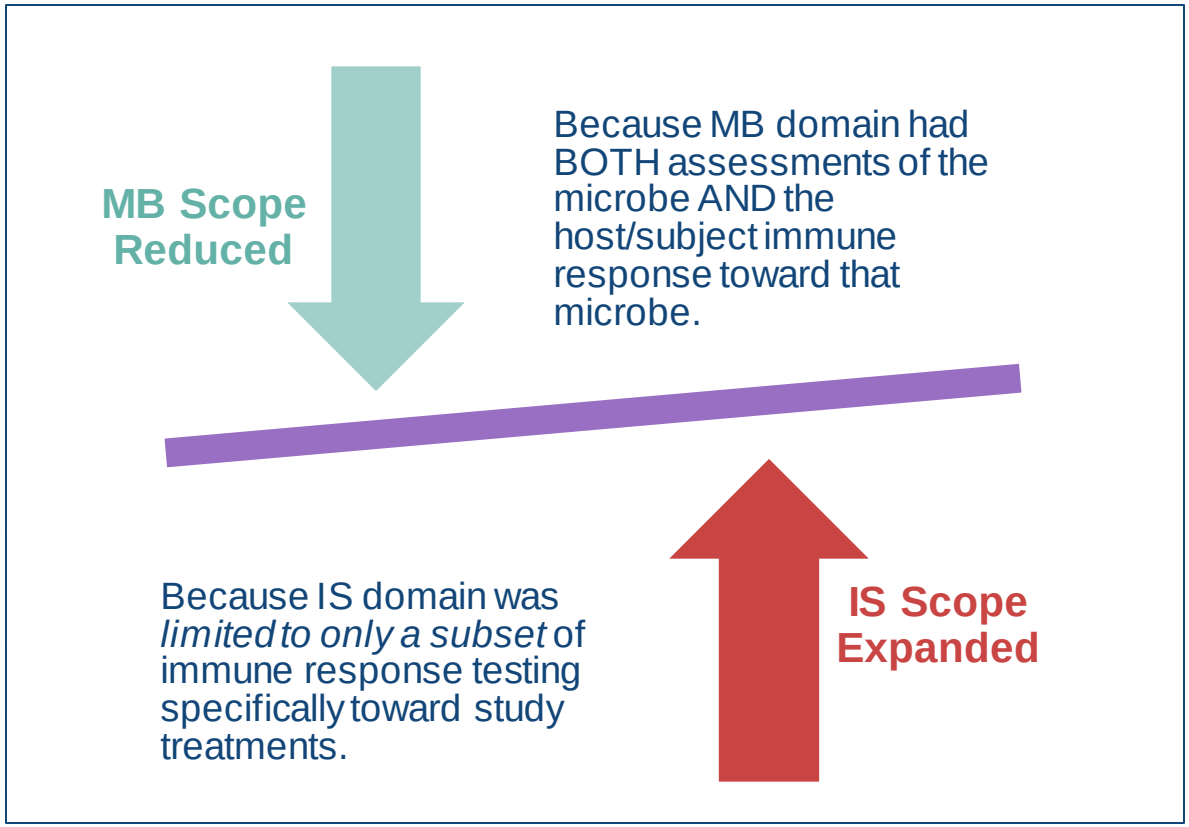
Scope Change for the MB Domain in the SDTMIG v3.4

Changes to the MB Domain Scope for the SDTMIG v3.4

- MB is used for the collection of assessment data pertain to the detection, identification, quantification and other characterizations (color, odor) of a non-host microorganism.
- (Typically) for tests that provide *direct* evidence of the presence (or absence) of the microorganism in the subject's sample, at the time of specimen testing.
    - Assays *are able to directly* capture and therefore detect a whole or parts of a microbe such as antigens (i,e. proteins, toxins), genetic material (i.e. DNA, RNA), and metabolic byproducts, etc. Results of such tests are typically reported in presence/absence and concentration.

- The presence of the anti-microbial antibody is the *host's* immune response toward a pathogen, and is an *indirect and surrogate* measure for prior or current infection. If a particular anti-microbial antibody is present, it doesn't necessarily signal a current and ongoing infection, nor the presence of the microorganism in the subject's sample, *at the time of specimen testing.*

- Antimicrobial antibody tests were part of the MB domain because they may also be used for microbial identification purposes, but they are passive host immune responses, and do not directly indicate the presence of a Microorg in the subject's specimen. Therefore, they are out of scope for the MB domain definition, and will be removed from MB in the SDTMIG 3.4.



A Summary

- **MB** is about the bug. Use MB for evidence of a microbe testing.
- **IS** is about the subject, use IS for host/subject immune response testing toward a microbe, or other antigens.

Impact on Controlled Terminology

- Timeline
- Tools & Resources

Impact on LB/MB/IS Controlled Terminology and Timeline on Upcoming Changes

The change in the LB, MB, and IS domain scope will result in the deprecation of approximately 800+ antibody and antibody-related TEST and TESTCD values from both the Lab and Microbiology domains, and instead,

- They will be remodeled in the IS domain, using IS domain standard variables including but not limited to: ISTEST-CD, ISBDAGNT (Binding Agent), and ISTSTDTL (Test Detail).
- CDISC controlled terminology teams will no longer publish humoral immune response antibody tests, as well as other antigen-stimulated cellular immune response tests, in LB and MB. These tests will only be modeled and published in IS.
- Actual terminology changes (deprecation) will happen in Dec 2023, P56 CT publication.
- Multiple announcements of the upcoming changes through public reviews and webinars since Dec 2022.

Hedging the Impact of the Changes – CDISC Education and Tools

Tools *already published* on www.cdisc.org to prepare for the transition:

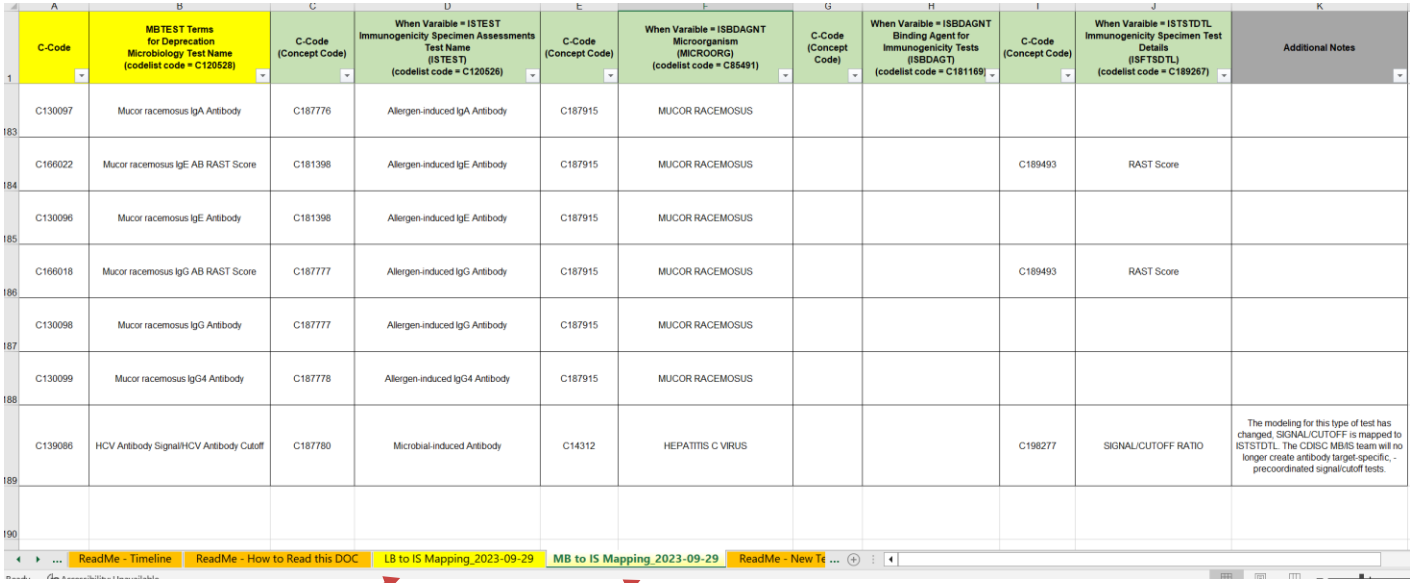
1. A Knowledge Base Article that provides in-depth analysis and explanation on the difficulties and problems that led to the LB/MB/IS domain scope updates and the changes made to these domains in the SDTMIG v3.4.
2. A Codetable Mapping file that shows how ***every*** deprecated code from the LB/MB domains will be re-modeled and mapped to the IS domain new standard variables.
3. Standards Development and CT Rules documents are published for IS and MB.
   - Variable usage, definitions and scope, as well as relationships between new standard variables
4. Webinars for public education:
   - Quarterly CT webinars.
   - Introduction Education webinar (June 22, 2023).
   - CDISC Interchange presentation.

***Most importantly, these changes had been communicated to the FDA for review and feedback.**

IS Terminology Codetable Mapping File

The deprecated LB and MB terms will be remapped to IS. The mapping can be found in the IS Terminology Codetable Mapping File, which helps users to:

- Assign the existing terms (which are going to be deprecated) from LB and MB to IS.
- Update dictionary, develop systems and programs in preparation for the SDTMIG v3.4 adaptation.
- **Traceability!!**



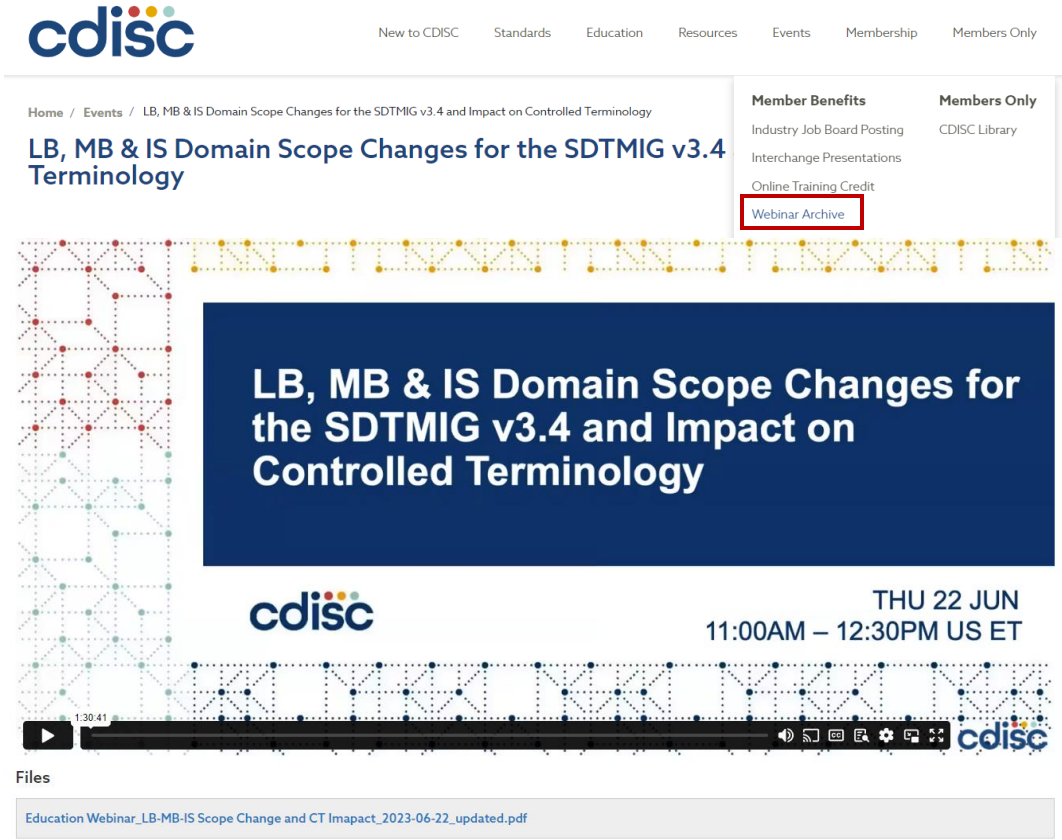
	A	B	C	D	E	F	G	H	I	J	K
1	C-Code	MBTEST Terms for Deprecation Microbiology Test Name (codelist code = C120528)	C-Code (Concept Code)	When Varaible = ISTEST Immunogenicity Specimen Assessments Test Name (ISTEST) (codelist code = C120526)	C-Code (Concept Code)	When Varaible = ISBDAGNT Microorganism (MICROORG) (codelist code = C85491)	C-Code (Concept Code)	When Varaible = ISBDAGNT Binding Agent for Immunogenicity Tests (ISBDAGT) (codelist code = C181169)	C-Code (Concept Code)	When Varaible = ISTSTDTL Immunogenicity Specimen Test Details (ISFTSDTL) (codelist code = C189267)	Additional Notes
183	C130097	Mucor racemosus IgA Antibody	C187776	Allergen-induced IgA Antibody	C187915	MUCOR RACEMOSUS					
184	C166022	Mucor racemosus IgE AB RAST Score	C181398	Allergen-induced IgE Antibody	C187915	MUCOR RACEMOSUS			C189493	RAST Score	
185	C130096	Mucor racemosus IgE Antibody	C181398	Allergen-induced IgE Antibody	C187915	MUCOR RACEMOSUS					
186	C166018	Mucor racemosus IgG AB RAST Score	C187777	Allergen-induced IgG Antibody	C187915	MUCOR RACEMOSUS			C189493	RAST Score	
187	C130098	Mucor racemosus IgG Antibody	C187777	Allergen-induced IgG Antibody	C187915	MUCOR RACEMOSUS					
188	C130099	Mucor racemosus IgG4 Antibody	C187778	Allergen-induced IgG4 Antibody	C187915	MUCOR RACEMOSUS					
189	C139086	HCV Antibody Signal/HCV Antibody Cutoff	C187780	Microbial-induced Antibody	C14312	HEPATITIS C VIRUS			C198277	SIGNAL/CUTOFF RATIO	The modeling for this type of test has changed, SIGNAL/CUTOFF is mapped to ISTSTDTL. The CDISC MBIS team will no longer create antibody target-specific, -precoordinated signal/cutoff tests.
190											

... ReadMe - Timeline | ReadMe - How to Read this DOC | LB to IS Mapping_2023-09-29 | MB to IS Mapping_2023-09-29 | ReadMe - New Te ...

LB to IS Mapping; MB to IS Mapping
show existing LBTESTs and MBTESTs to IS domain variables mapping.

For more information on this topic as well as FAQs…

- **Pubic Webinar**: LB, MB & IS Domain Scope Changes for the SDTMIG v3.4 and Impact on Controlled Terminology
- https://www.cdisc.org/events/webinar/lb-mb-domain-scope-changes-sdtmig-v3-4-and-impact-controlled-terminology
- Introduction on new IS domain standard variables, MB and IS domain scope changes, new examples, updates to examples in the published TAUGs, and impact on CT, etc.



- For more information and where to find the supporting tools and file, see the “Backup and Additional Slides” section

Backup and Additional Slides

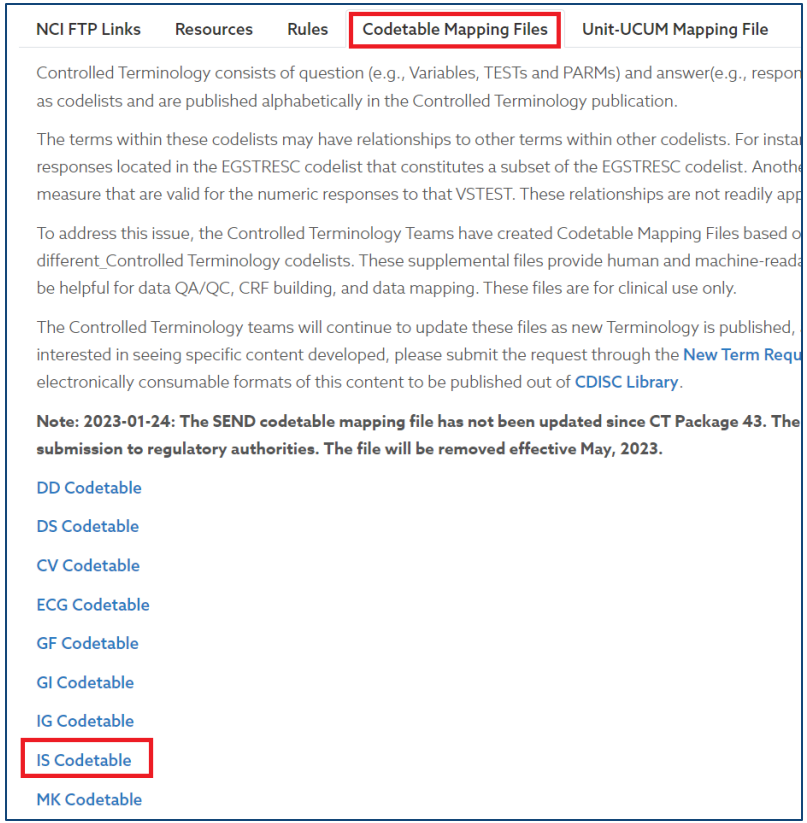
Summary on the Changes Made to the LB/MB/IS Domains in SDTMIG v3.4

1. Domain definitions and assumptions were updated to clearly define the scope of MB and IS domains and what type of data should be mapped to these domains.
2. New standard variables were created to support clear, consistent and meaningful representation of immune response testing data in the IS domain.
3. New examples were published to demonstrate how to model different immune response and microbiology tests which help to explain high-level modeling and mapping guiding principles.
   a) Antidrug antibody data modeling.
   b) Vaccine immunogenicity data modeling: both humoral and cell-medicated immune response testing.
   c) Others.
4. New controlled terminology were developed to better support and define the scopes of the new variables in the IG.
5. With domain scope changes, existing “immune response testing” terminology in MB and LB will be deprecated and remodeled in IS → this impacts about 400+ test codes.

Tools and Resources: IS Terminology Codetable Mapping File

The IS Terminology Codetable Mapping file can also be accessed from the: https://www.cdisc.org/standards/terminology/controlled-terminology

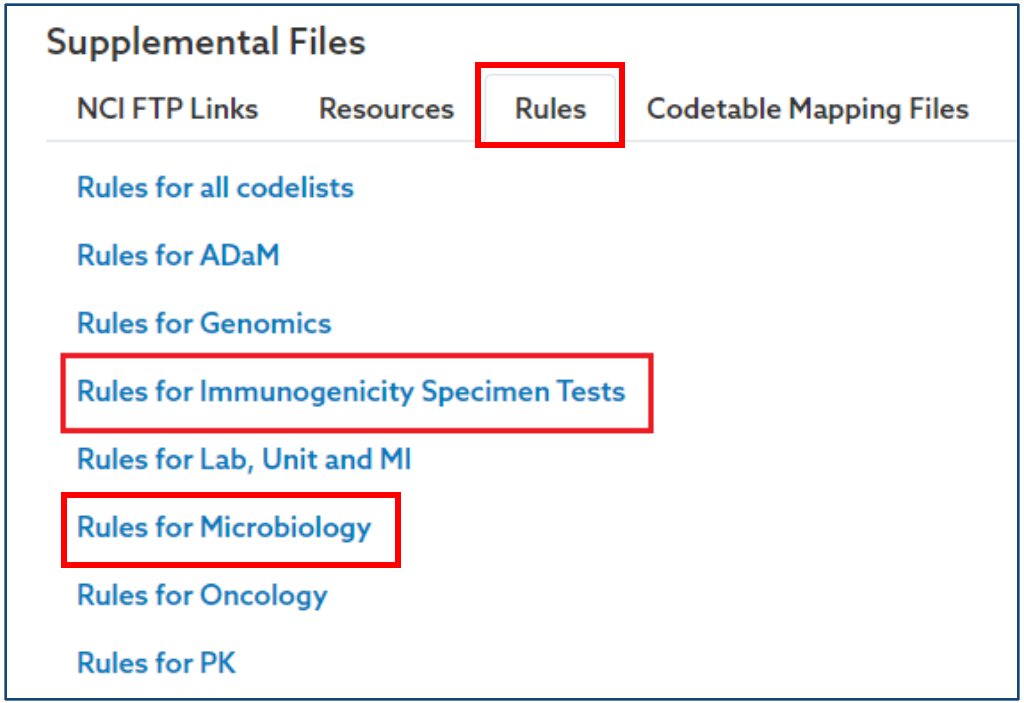
- In the Supplemental Files section.
- Under the Codetable Mapping File tab.



Tools and Resources: Rules for Immunogenicity Testing File

The Rules for Immunogenicity Testing and Rules for Microbiology files can also be accessed from the: https://www.cdisc.org/standards/terminology/controlled-terminology

- In the Supplemental Files section.
- Under the Rules tab.



Today and Future Directions

The CDISC Immunogenicity/Microbiology Subteam goal for 2023 is to:

- Support stakeholder implementation of immunogenicity and microbiology standards through outreach and development/publication of resources and new standards.

To achieve this goal, we are working toward deliverables related to:

- Communication of Standards
- Implementation Support
- Standards Development
- Refinements to IS and MB

In progress for 2023

Communication of Standards

- CT Quarterly Webinars
- LB, MB & IS Domain Scope Changes for the SDTMIG v3.4 and Impact on Controlled Terminology Webinar
- CDISC EU & US Interchange (April, October, 2023)
- Training Courses & Office Hours – New Variables, Examples, High-level modeling principles for OI, IS, MB, MS (Q2, 2024)

Implementation Support/Standards Development

- IS Knowledge Base Article (Published Aug 2022)
- IS & MB Rules Documents (Published Dec 2022)
- IS Codetable Mapping File (Published Dec 2022)
- IS and MB Example Collection (estimated mid to late 2023)
  - Update existing immunogenicity examples in LB in published TAUGs – remodel and map to IS
  - New MB examples to add to the SDTMIG v4.0

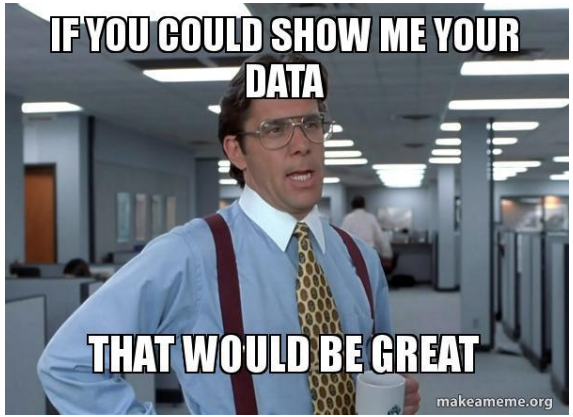
How you can be involved!

Become a CDISC MB/IS subteam volunteer.

- www.cdisc.org/volunteer
- Email Jordan.li@nih.gov to join the team

Contribute FAQs and use-case examples for modeling:

- Use-case should be real-life, de-identified and submission related.
- We would like to discuss your use-case with you.
- Reach out to Jordan Li, IS/MB subteam lead.



*Send your use-cases to us for evaluation if there are questions on how to map that data, or if you identify gaps in the current structure for MB, MS, IS and OI that need addressing.